5-2020

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

Laura Neubauer
Baptist Hospital of Miami, LauraNeu@baptisthealth.net

Radhan Gopalani
Baptist Hospital of Miami, radhang@baptisthealth.net

Faaria Quadri
Baptist Hospital of Miami, FaariaQ@baptisthealth.net

Mario Pascual
Baptist Health Medical Group; Miami Cardiac & Vascular Institute, MarioPa@baptisthealth.net

Heidi Clarke
Baptist Hospital of Miami, heidic@baptisthealth.net

Authors
Laura Neubauer, Radhan Gopalani, Faaria Quadri, Mario Pascual, Heidi Clarke, and Andrea Marr-Peralto

Baptist Hospital

BAPTIST HEALTH SOUTH FLORIDA

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

Laura Neubauer, Pharm.D., PGY-1 Pharmacy Resident

Baptist Hospital of Miami

Longitudinal Research Project

Disclosures

The following contributors have nothing to disclose regarding any financial or nonfinancial relationships with the products described, reviewed, or evaluated in this presentation:

- Laura Neubauer, Pharm.D.
- Radhan Gopalani, Pharm.D., BCPS
- Faaria Quadri, Pharm.D., BCPS
- Heidi Clarke, Pharm.D., BCCCP
- Mario Ignacio Pascual, M.D.
- Andrea-Marr Peralto, DNP, AGACNP, APRN
- Cathleen Charles, MSN, APRN, FNP-BC

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

Presentation Objective

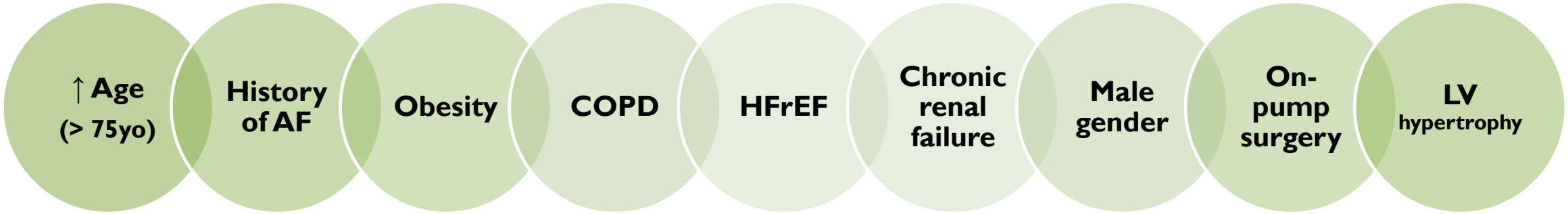
Discuss the impact of NSAID use on the incidence of atrial fibrillation and acute kidney injury in cardiac surgery patients

