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## Implementing Prophylactic Amiodarone in Heart Surgery to Reduce Post-Operative Atrial Fibrillation

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## 1                   Implementing Prophylactic Amiodarone in Heart Surgery to Reduce 2   Post-Operative Atrial Fibrillation

3                   Each year in the United States, approximately 300,000 patients undergo cardiac surgery  
4 for either valve replacement, coronary bypass, or a combination thereof.<sup>1</sup> Given the advances in  
5 technology, the risk of mortality is low, with 10 percent mortality being the uppermost routinely  
6 acceptable non-emergent calculated mortality.<sup>2</sup> The risk of morbidity from surgical  
7 complications may range upwards of 50 percent, with the most common significant complication  
8 being post-operative atrial fibrillation (POAF), affecting between 17 and 47 percent of those  
9 undergoing cardiac surgery.<sup>3</sup> POAF is not a benign complication, carrying its extensive list of  
10 secondary complications such as increased risk of bleeding and intracranial hemorrhage  
11 secondary to anticoagulation, reduced cardiac output, and increased length and cost of  
12 hospitalization. When untreated, POAF nearly doubles the risk for an ischemic stroke especially  
13 in the elderly.<sup>4</sup>

14                   Over the last decade, the trend of using perioperative amiodarone has been shown  
15 through randomized controlled trials to reduce the incidence of POAF; it has since gained  
16 widespread implementation in the cardiovascular surgery field.<sup>3</sup> The Society of Thoracic  
17 Surgeons (STS) oversees the outcome data for its member surgeons, and analysis of such data  
18 has revealed results consistent with the trial findings supporting the use of prophylactic  
19 amiodarone to reduce POAF in patients undergoing coronary artery bypass grafting (CABG) and  
20 heart valve replacement.<sup>2</sup>

### 21   **Local Problem**

22                   The rate of POAF was being tracked at a large Midwestern hospital. The STS reported  
23 the 2014 rate of POAF for isolated CABG patients of 14.6% at the hospital and 23.4% as the

24 national median.<sup>1</sup> Although below the national benchmark, a cardiac surgeon new to this hospital  
25 cited an 11% rate of POAF in his previous practice through utilization of perioperative  
26 amiodarone infusion in addition to the existing best practice of a long term beta-blocker  
27 medication regimen on all appropriate cardiac surgical patients.

28 After conduct of a literature review, a practice change was initiated to adopt peri-  
29 operative amiodarone administration on all cardiac surgical patients who were not otherwise  
30 contraindicated starting July 1, 2015. This hospital's surgical outcome data submitted to the  
31 Society of Thoracic Surgeons' Adult Cardiac Surgery Database was analyzed to identify if  
32 incidence of new POAF was reduced when compared to pre-implementation rates. Our goal was  
33 to answer the question: In the adult cardiac surgical population aged 18-90 without existing atrial  
34 fibrillation, does prophylactic administration of amiodarone peri-operatively reduce the  
35 incidence of new onset POAF when compared to patients who do not receive peri-operative  
36 amiodarone?

### 37 **Literature Review**

38 The prophylactic oral amiodarone for the prevention of arrhythmias that begin early after  
39 revascularization, valve replacement, or repair (PAPABEAR) trial was conducted in 2003. This  
40 double-blind randomized trial involved 601 patients undergoing non-emergent CABG and/or  
41 valve surgery from February 1999 and September 2003 at a tertiary care medical center.<sup>5</sup> The  
42 intervention consisted of the administration of oral amiodarone or a placebo six days prior to  
43 surgery through six days after surgery. The main outcome measure was atrial tachyarrhythmias  
44 lasting over five minutes and requiring intervention during the first six days after surgery, when  
45 POAF is most likely to occur.

