Prevention of Postoperative Atrial Fibrillation

STEPHEN TAN, PHARM.D.
UF HEALTH AT JACKSONVILLE

Disclosure

I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Objectives

Describe postoperative atrial fibrillation and its effect on mortality and morbidity
Identify and compare prophylactic treatment options for postoperative atrial fibrillation
Introduce ranolazine’s use and its effect on postoperative afib

Canadian Cardiovascular Society of Atrial Fibrillation Guidelines 2010: Prevention and Treatment of Atrial Fibrillation Following Cardiac Surgery

Atrial fibrillation facilitated by:
- Atrial trauma, stretch, ischemia, epicardial inflammation, hypoxia, acidosis, electrolyte disturbsances, and refractoriness changes due to sympathetic discharge

Incidence of POAF ranges from 30% for pts undergoing isolated CABG to 40% for pts undergoing valve replacement or repair to 50% undergoing both.

Evidence that incidence POAF increasing as older population undergoing more procedures
Peak incidence occurs between postop day 2 and 4
70% that develop tachyarrhythmia do so prior to end of post op day 4
94% do so prior to end of post op day 6

Question#1

True or False? Ranolazine is indicated by the FDA for prophylaxis of post-op Afib.
Answer: False
Risk factors
- Older age (highest predictive value), male, history of HTN, balloon pump, prolonged ventilation (>24hrs), and withdrawal of beta blocker therapy
- Operative variables: procedure performed, number of grafts, duration of surgery, & duration of aortic cross-clamp time

Consequences
- Patient discomfort/anxiety
- Hemodynamic deterioration
- Cognitive impairment
- Thromboembolic events: stroke
- Exposure to arrhythmia treatments
- Longer hospital stay
- Increased health costs

Prophylaxis
- Beta blocker drug therapy
- Recent meta-analysis of RCTs (31 RCTs, 4452 pts)
- Associated with reduction in the probability of POAF (OR 0.36, 95% CI 0.28-0.47, \(P<0.01\))
- Heterogeneity assessment: \(P<0.01\)
- Due to some trials allowing practice of permitting preoperative withdrawal of preexisting beta blocker therapy in those randomized to placebo group

Beta Blocker Length of Stay trial (BLOS)
- In pts not receiving beta-blocker therapy prior to study, study metoprolol associated with:
  - Greater acute reduction in HR (\(P<0.01\))
  - Greater acute reduction in cardiac index (\(P<0.01\))
- Increase in total hospital stay (\(P<0.02\))
- Evidence of continuing beta-blocker therapy after cardiac surgery is very strong

The recommendations above are based on a high level of evidence (A and B grades) and the absence of a consensus on the development of a new recommendation (Strong Recommendation, High-Quality Evidence). We suggest that patients who have been receiving a beta-blocker before cardiac surgery have that therapy continued after cardiac surgery. It is also noted that in the absence of contraindication, a number of patients will require beta-blocker therapy without personal benefit.
Canadian Cardiovascular Society of Atrial Fibrillation Guidelines 2010: Prevention and Treatment of Atrial Fibrillation Following Cardiac Surgery

Amiodarone
- 19 placebo controlled RCTs, 3295 pts
- Therapy assoc with reduction in probability of POAF (OR 0.50, CI 95% 0.43-0.59, P<0.001)
- Reduction in post-op ventricular tachy-arrhythmias (OR 0.39, CI 95% 0.26-0.58, P<0.01)
- Reduction in LOS (0.6 days, CI 95% 0.4-0.8 days, P<0.001)
- Reduction in hospital costs ($2527, CI 95% -$500-$5815, P=0.1)

Meta-analysis including adverse events
- Increased post-op bradycardia (OR 1.66, CI 95% 1.73-2.47)
- Meta-analysis of pre-op amiodarone vs. intra-op and post-op amiodarone administration
  - No statistical difference in prevention of POAF (P=0.86)

Sotalol for prevention of POAF
- Meta-analysis 9 placebo controlled trials, 1382 patients
- Reduced probability of POAF (OR 0.34, CI 95% 0.26-0.45, P<0.001)
- More likely to stop treatment vs placebo due to AEs (6% vs 1.9%, P=0.04)