Background

- 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

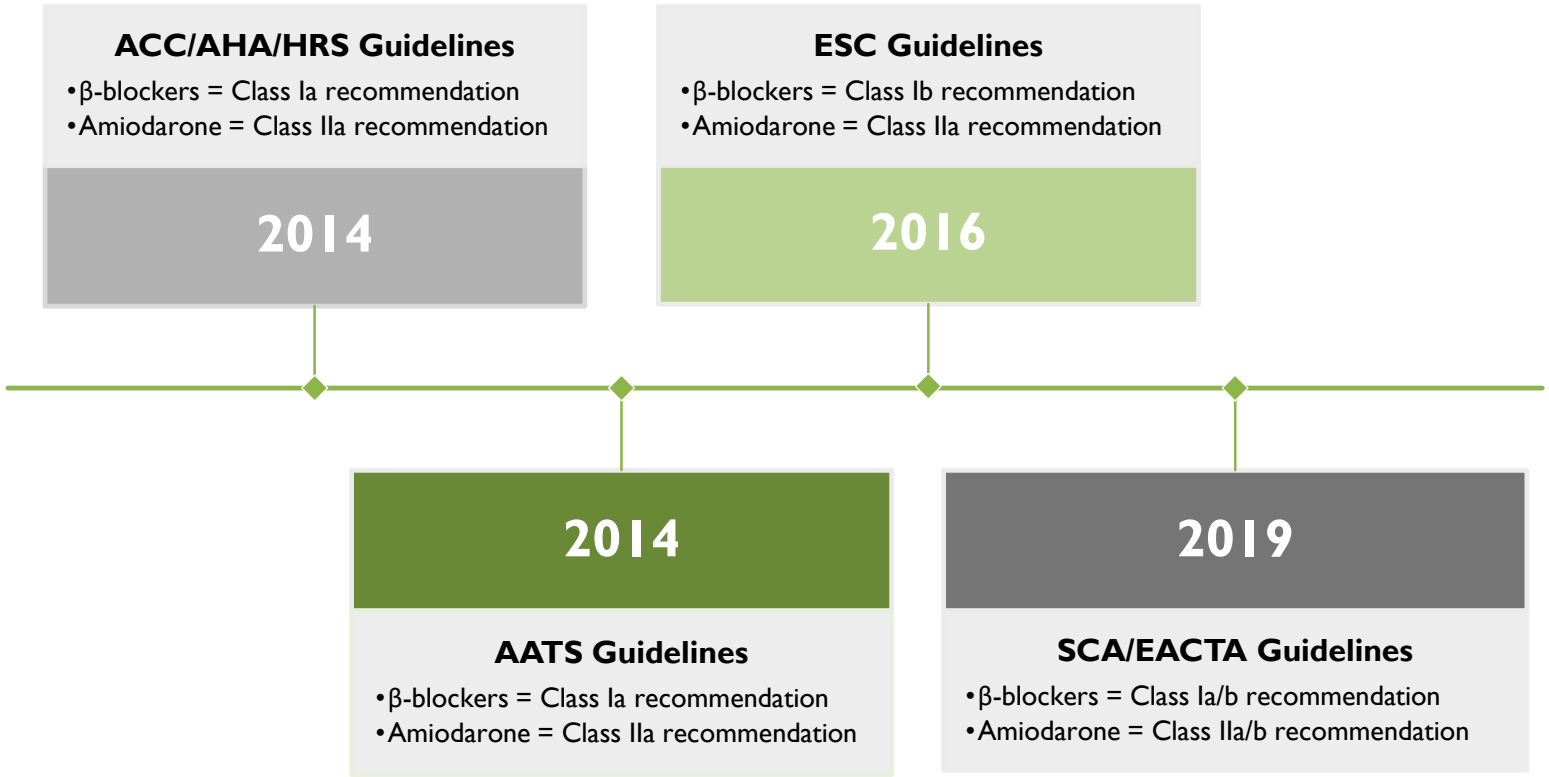
Burrage PS. *Current Anesthesiology Reports*. 2019;9:174-193.
Dobrev D. *Nat. Rev. Cardiol.* 2019;16:417-436.
Muehlschlegel JD. *Anesth Analg*. 2019;128(1):33–42.

Risk Factors for AFACS



Burrage PS. *Current Anesthesiology Reports*. 2019;9:174-193.
Muehlschlegel JD. *Anesth Analg*. 2019;128(1):33–42.

Guideline Recommendations for β-blockers and Amiodarone as AF Prophylaxis



January CT. *J Am Coll Cardiol.* 2014;64(21):2246-80.
Kirchhof P. *Rev Esp Cardiol (Engl Ed).* 2017;70(1):50.
Muehlschlegel JD. *Anesth Analg.* 2019;128(1):33–42.
Frendyl G. *J Thorac Cardiovasc Surg.* 2014;148(3):153-193.

