



Postoperative atrial fibrillation prophylaxis using a novel amiodarone order set

Joseph D. Phillips^{1,2#}, Eleah D. Porter^{1#}, Brendin R. Beaulieu-Jones², Kayla A. Fay¹, Rian M. Hasson^{1,2}, Timothy M. Millington^{1,2}, David J. Finley^{1,2}

¹Department of Surgery, Section of Thoracic Surgery, Dartmouth-Hitchcock Medical Center, Lebanon NH, USA; ²The Geisel School of Medicine at Dartmouth, Hanover, NH, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: JD Phillips, DJ Finley; (III) Provision of study materials or patients: JD Phillips, RM Hasson, TM Millington, DJ Finley; (IV) Collection and assembly of data: JD Phillips, ED Porter, KA Fay, BR Beaulieu-Jones; (V) Data analysis and interpretation: JD Phillips, ED Porter, BR Beaulieu-Jones, KA Fay, DJ Finley; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work and are co-first author.

Correspondence to: Joseph D. Phillips, MD, FACS. Section of Thoracic Surgery, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr., Lebanon, NH 03756, USA. Email: Joseph.D.Phillips@hitchcock.org.

Background: Studies have demonstrated that chemoprophylaxis following anatomic lung resection can reduce post-operative atrial fibrillation (POAF). However, it is unclear if non-anatomic wedge resection warrants prophylaxis, as previously published rates vary widely. The primary goal of this study was to assess an institutional rate of POAF following anatomic resections with implementation of a novel amiodarone administration regimen compared to wedge resections without prophylaxis.

Methods: We performed a retrospective cohort study of a prospectively maintained database and compared anatomic and wedge lung resection patients from 1/2015 to 4/2018. During the study period, a previously unpublished amiodarone order set consisting of a 300 mg IV bolus followed by 400 mg tablets TID \times 3 days was administered to anatomic resection patients \geq 65 who met criteria. Wedge resection patients were not intended to receive amiodarone prophylaxis. The primary outcome was POAF incidence. Risk factors for developing POAF were assessed.

Results: A total of 537 patients met inclusion where 56% underwent anatomic resection and 44% wedge resection. Overall, 5.4% of patients experienced POAF. There was a significant reduction in post-anatomic resection POAF as compared to historic rates without prophylaxis (9.3% *vs.* 20.3%, $P < 0.001$). A single wedge resection patient (0.4%) developed POAF. On multivariable analysis, the only independent POAF risk factor was age \geq 65 (OR: 5.41, 95% CI: 1.47–19.85).

Conclusions: Administration of our novel amiodarone order set reduces POAF after anatomic resection; however, POAF following wedge resection is too rare to warrant chemoprophylaxis.

Keywords: Atrial fibrillation (AF); thoracic surgery; wedge resection; anatomic lung resection; amiodarone prophylaxis

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Introduction

Postoperative atrial fibrillation (POAF) is a well-known complication following anatomic lung resection that occurs in up to 40% of patients without prophylaxis (1-3). In 2011 and 2014 respectively, the Society of Thoracic Surgeons (STS) and the American Association for Thoracic Surgery (AATS) published practice guidelines for the prevention of POAF following lung resection that recommend chemoprophylaxis such as beta blockers (BB), antiarrhythmics and calcium-channel blockers (CCB) (4,5). However, it is unclear if these recommendations are warranted after all types of lung resection. The STS provides an amiodarone dosing recommendation for lobectomy, but not sublobar resection. The AATS estimates the rate of POAF after wedge resection to be <5% and therefore only recommends prophylaxis for anatomic resection. Interestingly, they do not include reference to earlier studies that showed post-wedge resection rates of POAF to be over 20% (6,7). Contemporary data on the rate of POAF following wedge resection is lacking and the literature does not elucidate the need for prophylaxis.

Quantifying POAF after wedge resection and any subsequent need for prophylaxis is clinically relevant, as surgical indications continue to evolve. Historically, wedge resection was limited to the treatment of benign disease, metastasectomy, and other diagnostic testing (8-13). More recently it has been used in select patients as definitive treatment for early stage primary lung cancer (14-16). In this setting, a patient may undergo a lymph node dissection, which is a known risk factor for developing POAF (16-20). Despite this evolving paradigm, few studies have reported on the outcome of POAF following wedge resection alone or the need for prophylaxis (16,17,19,21). Older studies have reported a wide variability (4-25%) in the rate of POAF following wedge resection, and in the current minimally-invasive-era, the incidence and need for prophylaxis remains largely unknown (6,7,22,23).