Sotalol vs. standard β-blocker therapy
- Sotalol associated with reduction of POAF (OR 0.62, CI 95% 0.26-0.65, P<0.01)
- Sotalol was stopped more often than standard β-blocker therapy due to AEs (7.2% vs. 4.8%, P=0.25)
- Appears sotalol has a place in therapy
- Greater adverse event profile

Sotalol therapy for POAF after cardiac surgery is less well studied
- Appears sotalol has a place in therapy
- Greater adverse event profile

RECOMMENDATION
We recommend that patients who have a contraindication to β-blocker therapy before or after cardiac surgery be considered for prophylactic therapy with amiodarone to prevent postoperative AF (Strong Recommendation, High-Quality Evidence).

Values and preferences. This recommendation places a high value on minimizing the patient population exposed to the potential adverse effects of amiodarone and a lower value on data suggesting that amiodarone is more effective than β-blockers for this purpose.
Observational data that pts taking statins may have lower incidence of afib or other cardiac arrhythmias after coronary artery bypass surgery

Factors contributing to afib:
- Atrial refractoriness, operative trauma, rise in atrial pressure due to postoperative stunning, increase of atrial electrical susceptibility from rapid return of temp after cardioplegic arrest, atrial distention by fluid overload, chemical stimulation during infusion or inotropic drugs, reflex sympathetic activation, & pericardial or respiratory complications
- Advanced age and valve surgery

Increased LOS and costs ~$6356/patient

Observational evidence-statin treatment pts undergoing coronary bypass surgery lower incidence of POAF
Not yet validated in randomized controlled trial

Pretreatment of statins prior to elective cardiac surgery
Atorvastatin 40mg daily for 1 week prior

Exclusion Criteria
- Emergent cardiac surgery
- Hx of afib
- Previous or current treatment of statins
- Elevated liver enzymes
- Renal failure; SrCr >3
- Hx of liver or muscle dz
- Inflammatory dz that required treatment with steroids or NSAIDs

Primary Endpoint
- Incidence of post-operative in hospital afib
  - Afib had to last >5mins
  - Registered by monitoring system on rhythm strip or 12 lead ECG
  - Or angina that required intervention
  - Hemodynamic compromise

Secondary Outcomes
- Comparison of length of postoperative hospital stay
- Incidence of major adverse cardiac and cerebrovascular events
- Correlation of of postoperative peak CRP levels with occurrence of afib
- Identification of variables that were predictors of outcome
Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery Study (ARMYDA-3)

Results
- **Primary End Point**
  - POAF 35% in atorvastatin arm vs 57% on placebo (**P**=0.003)
  - Mean ventricular response
    - 115+/-12bpm in atorvastatin arm vs 118+/-15bpm in placebo (**P**=0.12)

- **Secondary End Points**
  - Mean postoperative hospital stay significantly lower in atorvastatin arm (6.3+/-1.2 vs. 6.9+/-1.4; **P**=0.001)
  - Occurrence of major cardiac & cerebrovascular events were similar in both arms
  - Baseline preoperative CRP levels were not significantly different

- **Multivariable analysis**
  - Atorvastatin 61% reduction in risk of afib after cardiac surgery (OR 0.39, 95% CI 0.18 to 0.85, **P**=0.017)
  - Postop peak CRP levels above median of 166 mg/L associated with higher risk (OR 2, 95% CI 1.2 to 7, **P**=0.01)
  - Pre-randomized to atorvastatin group also taking a beta-blocker showed 90% risk reduction of POAF (OR 0.1, 95% CI 0.02 to 0.25, **P**=0.0001)

- **Subgroup analysis**
  - Atorvastatin group
    - Lower risk irrespective of age, sex, presence of DM, HTN, and COPD
  - Treatment benefit more evident
    - Post randomization POAF by pass operation (OR 0.24, CI 0.13 to 0.47, **P**=0.0001)
    - Those with normal sized left atrium (OR 0.22, CI 0.10 to 0.48, **P**=0.001)