Literature Regarding NSAID Use

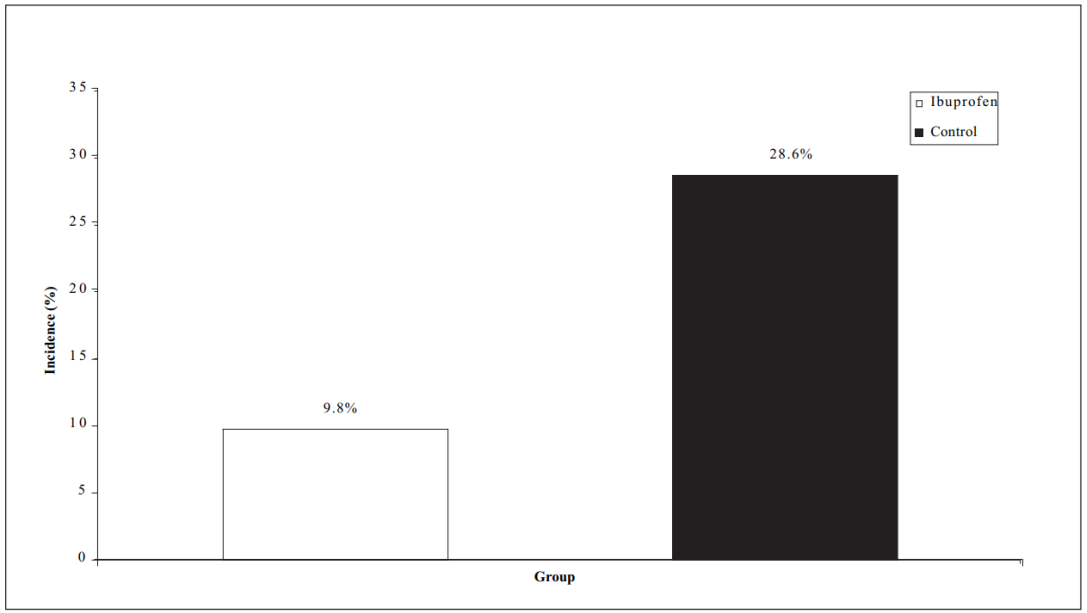


Figure 1. Incidence of new-onset atrial fibrillation following coronary artery bypass graft surgery

Efficacy of Nonsteroidal Anti-Inflammatory Medications for Prevention of Atrial Fibrillation Following Coronary Artery Bypass Graft Surgery (2004)

- **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

Cheruku KK,. *Prev Cardiol.* 2004;7(1):13-18.

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)

Horbach SJ. *Am J Med.* 2011;124(11):1036-42.

2017 Study at BHM

- 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:

	While Intubated	Post Extubation
Amiodarone	150 mg IV bolus followed by infusion at 1 mg/min x 6 hours → 0.5 mg/min x 18 hours	600 mg PO BID x 5d (cont infusion drip with PO if 24h infusion incomplete at the time of extubation)
Metoprolol tartrate	5 mg IV q6h (hold if SBP < 100, HR < 60 or if currently paced via epicardial wires)	25 mg PO BID, or 50 mg PO BID, or 75 mg PO BID (Hold for SBP < 100, or HR < 60)
NSAID	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 < 25 mL/min)	Ibuprofen 600 mg PO TID x 7d (Do not give if CrCl < 30 mL/min)

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

1^0

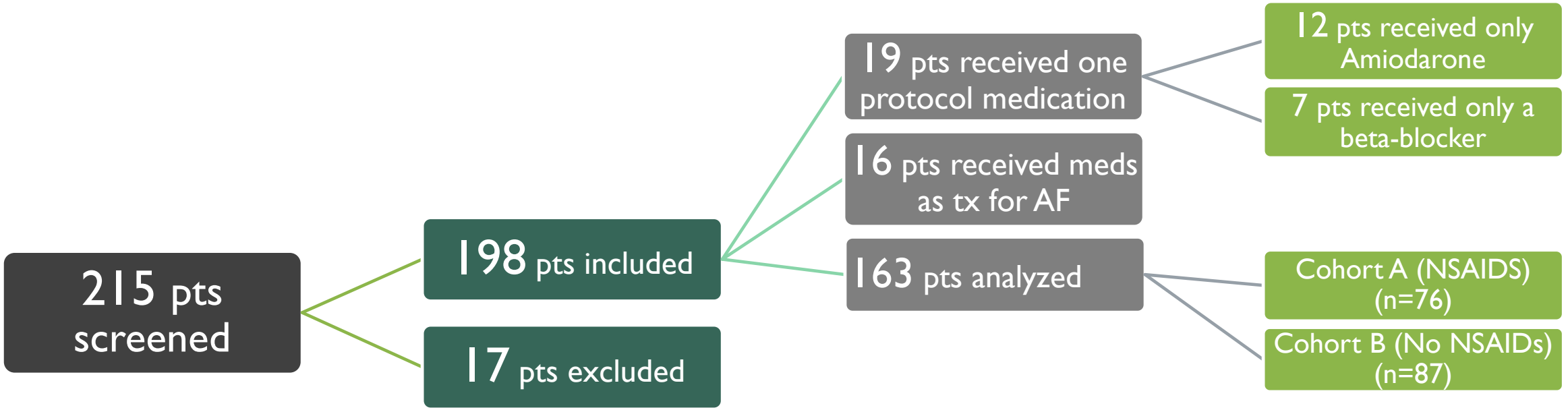
Incidence of new-onset AFACS within the first 7 days after surgery