In January 2015 an amiodarone-based POAF prophylaxis order set was introduced for anatomic resections at our institution. This was intended for post-anatomic lung resection patients who were at greatest risk for developing POAF: those ≥ 65 years of age (3,24-26). Wedge resection patients did not meet institutional criteria for automatic enrollment for this order set. The objectives of this study were to: (I) determine the rate of POAF following lung resection in our patient population

with use of this amiodarone order set; (II) describe our institutional experience implementing this order set for anatomic resection patients, and (III) identify risk factors for developing POAF. We hypothesized that the rate of POAF in anatomic resection patients using our amiodarone order set would be comparable to previously published rates, and that the rate following wedge resection alone would be <5%.

We present the following article in accordance with STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-180>).

Methods

Study design

This was a retrospective cohort study of a prospectively maintained thoracic surgery database. All consecutive patients who underwent anatomic lung resection (segmentectomy, single or bi-lobectomy, or pneumonectomy) or non-anatomic wedge resection for any indication at our 400-bed, academic quaternary care hospital between 1 January 2015 and 20 April 2018 were eligible for review. Our primary outcome was POAF, defined as AF lasting ≥ 30 seconds on telemetry or if documented by 12-lead electrocardiogram (4). All patients were placed on routine telemetry monitoring for at least 72 hours postoperatively or until discharge. Post-discharge, we reviewed charts to identify any onset of POAF occurring within 30 days of surgery as determined by documentation from our electronic medical record, outside provider/hospital records, or confirmed by electrocardiogram. Patients are typically seen in the thoracic surgery clinic 2-3 weeks after discharge. Records are routinely reviewed >90 days postoperatively to assess for any 30- and 90-day morbidity and mortality. Patients were excluded if they had a history of chronic atrial fibrillation (AF) or if they had a history of paroxysmal AF and were in AF on the day of surgery. Patients were also excluded if surgery was aborted or if they had a contraindication to receiving amiodarone (hypotension and cardiac electrical conduction abnormalities) (*Figure 1*).

Patient demographics, history of paroxysmal/chronic AF, chronic obstructive pulmonary disease (COPD), myocardial infarction (MI), body mass index (BMI), pulmonary function tests (PFTs), preoperative medication use, procedural data including extent of lymph node sampling/dissection, chest tube (CT) duration, length of stay (LOS), morbidity, and mortality were evaluated. The degree of lymph node

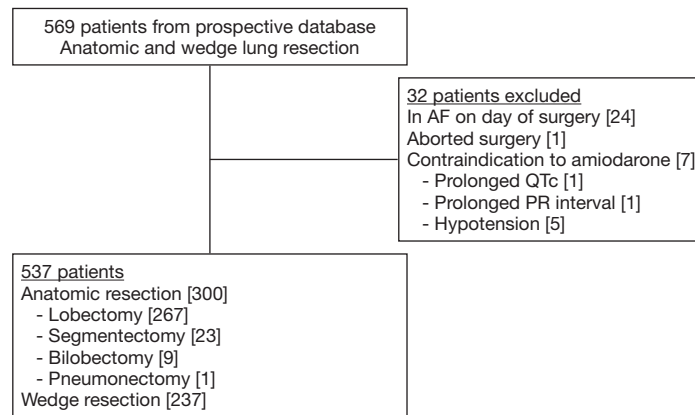


Figure 1 Flowchart of patient selection criteria. AF, atrial fibrillation.