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Figure 3. Postoperative peak levels of CRP. AF indicates atrial fibrillation; Atov, atorvastatin.
Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery Study (ARMYDA-3)

Discussion
- First RCT to demonstrate treatment with atorvastatin reduces new-onset POAF
- Shortens length of hospital stay in pts undergoing cardiac surgery with cardiopulmonary bypass
- Reduction in LOS 0.6 days
- Clinical and economic implications
  - 4.5 patients to prevent 1 episode of afib
  - 8 patients to avoid a postoperative LOS >7 days

Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery Study (ARMYDA-3)

A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement

Theoretical MOA
- n-3 polyunsaturated fatty acids (n3 PUFAs) induce low to moderate reactive oxygen species (ROS)
- activates nuclear factor erythroid 2-related factor 2 transcription factor
- up regulates gene expression of cardiomyocyte antioxidant enzymes
- such as catalase (CAT) & glutathione peroxidase (GSHPx)
- decreases vulnerability of myocardial tissue to oxidative challenge

A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement

Accumulated evidence suggest role for oxidative stress in ischemia-reperfusion injury

Study of biomarkers derived from reactive oxygen species
- Relation to POAF
- NADPH oxidase increased activity during cardiac reperfusion
  - Independently associated with increased risk for POAF
- Serum peroxide levels also associated with increased risk

A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement

Some clinical trials (Rodrigo R. et al.) used vitamin C and E to prevent POAF
- Reduced early recurrence rates following cardioversion
n-3 PUFAs also have shown favorable effects with this aim as well (Mariscalco G. et al.)
Omega-3 Fatty Acid for Prevention of Post Operative Atrial Fibrillation trial (OPERA)
- Found no beneficial effect of this treatment

A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement

Purpose: reinforcement of the antioxidant system leads to a cardioprotective effect against the occurrence of POAF in patients subject to on-pump cardiac surgery

Randomized, double-blind placebo controlled
- 367 pts admitted for cardiac surgery
- University of Chile Clinical Hospital & San Juan de Dios Hospital
- Feb 2010 - December 2011
A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement

Population
- >18 years, scheduled for CABG, valve surgery, or both in sinus rhythm
- Excluded:
  - Pts in previous arrhythmia
  - Previous MI
  - Current use of amiodarone, or sotalol
  - Severe CHF (NYHA III or IV)
  - Presence of prosthetic valves
  - Congenital vascular disease
  - Left atrial diameter >50mm
  - Conditions associated with oxidative stress or inflammation

A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement

n-3 PUFAs arm
- Formulation: eicosapentaenoic (EPA) & docosahexaenoic (DHA) acids in (1:2 EPA:DHA)
- 2 gram daily dose given 7 days prior to surgery
- Vitamin C (1g/day) & vitamin E (400 IU/day) given 2 days prior to surgery
- Continued until discharge

Placebo arm given equal number of identical capsules

A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement

Primary outcome: occurrence of ECG confirmed POAF from surgery to discharge
- ECG documented arrhythmia >1min was documented as POAF

Secondary outcomes:
- oxidative stress related biomarkers in atrial tissue/blood plasma
- Blood inflammation indexes

A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement

Primary outcome results
- 203 patients
- Comparable baseline characteristics
- POAF occurred in 9.7% of supplement group vs.
  - 32% of the placebo group (RR 0.28; 95% CI 0.14 to 0.56; \( p < 0.001 \))
  - 24 of 30 patients that developed afib between the 2nd and 3rd post op days were in the placebo group (\( p = 0.006 \))

Mean time to POAF was
- 3.3 +/- 0.7 days for the supplement group vs.
  - 2.0 +/- 0.4 days for the placebo group

Those on placebo were 3.62x more likely to develop POAF at any day compared to supplemental group (hazard ratio 3.62; 95% CI 1.78 to 7.36; \( p < 0.001 \))

NNTT was 4.7 pts (95% CI 3.3 to 11.4)
A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement

LOS
- In ICU for supplemental group: 2.87 ± 0.44 and placebo group: 3.08 ± 0.54 (p=0.76)
- In hospital for supplemental group: 8.77 ± 0.37 days vs. 9.57 ± 0.66 days for placebo (p=0.05)

2° outcomes: Oxidative stress biomarkers
- Day 5 after start of supplement
  - Malondialdehyde (MDA) levels 59.6% higher than baseline (p<0.01)
- Day 5 after start of placebo
  - MDA levels 45.6% higher than baseline (p<0.01)
- Interestingly, no significant difference in MDA levels at time 0 following supplement

Plasma vs. atrial tissue correlation?
- Strong direct correlation in both groups
- No significant difference

However
- Pts with POAF had significantly higher levels of atrial MDA (4.47 vs. 3.85 µmol/mg protein; p<0.01 at time of surgery)

Post-op day 1
- Placebo & supplement group: 3.6x & 2.2x greater C-reactive protein (CRP) vs. pre-op levels (p<0.01)
- Supplement group 35.4% lower than placebo group (p<0.05)
- Day -2: supplement group 32.5% higher leukocyte count than baseline (p<0.05)
- Post-op day 1: placebo & supplement group 73.8% & 36.2% increase in leukocyte count (p<0.05)
- Leukocyte count 22.2% lower in supplement group vs. placebo at this time (p<0.05)
A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement

Discussion
- Combination of indirect antioxidant effects of n-3 PUFAs
- Direct oxidant effects of Vit C & E
- Decreased vulnerability of atrial tissues
- Noteworthy reduction of 66%
- Assessment of oxidative stress and inflammatory biomarkers
  - Increase in ROS induced by n-3 PUFAs as seen by increase in plasma MDA levels
  - Reduction of ferric-reducing ability of plasma or erythrocyte thiols index
  - Response maybe due to both increased scavenging and decreased production of ROS

Vitamin C possibly enhanced synergistic antioxidant potential administered with Vit E
- Previous studies which failed to show benefit of n-3 PUFAs
  - Formulation ratio of 1.24 EPA:DHA
  - Data here EPA:DHA ratio 0.5
  - Support from additional trials using this ratio -> benefit in POAF
- Meta-regression analysis did show trend to benefit with n-3 PUFAs

A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement
More recent including published controlled trials support n-3 PUFAs therapy reduced incidence of POAF (Singh M, et al.)

Limitations
- Did not assess n-3 PUFAs pleitropic effects other than those related to oxidative stress & inflammation

A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement
Vitamin C possibly enhanced synergistic antioxidant potential administered with Vit E

Low cost
- Short-term
- Easily available
- Reduced vulnerability of myocardial tissue
- May improve outcomes of pts undergoing on-pimp cardiac surgery, as well as other surgeries involving atrial fibrillation risk

A Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement
Vitamin C possibly enhanced synergistic antioxidant potential administered with Vit E

Effect of preoperative administration of allopurinol in patients undergoing surgery for valvular heart diseases

Myocardial tissue damage theoretically minimized
- Free radical scavengers
- Antioxidants
Allopurinol reduces production of reactive oxygen species:
- Inhibits xanthine oxidase(XO)
Effect of preoperative administration of allopurinol in patients undergoing surgery for valvular heart diseases

Double blind placebo controlled
50 patients
25 allopurinol 300mg night prior and day of
Oct 2008-Dec 2008
- Open heart surgery under Cardiopulmonary bypass
- Dept Cardiothoracic and Vascular Surgery
- All India Institute of Medical Sciences
Pilot study

Discussion
Allopurinol group fare better
- Increased conversion back to NSR
- Remain in NSR
- Decreased inotropic requirements
- Decreased mechanical ventilation
- Shorter hospital stay

Limited
- Small sample size
- No cardiac output measures
- Cardiac performance measured by inotrope use
- Shorter mechanical ventilation used as measure of better pulmonary function

Comparison of Effectiveness and Safety of Ranolazine Versus Amiodarone for preventing Atrial Fibrillation After Coronary Artery Bypass Grafting

