Pharmacological Prevention of Atrial Fibrillation after Cardiac Surgery with and without the Use of Nonsteroidal Anti-inflammatory Drugs

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Pharmacological Prevention of Atrial Fibrillation After Cardiac Surgery With and Without the Use of Nonsteroidal Anti-inflammatory Drugs

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Longitudinal Research Project
Disclosures

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Abbreviations

- **ACC/AHA/HRS**: American College of Cardiology/American Heart Association/Heart Rhythm Society
- **AF**: Atrial Fibrillation
- **AFACS**: Atrial Fibrillation After Cardiac Surgery
- **AKI**: Acute Kidney Injury
- **AVR**: Aortic Valve Replacement
- **BHM**: Baptist Hospital of Miami
- **BHSF**: Baptist Health South Florida
- **CABG**: Coronary Artery Bypass Graft
- **CKD**: Chronic Kidney Disease
- **COPD**: Chronic Obstructive Pulmonary Disease
- **ICU**: Intensive Care Unit
- **HFrEF**: Heart Failure with a reduced Ejection Fraction
- **LA**: Left Atrium
- **LOS**: Length of Stay
- **LV**: Left Ventricle
- **LVEF**: Left Ventricular Ejection Fraction
- **MVR**: Mitral Valve Replacement
- **NSAIDs**: Nonsteroidal Anti-Inflammatory Drugs
- **PMH**: Past Medical History
- **SCA/EACTA**: Society of Cardiovascular Anesthesiologists / European Association of Cardiothoracic Anesthesiology
- **SD**: Standard Deviation
- **SMH**: South Miami Hospital
- **Tx**: Treatment
Discuss the impact of NSAID use on the incidence of atrial fibrillation and acute kidney injury in cardiac surgery patients
Post-operative atrial fibrillation is the most common complication following cardiac surgery

- 25% following CABG
- 30% following valvular surgery
- 40-50% following CABG/valvular procedures

AFACS is associated with

- ↑ Morbidity – stroke, infection, GI/renal dysfunction
- ↑ Mortality
- ↑ LOS (ICU and hospital)
- ↑ Financial burden
- ↑ Readmission rates
Risk Factors for AFACS

- ↑ Age (> 75yo)
- History of AF
- Obesity
- COPD
- HFrEF
- Chronic renal failure
- Male gender
- On-pump surgery
- LV hypertrophy

Guideline Recommendations for β-blockers and Amiodarone as AF Prophylaxis

ACC/AHA/HRS Guidelines
- β-blockers = Class Ia recommendation
- Amiodarone = Class IIa recommendation

ESC Guidelines
- β-blockers = Class Ib recommendation
- Amiodarone = Class IIa recommendation

AATS Guidelines
- β-blockers = Class Ia recommendation
- Amiodarone = Class IIa recommendation

SCA/EACTA Guidelines
- β-blockers = Class Ia/b recommendation
- Amiodarone = Class IIa/b recommendation

- **Primary Outcome**: Incidence of atrial fibrillation in the immediate postoperative period (7 days post-op or until discharge, whichever came first)

- **Study Groups**:
  - Experimental Group: IV ketorolac (30mg IV q6g x 48h) followed by PO ibuprofen (600mg PO TID x 7d)
  - Control Group: Placebo

- **Results**: Incidence of AFACS was significantly lower in the group that received NSAIDs compared to placebo (9.8% vs 28.6%, p=0.017), with no significant difference in renal failure

Literature Regarding NSAID Use

Naproxen as Prophylaxis against Atrial Fibrillation after Cardiac Surgery: The NAFARM Randomized Trial (2011)

**Primary Outcome**
Occurrence of atrial fibrillation in the first 5 postoperative days

**Experimental Group**
Naproxen 275 mg PO q12h x 5d

**Control Group**
Placebo

**Results**
- **No significant difference in AFACS**
  - (7.3% vs 15.2%, p=0.11)
- **Naproxen group**
  - ↓ duration of AF
    - (0.35h vs 3.74h, p=0.04)
  - ↑ in renal failure
    - (7.3% vs 1.3%, p=0.06)

In 2017, a study done at BHM showed that incidence of AFACS decreased from 36% to 22% following implementation of a prevention protocol that included metoprolol, amiodarone and NSAIDs.