46           The researchers reported reduced incidence of POAF among the experimental group  
47 (16.1%) as compared to the placebo group (29.5%), with a hazard ratio of 0.52. Patients who  
48 received amiodarone experienced reduced length of hospital stay by an average of 0.7 days, and  
49 decreased incidence of atrial and ventricular arrhythmias in the week before and after cardiac  
50 surgery.<sup>5</sup>

51           A Cochrane review by Arsenault et al. addressed all the documented interventions for  
52 preventing POAF in patients undergoing heart surgery. They reported odds ratios of beta  
53 blockers (0.33), sotalol (0.34), magnesium (0.55), amiodarone (0.43), atrial pacing (0.47), and  
54 posterior pericardiotomy (0.35); they concluded all interventions were effective in reducing the  
55 likelihood of POAF. They also found that prophylactic intervention decreased length of stay by  
56 16 hours and saved approximately \$1250 per patient.<sup>3</sup>

57           Mitchell et al. have also shown the administration of concomitant beta blockers and  
58 amiodarone further reduces the incidence of POAF. However it can be difficult for some patients  
59 to tolerate the potential side effects of oral amiodarone, including nausea and bradycardia,  
60 resulting in poor compliance by patients with medication self-administration.<sup>5</sup>

61           Arsenault et al. found that timing of the dose of perioperative amiodarone varied among  
62 preoperatively, intraoperatively, and postoperatively. Also, amiodarone was given both orally  
63 and intravenously, with no statistically significant difference in reduction of POAF.<sup>3</sup> The benefit  
64 of the acute inpatient setting with advanced monitoring allows for preoperative dosing of beta  
65 blockers while allowing for dosing of intravenous amiodarone while under anesthesia  
66 monitoring. In such setting, the variable of compliance due to nausea and bradycardia was  
67 avoided.

68 Negative side effects exist with amiodarone usage when compared to placebo treatment,  
69 and include prolongation of the QT interval (1.3 percent versus 0 percent) and bradycardia  
70 requiring temporary epicardial pacing (5.7 percent versus 2 percent).<sup>5</sup> Treatment of postoperative  
71 atrial fibrillation lasting greater than 24 to 48 hours usually requires anticoagulation with  
72 warfarin unless outweighed by the risk of surgical bleeding.<sup>6</sup> Unlike chronic atrial fibrillation,  
73 most POAF is temporary and will revert to the patient's underlying rhythm within six weeks of  
74 surgery.<sup>7-8</sup>

### 75 **Cost Benefit**

76 In a large Cochrane review, researchers have shown a cost savings of \$1250 per patient  
77 and 0.7 hospital days when POAF is ameliorated.<sup>3</sup> This does not include the reduced requirement  
78 of other medications to treat the atrial fibrillation such as warfarin and its associated frequent  
79 testing for international normalized ratio (INR) and enoxaparin bridging as well as treatment for  
80 any cerebrovascular accidents that result from embolic events of the atrial fibrillation. Other  
81 potential costs include cardiac event monitors which may be worn for a month or more, and  
82 medications for heart failure being required if the patient does not tolerate the loss of atrial kick  
83 as a consequence of atrial fibrillation.

84

### 85 **Framework**

86 The framework selected for this project is Lewin's model of change. This framework was  
87 selected for its simple approach of implementing clinical changes through the components of  
88 unfreezing, change, and refreezing.<sup>9</sup> The unfreezing process from the previous practice of not  
89 using perioperative amiodarone for reduction of postoperative atrial fibrillation has been  
90 performed and the change phase of implementing the new practice has been underway since July

91 1, 2015. The refreezing phase begins with the determination of the change as beneficial and  
92 appropriate as a continued practice until further research would restart the cycle.

### 93 **Methods**

#### 94 **Ethical Issues**

95 The institutional review boards (IRB) of the applicable hospital and educational  
96 institution approved this project prior to data acquisition and analysis. The project was deemed  
97 IRB exempt by both parties. Human subject protection was maintained through de-identification  
98 of data prior to receipt by the investigator by the systems analyst who routinely queries the  
99 hospital's data database. Data was secured on a password protected computer.