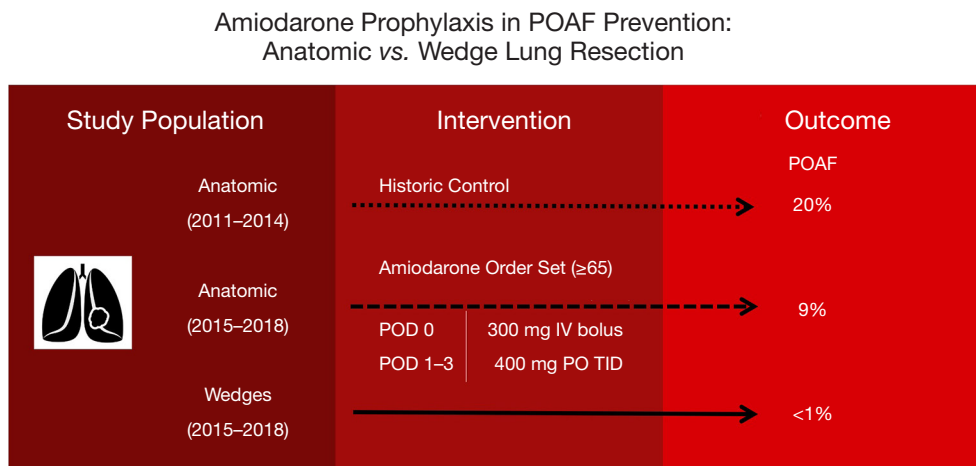


Figure 2 Graphical abstract.

sampling/dissection was classified as either hilar (N1 lymph nodes up to the ipsilateral hilar lymph nodes) or mediastinal (N2 lymph nodes up to the ipsilateral mediastinal lymph nodes or more). Surgical approach was determined by attending surgeon and included video-assisted thoracoscopic surgery (VATS), robotic-assisted VATS, and thoracotomy. Pathology was designated as either benign, primary cancer, or metastatic. All patients were monitored on telemetry postoperatively. POAF with rapid ventricular response was managed according to institutional practice: medical management or cardioversion if hemodynamically unstable. Duration of surgery was calculated by the difference in time between intubation and extubation. All patients were extubated prior to leaving the operating room. Prolonged air leak was defined as one lasting greater than 5 days, consistent with STS quality metrics (27). Complications

within 30 days as classified by Clavien-Dindo (CD) were evaluated (28,29).

Amiodarone order set

Prior to 2015, thoracic surgery coverage at our institution was inconsistent and lung resection patients did not receive POAF prophylaxis. In January 2015, the section of thoracic surgery was formed. A prophylactic amiodarone order set was implemented and intended for anatomic lung resection patients ≥ 65 years of age without a contraindication to taking amiodarone (e.g., hypotension or conduction abnormalities) (Figure 2). Patients on preoperative BBs or CCBs were initially eligible to receive amiodarone in addition to continuing their baseline medication. During the final 6 months of the study period, we elected to no longer

administer the order set to these patients due to a potential risk of heart block. Patients were continued on their home medication regimen postoperatively. Electrolytes are monitored and repleted per standard protocol, but were not recorded for the purposes of this study. Use of amiodarone outside of intended parameters was at the discretion of the surgeon. The order set was adopted from an unpublished protocol used at Memorial Sloan Kettering Cancer Center and is a combination of the STS and AATS guideline recommendations for amiodarone dosing (4,5). The order set consisted of a postoperative intravenous (IV) bolus of 300 mg of amiodarone given over 1 hour in the post-anesthesia care unit (PACU). This was followed by 3 days of 400 mg amiodarone tablets taken orally 3 times per day. If a patient was discharged prior to completion of the regimen, they were given a prescription to complete as an outpatient. We elected to use this dosing and administration as it was the most practical for our institution. Many patients are initially unable to take pills in the PACU, policies at our hospital do not allow intravenous administration of amiodarone on the floor, and our average LOS is three days. Wedge resection patients were not intended to receive amiodarone prophylaxis and therefore only did so inadvertently or potentially if directed by the attending surgeon.

Statistical methods

Univariate analysis was performed to assess for differences in preoperative, intraoperative, and postoperative characteristics. Where applicable, missing data elements were censored and noted in table footnotes. Two-tailed Student's *t*-tests were used for continuous variables and chi-square tests were used for categorical variables. To assess for risk factors of POAF and adjust for possible confounders, a multivariable logistic regression model was created using POAF as the dependent variable; independent variables were identified using an entry threshold of $P < 0.10$ on univariate analysis or based upon presumed or known clinical relevance. The discriminatory power of the model was based on c-statistic values. The final model included age (≥ 65 vs. < 65), surgical approach [thoracotomy vs. minimally invasive (VATS and robotic-assisted VATS)], operative time (continuous in 15-minute increments), and location of resection (categorical: upper, middle, or lower lobe). In addition, sensitivity analysis was performed by discretely adding variables that were felt to potentially impact the outcome but were not included in the model because they

were not significant on unadjusted analysis: lymph node dissection (N1 and N2), CT duration, and preoperative BB use. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using STATA (Version 15.1, StataCorp).