The following protocol was implemented across BHSF hospitals:

<table>
<thead>
<tr>
<th>Amiodarone</th>
<th>While Intubated</th>
<th>Post Extubation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150 mg IV bolus followed by infusion at 1 mg/min x 6 hours → 0.5 mg/min x 18 hours</td>
<td>600 mg PO BID x 5d (cont infusion drip with PO if 24h infusion incomplete at the time of extubation)</td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>5 mg IV q6h (hold if SBP &lt; 100, HR &lt; 60 or if currently paced via epicardial wires)</td>
<td>25 mg PO BID, or 50 mg PO BID, or 75 mg PO BID (Hold for SBP &lt; 100, or HR &lt; 60)</td>
</tr>
<tr>
<td>NSAID</td>
<td>Ketorolac 30 mg IV q6h x 48 hours (or while intubated) (CrCl 25-50 mL/min, use 15 mg IV q6h; do not use if pt is actively bleeding or CrCl &lt; 25 mL/min)</td>
<td>Ibuprofen 600 mg PO TID x 7d (Do not give if CrCl &lt; 30 mL/min)</td>
</tr>
</tbody>
</table>
Current Practices at BHM and SMH

- Considerations regarding current AFACS prevention protocol:
  - Potential increase in AKI/renal failure due to around the clock administration of NSAIDs
  - Inherent risk of AKI in ~35% of patients after cardiac surgery; increases postoperative mortality rates to over 60%

- At both BHM and SMH, these risks have prompted healthcare providers to avoid the use of NSAIDs post-cardiac surgery
Research Purpose

To assess if NSAIDs affect patient outcomes when they are used to prevent AFACS
Study Design

Retrospective chart review of patients who underwent an open-heart procedure (CABG, MVR, AVR, double valve replacement, combination CABG/valvular replacement surgery, aortic surgery) at either BHM or SMH and received pharmacological prophylaxis to prevent AFACS

Study Population:
- Cohort A (NSAIDs): metoprolol, amiodarone and NSAIDs
- Cohort B (No NSAIDs): metoprolol and amiodarone
Eligibility Criteria

**Inclusion Criteria**
- Adult patients (≥ 18 years old)
- Underwent one of the following cardiac surgeries: CABG, MVR, AVR, Double valve replacement, combination CABG/valvular, Aortic Surgery
- Underwent cardiac surgery between 5/1/2019 and 12/20/2019
- Received at least one of the protocol medications

**Exclusion Criteria**
- Patients who are pregnant
- Patients who are incarcerated
Data Collection Method

- All patients who underwent open-heart surgery at either BHM or SMH between 5/1/2019 and 12/20/2019 were screened for inclusion/exclusion criteria.

- On screening, patients were separated into Cohort A or Cohort B based on prophylactic therapy received:
  - Cohort A (NSAIDs): 3 drugs (metoprolol, amiodarone and NSAIDs)
  - Cohort B (No NSAIDs): 2 drugs (metoprolol and amiodarone)
Study Outcomes

1. Incidence of new-onset AFACS within the first 7 days after surgery

2. Postoperative incidence of AKI (↑ in Scr ≥ 0.3 mg/dL in 48h or ↑ in Scr to ≥1.5x baseline in 7 days)
   - ICU length of stay (days)
   - Hospital length of stay (days)
Results
Patient Selection

215 pts screened

198 pts included

17 pts excluded

19 pts received one protocol medication

16 pts received meds as tx for AF

163 pts analyzed

12 pts received only Amiodarone

7 pts received only a beta-blocker

Cohort A (NSAIDS) (n=76)

Cohort B (No NSAIDs) (n=87)