#### 100 **Design and Setting**

101 For this project, we utilized a retrospective, case-controlled design with pre/post  
102 intervention analysis using the STS database for tracking outcome variables. The objective was  
103 to determine if there was a difference in the rate of POAF after implementing perioperative  
104 dosing of amiodarone to the cardiac surgical population at a large northern Illinois metropolitan  
105 hospital. Since July 1, 2015, nearly all patients have received 150mg intravenous amiodarone  
106 infusion given by the perfusionist once the cardiopulmonary bypass phase of the surgery is  
107 complete. The previous practice included a ventricular anti-arrhythmic lidocaine, given in 100mg  
108 intravenous dosing one time in a similar fashion by the perfusionist. All patients included in this  
109 study were under the care of the surgeon with an established practice at the hospital and would  
110 serve as the control group in future ad hoc research once a sufficient sample data for the new  
111 surgeon was aggregated for comparison.

#### 112 **Sample**

113           The sample for the study was all patients aged 18-90 who underwent cardiac surgery at a  
114 large northern Illinois metropolitan hospital between January 1, 2015 and December 31, 2015  
115 and had either isolated coronary artery bypass grafting (CABG), isolated aortic or mitral valve  
116 replacement or repair, or combination CABG and valvular surgery. Any patient with documented  
117 pre-operative atrial fibrillation was not included in POAF calculations and any patient with  
118 profound bradycardia peri-operatively, heart block, or documented allergy to amiodarone did not  
119 receive the amiodarone infusion. Comparison was made between the rates of POAF in those who  
120 underwent surgery January 1, 2015 until June 30, 2015 and did not receive amiodarone infusion,  
121 and those who underwent cardiac surgery from July 1, 2015 to December 31, 2015 and did  
122 receive amiodarone infusion. Publicly available STS database reference data was utilized for  
123 evaluation the national rates of POAF during 2015 for comparison against the research hospital  
124 POAF rate.

#### 125 **Instrument**

126           The research tool we used was the STS Adult Cardiac Surgery Database for evaluation of  
127 cardiac surgical outcome data. The STS database is a validated instrument which undergoes site-  
128 specific audit on a rotating basis to guarantee reliability and validity of all data. The most recent  
129 audit at the research facility was in 2014 and revealed no deficiencies. The STS database is a  
130 powerful research database with over 100 publications derived from the STS database outcome  
131 data.<sup>2</sup> Variables are routinely upgraded through changes in definitions of each variable to best  
132 align with practice guidelines and evidence-based medicine. The most recent upgrade in variable  
133 definition was in 2014 and no further upgrades were performed during the timeline of this  
134 research.

135 All data of STS participant hospitals is maintained as their own property and may be  
136 accessed without additional consent of STS. Use of the entire Adult Cardiac Surgical Database  
137 would prompt additional STS consent; therefore, only hospital-specific STS Adult Cardiac  
138 Surgical Database variable data and only publicly reported national data were used. Our  
139 variables were evaluated using IBM SPSS version 23 software, and Pearson's  $\chi^2$  analysis was  
140 used for nominal variables. Statistical significance was set at  $p=.05$ , and power of 0.80.

141

142

### Results

143 The study site hospital performed 165 total cardiac surgery cases in 2015. During the  
144 January 1 – June 30, 2015 pre-intervention period, a total of 65 isolated CABG, 16 aortic valve  
145 surgeries, five mitral valve surgeries, eight combination CABG plus valve surgeries, and one  
146 isolated aneurysm repair were performed. From July 1 – December 31, 2015, 44 isolated CABG  
147 surgeries, 11 aortic valve surgeries, eight mitral valve surgeries, and eight combination CABG  
148 plus valve surgeries were performed. Our team applied the exclusion criteria to the data sets and  
149 all pre-intervention data was included. Our post-intervention data included six cases which were  
150 excluded since they had a different surgeon perform the case; differing surgical techniques may  
151 have confounded the results. Also, four cases were excluded from the post-intervention group  
152 because patients did not receive amiodarone post-operatively and did not meet the confines of  
153 the study design. The resulting sample population included 95 pre-intervention cases and 60  
154 post-intervention cases, for a total sample of 155 cases.