2^0

- 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



Reason for Exclusion	n=17
Did not receive prophylactic therapy for AFACS	8
Surgery performed outside of study period	9

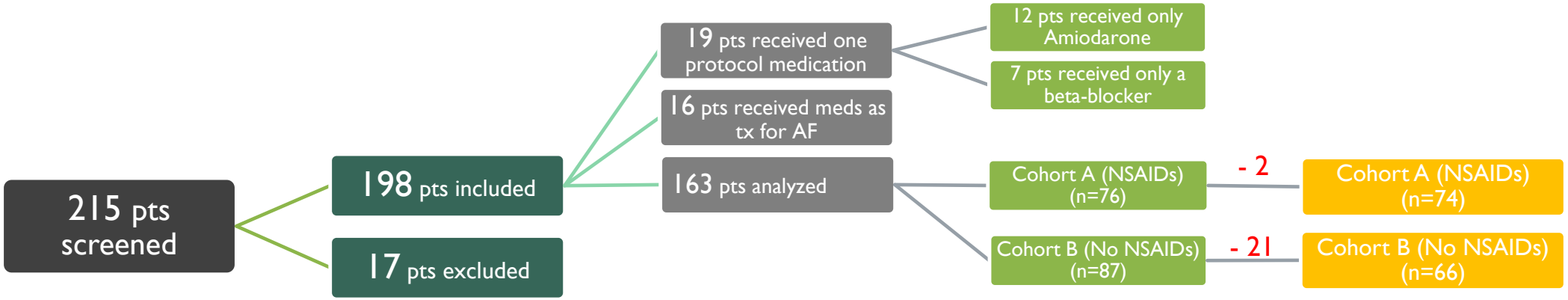
Demographics and Baseline Characteristics

	NSAIDs n=76	No NSAIDs n=87	*p*-value
Mean age, years (SD)	62 ± 9	65 ± 10.5	0.07
Age ≥ 75 years – n (%)	6 (7.9)	17 (19.5)	0.03
Gender – male, n (%)	62 (81.6)	65 (74.7)	0.29
BMI (kg/m^2)			
• 18.5 – 24	9 (11.8)	22 (25.3)	0.03
• 25 - 30	31 (40.8)	28 (32.2)	0.25
• ≥ 31	36 (47.4)	37 (42.5)	0.54
Hospital			
• BHM	64 (84.2)	70 (80.5)	0.53
• SMH	12 (15.8)	17 (19.5)	0.53
CABG – n (%)	63 (82.9)	73 (83.9)	0.86
• CABG x1	13 (17.1)	8 (9.2)	0.12
• CABG x2	23 (30.3)	24 (27.6)	0.66
• CABG x3	23 (30.3)	30 (34.5)	0.58
• CABG x4	4 (5.3)	11 (12.6)	0.11
Valvular Surgery – n (%)	12 (15.8)	11 (12.6)	0.56
• AVR	10 (13.2)	10 (11.5)	0.59
• MVR	2 (2.6)	1 (1.5)	0.59
CABG + Valvular Surgery – n (%)	1 (1.3)	1 (1.5)	0.92

	NSAIDs n=76	No NSAIDs n=87	*p*-value
PMH – n (%)			
• Hypertension	60 (78.9)	70 (80.5)	0.81
• Hyperlipidemia	59 (77.6)	53 (60.9)	0.02
• Type 2 Diabetes	30 (39.5)	37 (42.5)	0.69
• Hypothyroidism	8 (10.5)	6 (6.9)	0.41
• Tobacco Use			
• Current	11 (14.5)	14 (16.1)	0.77
• Former	31 (40.8)	17 (19.5)	< 0.01
• Peripheral Artery Disease	2 (2.6)	6 (6.9)	0.21
• Myocardial Infarction	16 (21.1)	17 (19.5)	0.81
• Chronic Kidney Disease	2 (2.6)	21 (24.1)	< 0.01
• Stage I	0	0	
• Stage II	0	0	
• Stage III	2	18	
• Stage IV	0	0	
• Stage V	0	3	
Baseline Scr – mean (SD)	0.94 ± 0.23	1.5 ± 1.8	< 0.01