The study was approved by the Institutional Review Board at Dartmouth College and Dartmouth-Hitchcock Medical Center (IRB# 31040) and was granted a waiver of consent given its retrospective nature.

Results

Perioperative patient characteristics stratified by resection type

During the study period, 537 patients underwent lung resection with 300 (56%) undergoing anatomic resection and 237 (44%) wedge resection. Anatomic resection patients included segmentectomy ($n=23$), single lobectomy ($n=267$), bi-lobectomy ($n=9$), and pneumonectomy ($n=1$). Patients undergoing wedge resection were more likely to be male and less likely to have a history of COPD in comparison to those undergoing anatomic resection (Table 1). However, there were no differences in regard to the distribution of patients aged ≥ 65 years, a history of paroxysmal AF or MI, preoperative use of BB/CCB or baseline PFTs. Anatomic resection patients were significantly more likely to have undergone a robotic-assisted VATS or thoracotomy as compared to wedge patients. Anatomic resection patients were also more likely to have surgery in the right hemithorax and tissue pathology of primary malignancy. As expected, anatomic patients had a significantly longer operative time, occurrence of lymph node sampling (both overall and for hilar and mediastinal nodal stations), and administration of the amiodarone order set. Order set administration to the intended inclusion group occurred in 89% (136/152) of anatomic resection patients ≥ 65 . No patients were taking amiodarone preoperatively. Of the 16 eligible patients who did not receive amiodarone, 3 were on BBs during the last 6 months of the study and thus ineligible. Five patients were on BBs prior to the last 6 months, but amiodarone was withheld secondary to bradycardia in the PACU. Additional details are displayed in Figure 3. In the wedge resection patients, 3.0% (7/237) received the order set outside of intended indications. All 7 were ≥ 65 years of age. There were no major adverse events associated with the use of amiodarone in our study.

Table 1 Perioperative characteristics in anatomic vs. wedge resection patients

Variable	Anatomic (n=300), N (%)	Wedge (n=237), N (%)	P value
Age ≥65 years	152 (50.7)	108 (45.6)	0.241
Gender			
Male	140 (46.7)	137 (57.8)	0.010
Past medical history			
Paroxysmal AF*	12 (4.0)	18 (7.6)	0.072
MI	20 (6.7)	7 (3.0)	0.051
COPD	85 (28.3)	45 (19.0)	0.012
Body mass index			0.035
≤18	5 (1.7)	13 (5.5)	
18–30	212 (70.7)	153 (64.6)	
≥30	83 (27.7)	71 (30.0)	
Preoperative PFTs (mean ± SD) [#]			
FEV1 % predicted	80.0±18.6	81.5±23.8	0.452
DLCO % predicted	79.8±18.9	80.0±22.7	0.941
Preoperative Medication Use			
Statin	125 (41.7)	72 (30.4)	0.007
Beta blocker	28 (9.3)	25 (10.5)	0.639
Calcium channel blocker	7 (2.3)	6 (2.5)	0.876
Surgical approach			<0.001
Thoracotomy (“open”)	56 (18.7)	10 (4.2)	
Robotic-assisted VATS	162 (54.0)	34 (14.4)	
VATS	82 (27.3)	193 (81.4)	
Side of procedure			0.011
Left	120 (40.0)	120 (50.6)	
Right	180 (60.0)	115 (48.5)	
Bilateral	–	2 (0.8)	
Location of procedure			0.179
Lower lobe	104 (34.7)	106 (44.7)	
Middle lobe	21 (7.0)	11 (4.6)	
Upper lobe	175 (58.3)	120 (50.6)	
Surgical pathology			<0.001
Benign disease	14 (4.7)	126 (53.2)	
Metastatic disease	20 (6.7)	57 (24.0)	
Primary malignancy	266 (88.7)	54 (22.8)	
NSCLC	260	51	
Other ^a	6	3	