Amiodarone frequently used to decrease AF after CABG
Ranolazine antianginal agent
- Inhibits abnormal late sodium channel current in atrium
- Intracellular calcium handling producing energy-sparing effect
- Potent inhibitor of afterdepolarizations
- Induces significant postrepolarization refractoriness of atrial tissue
- More difficult for AF to sustain
Short Course of Ranolazine for the Prevention of Post-operative Atrial Fibrillation Following Coronary Artery Bypass Grafting and Valve Surgeries

Ranolazine: the antiarrhythmic

- Inhibition of late atrial inward \( I_{Na} \) and outward \( I_K \) currents
  - Prolongs action potential duration
- Inhibits outward \( I_K \) currents
  - Prolongs post-repolarization refractory period
- More difficult to develop and to sustain an atrial arrhythmia

Circulation. 2006;113:2462-2472.

Ranolazine for POAF Prevention Following CABG Surgeries

Miles RH, et al.
- Retrospective (n=182)
- Ranolazine 1500 mg x1 day of surgery, then 1000 mg PO BID x10–14 days
- POAF:
  - Ranolazine: 32 (17.5%)
  - Amiodarone: 56 (26.5%)
  - \( P = 0.035 \)

Tagarakis GI, et al.
- Prospective (n=34)
- Ranolazine 375 mg PO BID 3 days prior to surgery until discharge
- POAF:
  - Ranolazine: 3 (8.8%)
  - Usual care: 21 (30.8%)
  - \( P < 0.001 \)


Primary Endpoint

Incidence of POAF development following a cardiac surgery

POAF Stratified by Surgery Type

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Ranolazine (n=50), n(%)</th>
<th>Control (n=102), n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>4 (12.5)</td>
<td>25 (35.7)</td>
<td>0.016</td>
</tr>
<tr>
<td>Valve</td>
<td>1 (6.25)</td>
<td>14 (53.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Valve + CABG</td>
<td>0</td>
<td>4 (66.7)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Abbreviations: CABG = coronary artery bypass grafting.

Kaplan-Meier Curve

POAF-Free Survival

Short Course of Ranolazine for the Prevention of Post-operative Atrial Fibrillation Following Coronary Artery Bypass Grafting and Valve Surgeries

Ranolazine 1000 mg by mouth twice daily beginning in pre-operative period (1 dose) and continuing post-operatively until:

- Post-operative day 7
- Hospital discharge
- Potential adverse event
Secondary Endpoints

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ranolazine (n=50)</th>
<th>Control (n=102)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU LOS following cardiac surgery, days (IQR)</td>
<td>5 (4–7)</td>
<td>6 (4–7)</td>
<td>0.26</td>
</tr>
<tr>
<td>30-day readmission for cardiac causes, n (%)</td>
<td>5 (10)</td>
<td>24 (24)</td>
<td>0.05</td>
</tr>
<tr>
<td>30-day cardiovascular mortality, n (%)</td>
<td>0</td>
<td>4 (4)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

* Abbreviations: ICU = intensive care unit; LOS = length of stay; IQR = interquartile range

Clinical Implications

Perioperative ranolazine is reasonable as prophylactic therapy for patients undergoing cardiac surgery at risk for POAF.

At UF Health Jacksonville, ranolazine will be ordered for all patients undergoing a CABG or valve surgery who do not possess a contraindication to therapy.

Future directions
1. Postoperative order set modification
2. Surgery resident education module
3. Grant-funded, prospective, multicenter research

Summary

Post-operative atrial fibrillation multicenter causas
Several prophylactic strategies for prevention
Low cost
Low risk
Many require pre-op preparation for effectiveness
Additional studies needed to prioritize effectiveness

Short Course of Ranolazine for the Prevention of Post-operative Atrial Fibrillation Following Coronary Artery Bypass Grafting and Valve Surgeries

Potential effects from ranolazine
- Decreased POAF development
- Reduced 30-day readmission for a cardiac cause
- Greater incidence of symptomatic hypotension

References


DH1  Look into appointments after DC - looks like all had one scheduled within X weeks - did pts come a similar % of the time?  
Drayton Hammond, 4/25/2014
References


Questions????