155 We collected 25 variables on each case for pre- and post-interventional analysis (see  
156 Appendix 1). Data was cleaned and prepared using Microsoft Excel 2013, and was then  
157 transferred into IBM SPSS version 23 for data analysis. Descriptive statistics and Pearson's  $\chi^2$



158 analysis were performed on our research question. Cramer's  $V$  was calculated to help evaluate  
159 effect size secondary to the results of  $\chi^2$  analysis.

160 We analyzed all variables collected using Levene's test to evaluate equality of variance  
161 between the pre- and post-interventional group, and found no significant difference. Independent  
162  $t$ -tests for continuous variables and Pearson  $\chi^2$  testing for categorical data were then used to  
163 determine if any significant difference existed between the pre- and post-interventional group,  
164 and found no statistically significant differences between the groups (see Appendix 3). Fisher's  
165 test was used when values for Pearson  $\chi^2$  analysis were less than five per cell.

### 166 **Overall Rate of Post-Operative Atrial Fibrillation**

167 Our first calculation included all surgery types (CABG, isolated aortic or mitral valve, or  
168 CABG plus valve combination surgery). The pre-interventional group ( $n = 95$ ) had 17.9% of the  
169 patients with new onset post-operative atrial fibrillation ( $n = 17$ ). The post-interventional group  
170 ( $n = 60$ ) had many fewer cases ( $n=5$ ) representing 8.3% incidence of POAF. Despite this  
171 considerable decrease in percentage and frequency, we did not achieve statistical significance ( $\chi^2$   
172 [ $1, N = 155$ ] = 2.76,  $p = .097$ ,  $V = .13$ ). Cramer's  $V$  of .13 represented a negligible association  
173 between our intervention and the outcome of reduced POAF.

174 We also analyzed the relationships between all variables to look for variation between the  
175 pre- and post-interventional groups, and no statistically significant differences were identified.  
176 The elements in each group analyzed included race, age, BMI, STS predicted risk of mortality,  
177 STS predicted risk of morbidity or mortality (which include calculations about previous health  
178 state and organ function), ICU length of stay, ventilator days, and overall hospital length of stay,  
179 and preoperative left ventricular ejection fraction.

### 180 **Subgroup Analysis**

181           Since the relative risks of the incidence of POAF vary with the level of surgical  
182 complexity, and since significance was not obtained despite considerable improvement in the  
183 overall incidence of POAF, further investigation was performed to identify each surgical  
184 subgroup and uniquely analyzed. These subgroups included: isolated CABG, isolated aortic  
185 valve surgery, isolated mitral valve surgery, combination CABG and valve surgery, and other  
186 surgeries not otherwise included.

187 Isolated CABG.

188           The pre-interventional group constituted 65 isolated CABG surgeries with 10 cases of  
189 POAF (15.4%) compared to the post-interventional group of 37 isolated CABG surgeries with 2  
190 cases of POAF (5.4%). This represented the largest population of surgeries performed in each of  
191 the pre- and post-intervention categories, and although the incidence rate was roughly one-third  
192 of the pre-intervention rate, it did not reach statistical significance ( $\chi^2 [1, N = 102] = 2.26, p =$   
193  $.203, V = .15$ ).

194 Isolated Aortic Valve Surgery.

195           The pre-interventional group constituted 16 isolated aortic valve surgeries with five cases  
196 of POAF (31.25%) compared to the post-interventional group of 10 isolated aortic valve  
197 surgeries with 3 cases of POAF (30%). POAF incidence rates were not statistically affected by  
198 our intervention in this category ( $\chi^2 [1, N = 26] = .005, p = 1, V = .13$ ).