Controlling for Confounding Factors

- 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

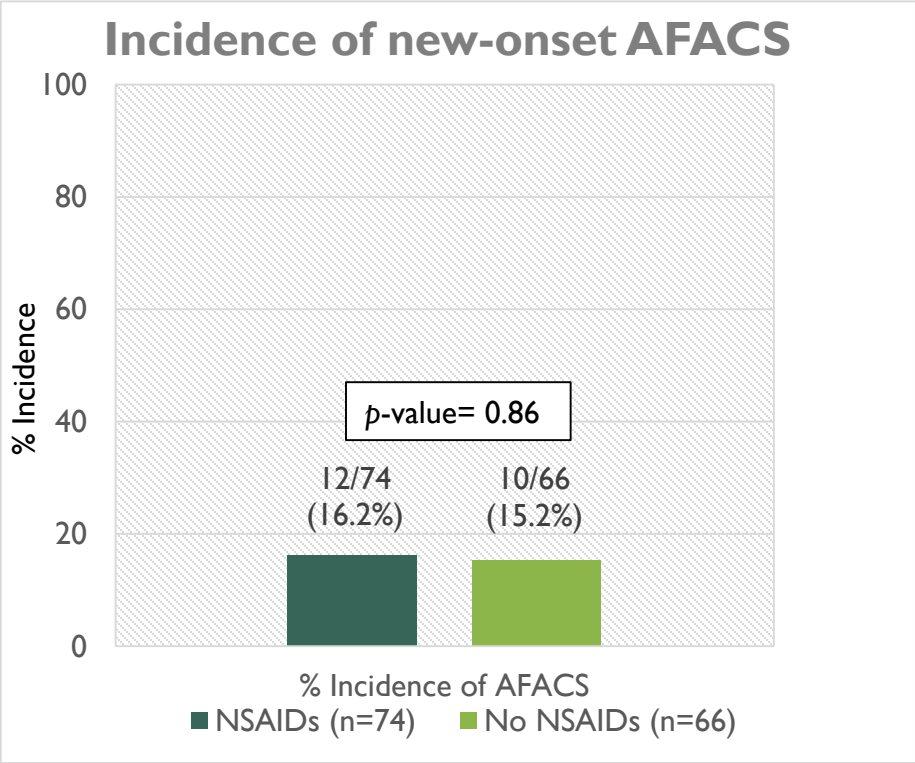


Risk Factors for AFACS

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

Study Outcomes

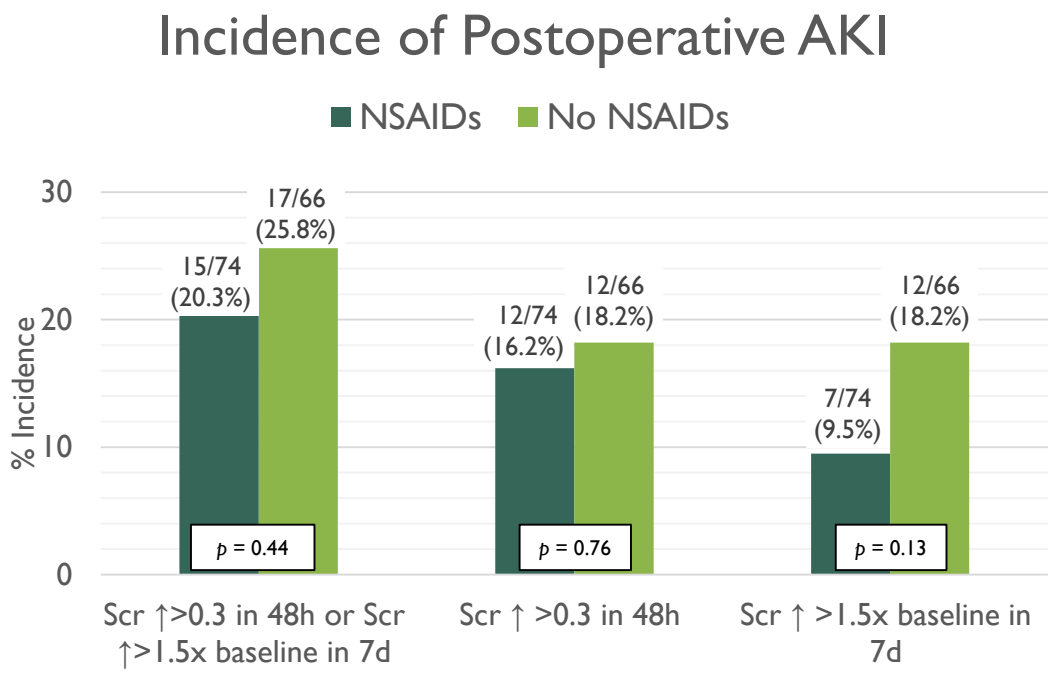
1^0 Outcome



2^0 Outcomes

	NSAIDs (n=74)	No NSAIDs (n=66)	*p*-value
Incidence of AKI – n (%)			
• Scr ↑ ≥ 0.3 mg/dL in 48h or ↑ ≥ 1.5x baseline in 7d	15 (20.3)	17 (25.8)	0.44
• Scr ↑ ≥ 0.3 mg/dL in 48h	12 (16.2)	12 (18.2)	0.76
• Scr ↑ ≥ 1.5x baseline in 7d	7 (9.5)	12 (18.2)	0.13
Mean ICU length of stay, days (SD)	2.3 ± 2.0	2.8 ± 2.2	0.23
Mean hospital length of stay, days (SD)	10.6 ± 6.1	11.0 ± 4.6	0.63

Study Outcomes – Incidence of AKI



	NSAIDs (n=74)	No NSAIDs (n=66)	*p*-value
Baseline Scr on admission – mean (SD)	0.92 ± 0.2	1.1 ± 0.4	< 0.01
Baseline Scr after surgery – mean (SD)	0.90 ± 0.2	1.02 ± 0.3	< 0.01
Maximum Scr after surgery – mean (SD)	1.07 ± 0.3	1.30 ± 0.5	< 0.01
# doses of NSAIDs postoperatively – mean (SD)	4.7 ± 4.9	0	–
Postoperative hypotension requiring vasopressors – n (%)	61 (82.4)	57 (86.4)	0.52
• # vasopressors used – n (%)			
• 1	33	20	0.08
• 2	28	25	0.99
• 3	0	12	< 0.01
• Mean # days on vasopressor therapy (SD)	1.7 ± 0.8	2.0 ± 1.0	0.06
Postoperative dehydration (BUN:Scr ≥ 20:1) – n (%)	50 (67.6)	42 (63.6)	0.62

Discussion

- 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

Conclusion

- 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.

Self-Assessment Question

- 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.
- Andrea-Marr Peralto, DNP, AGACNP, APRN
- Cathleen Charles, MSN, APRN, FNP-BC

References

1. Burrage PS, Low YH, Campbell NG, et al. New-Onset Atrial Fibrillation in Adult Patients After Cardiac Surgery. *Current Anesthesiology Reports*. 2019;9:174-193.