Reason for Exclusion | n=17
--- | ---
Did not receive prophylactic therapy for AFACS | 8
Surgery performed outside of study period | 9
# Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NSAIDs n=76</th>
<th>No NSAIDs n=87</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>62 ± 9</td>
<td>65 ± 10.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Age &gt; 75 years – n (%)</td>
<td>6 (7.9)</td>
<td>17 (19.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Gender – male, n (%)</td>
<td>62 (81.6)</td>
<td>65 (74.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 18.5 – 24</td>
<td>9 (11.8)</td>
<td>22 (25.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>• 25 - 30</td>
<td>31 (40.8)</td>
<td>28 (32.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>• ≥ 31</td>
<td>36 (47.4)</td>
<td>37 (42.5)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• BHM</td>
<td>64 (84.2)</td>
<td>70 (80.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>• SMH</td>
<td>12 (15.8)</td>
<td>17 (19.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>CABG – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CABG x1</td>
<td>13 (17.1)</td>
<td>8 (9.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>• CABG x2</td>
<td>23 (30.3)</td>
<td>24 (27.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>• CABG x3</td>
<td>23 (30.3)</td>
<td>30 (34.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>• CABG x4</td>
<td>4 (5.3)</td>
<td>11 (12.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Valvular Surgery – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• AVR</td>
<td>12 (15.8)</td>
<td>11 (12.6)</td>
<td>0.56</td>
</tr>
<tr>
<td>• MVR</td>
<td>10 (13.2)</td>
<td>10 (11.5)</td>
<td>0.59</td>
</tr>
<tr>
<td>CABG + Valvular Surgery – n (%)</td>
<td>2 (2.6)</td>
<td>1 (1.5)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>NSAIDs n=76</th>
<th>No NSAIDs n=87</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMH – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hypertension</td>
<td>60 (78.9)</td>
<td>70 (80.5)</td>
<td>0.81</td>
</tr>
<tr>
<td>• Hyperlipidemia</td>
<td>59 (77.6)</td>
<td>53 (60.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>• Type 2 Diabetes</td>
<td>30 (39.5)</td>
<td>37 (42.5)</td>
<td>0.69</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
<td>8 (10.5)</td>
<td>6 (6.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>• Tobacco Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Current</td>
<td>11 (14.5)</td>
<td>14 (16.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>• Former</td>
<td>31 (40.8)</td>
<td>17 (19.5)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>• Peripheral Artery Disease</td>
<td>2 (2.6)</td>
<td>6 (6.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>• Myocardial Infarction</td>
<td>16 (21.1)</td>
<td>17 (19.5)</td>
<td>0.81</td>
</tr>
<tr>
<td>• Chronic Kidney Disease</td>
<td>2 (2.6)</td>
<td>21 (24.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Baseline Scr – mean (SD)</td>
<td>0.94 ± 0.23</td>
<td>1.5 ± 1.8</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
To control for the disproportionate number of patients in Cohort B with renal dysfunction at baseline, patients with a PMH of CKD were removed from each cohort prior to analysis of the primary and secondary outcomes.

- 215 pts screened
- 198 pts included
- 17 pts excluded
- 19 pts received one protocol medication
- 16 pts received meds as tx for AF
- 12 pts received only Amiodarone
- 7 pts received only a beta-blocker
- Cohort A (NSAIDs) (n=76)
- Cohort B (No NSAIDs) (n=87)
- 163 pts analyzed
- Cohort A (NSAIDs) (n=74)
- Cohort B (No NSAIDs) (n=66)
## Risk Factors for AFACS

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>NSAIDs (n=74)</th>
<th>No NSAIDs (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMH of AF − n (%)</td>
<td>4 (5.4)</td>
<td>3 (4.5)</td>
<td>0.82</td>
</tr>
<tr>
<td>Reduced LVEF prior to surgery − n (%)</td>
<td>14 (18.9)</td>
<td>20 (30.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>• LVEF 40-49% (mild dysfunction)</td>
<td>9 (12.2)</td>
<td>10 (15.2)</td>
<td>0.61</td>
</tr>
<tr>
<td>• LVEF 30-39% (moderate dysfunction)</td>
<td>3 (4.1)</td>
<td>5 (7.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>• LVEF &lt; 30% (severe dysfunction)</td>
<td>2 (2.7)</td>
<td>5 (7.6)</td>
<td>0.19</td>
</tr>
<tr>
<td>PMH of COPD − n (%)</td>
<td>3 (4.1)</td>
<td>1 (1.5)</td>
<td>0.37</td>
</tr>
<tr>
<td>PMH of coronary artery stenosis</td>
<td>62 (83.8)</td>
<td>57 (86.4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Age ≥ 75 years − n (%)</td>
<td>6 (8.1)</td>
<td>11 (16.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Type of procedure − n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• On-pump</td>
<td>71 (95.9)</td>
<td>65 (98.5)</td>
<td>0.37</td>
</tr>
<tr>
<td>• Avg. time on cardiopulmonary bypass – hours (SD)</td>
<td>1:25 ± 0:36</td>
<td>1:43 ± 0:51</td>
<td>0.01</td>
</tr>
<tr>
<td>• Off-pump</td>
<td>3 (4.1)</td>
<td>1 (1.5)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypotension requiring vasopressors post-op − n (%)</td>
<td>61 (82.4)</td>
<td>56 (84.8)</td>
<td>0.70</td>
</tr>
</tbody>
</table>
**Study Outcomes**