199 Isolated Mitral Valve Surgery.

200           The pre-interventional group constituted five isolated mitral valve surgeries with zero  
201 cases of POAF (0%) compared to the post-interventional group of seven isolated mitral valve  
202 surgeries with zero cases of POAF (0%). As there were no cases of POAF related to isolated  
203 mitral valve surgery, no further analysis was performed.



227 performed in conjunction with a long term beta-blocker and likely represents a decreased pre-  
228 interventional relative risk of atrial fibrillation. Our strategy was to augment our existing beta-  
229 blocker strategy with the addition of a second agent, and our results were likely diminished.

230       Regardless of achieving statistical significance, we have shown a positive relationship  
231 between intervention and outcome, following known evidence based practice. Our 5.4% post-  
232 intervention POAF incidence rate for isolated CABG when compared to the 2014 national  
233 average of 23.4% rather than our 15.4% would be much more likely to achieve statistical  
234 significance.

### 235                                       **Limitations**

236       Limitations of this project include the case controlled retrospective design. Although we  
237 were able to accurately collect data due to the STS Adult Cardiac Surgical Database, this did  
238 confine us to using only the database's variables for analysis. The design would be improved  
239 with a prospective design, but due to the confines of this research timeline, was not an option as  
240 this practice change was implemented before IRB approval would have been granted.

241       Subsequent ad hoc research will be focused on variables such as the oral amiodarone  
242 regimen vs. peri-operative dosing alone with regards to a statistically significant further decrease  
243 in POAF. Also, our sample data was appropriately de-identified prior to our analysis and our  
244 IRB approval included waiver of informed consent. Chart review was not an option to look for  
245 secondary data elements not included in the confines of IRB protocol. Subsequent testing would  
246 be useful to include a prospective view with informed consent to allow for longitudinal follow-  
247 up with subjects from during this first study timeline.

248       Another limitation of this study is its single-site, single surgeon design. The surgical  
249 outcomes present at the researcher's hospital may not represent uniform practice amongst all like

250 surgeons. Also, there is no option with this type of research to have patients serve as their own  
251 control, as subsequent cardiac surgery has increased risk of mortality and complications such as  
252 POAF. Therefore, only a prospective, randomized, double-blind study would be ideal for proper  
253 experimental design and was not an option for the timeline of this project.

#### 254 **Strengths**

255 Strengths of this project include an increased awareness by the cardiac surgery team of  
256 the common POAF complication, its treatment, and sequelae if untreated. We have seen an  
257 appreciable decrease in POAF beyond the timeline of the post-intervention data collection and  
258 have continued to provide the peri-operative amiodarone dose on all patients. A previous attempt  
259 to have pre-operative oral amiodarone given for several days was made several years ago and  
260 was halted due to surgeon concern of unknown or inconsistent patient compliance, common side  
261 effects of nausea, and several cases of delay of surgery.

#### 262 **Conclusions**

263 We sought to evaluate a practice change instituted July 1, 2015 at a large Midwestern  
264 cardiac surgical hospital to address concerns about an observed increased rate of POAF. We did  
265 not find out initial practice change to be statistically significant, but did find an overall reduction  
266 in rate of POAF from 17.9% to 8.3%. With the negative cardiac effects and doubled embolic  
267 stroke risk, any effort should be made to ameliorate POAF prior to its inception. We must  
268 employ proactive evidence-based strategies to foster financial stewardship in healthcare, as finite  
269 healthcare dollars and prevention-based repayment remain the standard. Any effort to reduce  
270 hospital days, improve patient outcomes, improve patient satisfaction, and reduce overall cost of  
271 care is not only prudent; it is imperative for continued success in a tenuous era of healthcare  
272 finances.

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