2. Dobrev D, Aguilar M, Heijman J, et al. Postoperative atrial fibrillation: mechanisms, manifestations and management. *Nat. Rev. Cardiol.* 2019;16:417-436.
3. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. *J Am Coll Cardiol.* 2014;64(21):2246-80.
4. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Rev Esp Cardiol (Engl Ed).* 2017;70(1):50.
5. Hillis LD, Smith PK, Anderson JL, et al. Special Articles: 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Anesth Analg.* 2012;114(1):11-45.
6. Muehlschlegel JD, Burrage PS, Ngai JY, et al. Society of Cardiovascular Anesthesiologists/ European Association of Cardiothoracic Anaesthetists Practice Advisory for the Management of Perioperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery. *Anesth Analg*. 2019;128(1):33–42.
7. Cheruku KK, Ghani A, Ahmad F, et al. Efficacy of nonsteroidal anti-inflammatory medications for prevention of atrial fibrillation following coronary artery bypass graft surgery. *Prev Cardiol.* 2004;7(1):13-18.
8. Horbach SJ, Lopez RD, da C Guaragnc a JC, et al. Naproxen as prophylaxis against atrial fibrillation after cardiac surgery: the NAFARM randomized trial. *Am J Med.* 2011;124(11):1036-42.
9. Frendyl G, Sodickson AC, Chung MK, et al. 2014 AATS Guidelines for the Prevention and Management of Peri-Operative Atrial Fibrillation and Flutter (POAF) for Thoracic Surgical Procedures. *J Thorac Cardiovasc Surg.* 2014;148(3):153-193.

Baptist Hospital

BAPTIST HEALTH SOUTH FLORIDA

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

Laura Neubauer, Pharm.D., PGY-1 Pharmacy Resident

Baptist Hospital of Miami

Longitudinal Research Project