### 1° Outcome

#### Incidence of new-onset AFACS

- **NSAIDs** (n=74): 12/74 (16.2%)
- **No NSAIDs** (n=66): 10/66 (15.2%)

p-value = 0.86

### 2° Outcomes

<table>
<thead>
<tr>
<th>Incidence of AKI – n (%)</th>
<th>NSAIDs (n=74)</th>
<th>No NSAIDs (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scr ↑ ≥ 0.3 mg/dL in 48h or ↑ ≥ 1.5x baseline in 7d</td>
<td>15 (20.3)</td>
<td>17 (25.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>Scr ↑ ≥ 0.3 mg/dL in 48h</td>
<td>12 (16.2)</td>
<td>12 (18.2)</td>
<td>0.76</td>
</tr>
<tr>
<td>Scr ↑ ≥ 1.5x baseline in 7d</td>
<td>7 (9.5)</td>
<td>12 (18.2)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

- **Mean ICU length of stay, days (SD)**: 2.3 ± 2.0 vs. 2.8 ± 2.2, p = 0.23
- **Mean hospital length of stay, days (SD)**: 10.6 ± 6.1 vs. 11.0 ± 4.6, p = 0.63
Study Outcomes – Incidence of AKI

Incidence of Postoperative AKI

- **NSAIDs**
- **No NSAIDs**

- Baseline Scr on admission – mean (SD)
  - NSAIDs (n=74): 0.92 ± 0.2
  - No NSAIDs (n=66): 1.1 ± 0.4
  - p-value: < 0.01

- Baseline Scr after surgery – mean (SD)
  - NSAIDs (n=74): 0.90 ± 0.2
  - No NSAIDs (n=66): 1.02 ± 0.3
  - p-value: < 0.01

- Maximum Scr after surgery – mean (SD)
  - NSAIDs (n=74): 1.07 ± 0.3
  - No NSAIDs (n=66): 1.30 ± 0.5
  - p-value: < 0.01

- # doses of NSAIDs postoperatively – mean (SD)
  - NSAIDs (n=74): 4.7 ± 4.9
  - No NSAIDs (n=66): 0

- Postoperative hypotension requiring vasopressors – n (%)
  - NSAIDs (n=74): 61 (82.4)
  - No NSAIDs (n=66): 57 (86.4)
  - p-value: 0.52

  - # vasopressors used – n (%)
    - 1
      - NSAIDs (n=74): 33
      - No NSAIDs (n=66): 20
      - p-value: 0.08
    - 2
      - NSAIDs (n=74): 28
      - No NSAIDs (n=66): 25
      - p-value: 0.99
    - 3
      - NSAIDs (n=74): 0
      - No NSAIDs (n=66): 12
      - p-value: < 0.01

- Mean # days on vasopressor therapy (SD)
  - NSAIDs (n=74): 1.7 ± 0.8
  - No NSAIDs (n=66): 2.0 ± 1.0
  - p-value: 0.06

- Postoperative dehydration (BUN:Scr ≥ 20:1) – n (%)
  - NSAIDs (n=74): 50 (67.6)
  - No NSAIDs (n=66): 42 (63.6)
  - p-value: 0.62
There was no difference in the incidence of new-onset AFACS between cohorts (16.2% vs 15.2%, p=0.86)

There was no difference in the incidence of AKI between cohorts (20.3% vs 25.8%, p=0.44)
  - The numerically higher rates of AKI in patients who did not receive NSAIDs can be attributed to:
    - Worse renal function at baseline
    - Higher requirement of vasopressor therapy post surgery

The difference in length of stay between cohorts was not statistically significant
Limitations

1. Retrospective study design

2. Small study population
   - Anticipated ~100 patients in each cohort; only 163 patients met inclusion criteria, with 140 patients total being included in the final analysis

3. Selection bias
   - Patients with PMH of CKD were later removed from each cohort to control for this confounding factor

4. Confounding factors that could have impacted results in Cohort B
   - Renal function at baseline
   - Number of patients ≥ 75 years old
   - Postoperative hypotension requiring vasopressor therapy
   - Duration of vasopressor therapy
When administered after an open-heart procedure, NSAIDs did not impact the incidence of postoperative atrial fibrillation, incidence of AKI or length of stay.

Given the risks of acute renal failure after cardiac surgery and the lack of benefit in the prevention of atrial fibrillation, these results support the removal of NSAIDs from the postoperative atrial fibrillation prevention protocol.
The rationale for the inclusion of NSAIDs in an AFACS prevention protocol includes which of the following?

A. Mild side effect profile
B. Pain relief
C. Anti-inflammatory effects
D. Low cost medications
Acknowledgements

- Radhan Gopalani, Pharm.D., BCPS
- Faaria Quadri, Pharm.D., BCPS
- Heidi Clarke, Pharm.D., BCCCP
- Mario Ignacio Pascual, M.D.
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