Table 1 (continued)

Table 1 (continued)

Variable	Anatomic (n=300), N (%)	Wedge (n=237), N (%)	P value
Operative Time (min, mean ± SD)	271.7±78.4	137.0±48.6	<0.001
Lymph node sampling ^p	294 (98.3)	43 (18.1)	<0.001
Hilar (N1) dissection	275 (92.3)	32 (13.6)	<0.001
Mediastinal (N2) dissection	276 (92.6)	37 (15.7)	<0.001
Amiodarone prophylaxis	152 (50.7)	7 (3.0)	<0.001
≥65 years	136	7	

* , patients with paroxysmal AF who were not in normal sinus rhythm on the day of surgery were excluded; # , excludes FEV1 & DLCO data missing in 58 patients (7 anatomic, 51 wedge); only DLCO data missing in 14 patients (8 anatomic, 6 wedge); ^a , other includes small cell lung cancer, lymphoma, mesothelioma, and a combined neuroendocrine tumor with NSCLC; ^b , hilar (N1): lymph node dissection up to the ipsilateral hilar lymph nodes, Mediastinal (N2): lymph node dissection up to the ipsilateral mediastinal lymph nodes or more. AF, atrial fibrillation; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; PFT, pulmonary function test; FEV1, forced expiratory volume in 1 second; DLCO, diffusion lung capacity for carbon monoxide; VATS, video-assisted thoracic surgery; NSCLC non-small cell lung cancer.

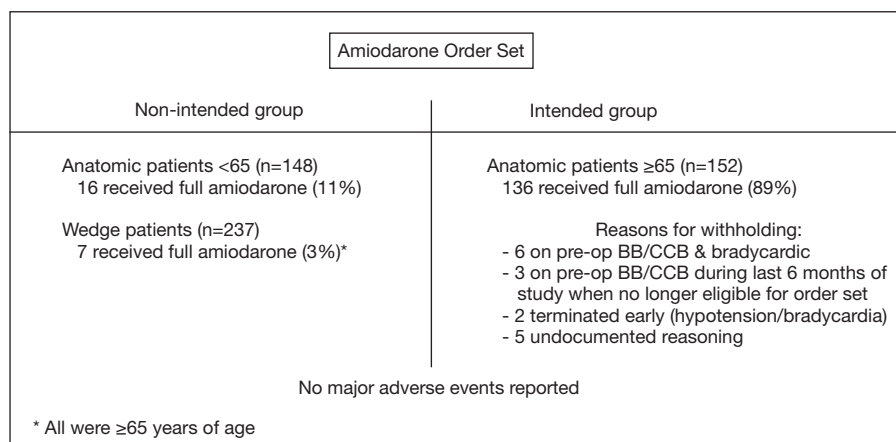


Figure 3 Order set implementation, adherence, and outcomes.

POAF and non-POAF outcomes

All patients had at least 30-day follow-up. A summary of postoperative outcomes between anatomic and wedge resection patients is given in Table 2. In total, POAF occurred in 29 patients (5.4%) and only one had undergone a wedge resection. The rate of POAF was significantly lower in wedge resection patients as compared to anatomic patients (0.4% vs. 9.3%, $P<0.001$). The mean time to development of POAF was 2.3 ± 2.4 days (range, 0 to 13 days). The single wedge resection patient who developed POAF was female, 81 years of age, underwent a VATS right upper lobe wedge resection without lymph node sampling, and did not receive the amiodarone order set. Her POAF

resolved with administration of a BB 4 hours after onset.

The rate of POAF following anatomic resection in patients following implementation of the order set was significantly lower than our institutional historic rate (9.3% vs. 20.3%, $P<0.001$). The historic rate was calculated from consecutive anatomic resection patients between 2011 and 2014 (n=217). The distribution of patients ≥65 was similar during the two time periods (58.4% vs. 50.3%, $P=0.067$). However, patients in 2011 to 2014 were significantly more likely to have undergone a thoracotomy (76.2% vs. 18.7%, $P<0.001$). Further comparisons to the historical cohort were not able to be performed secondary to limited documentation, inconsistent thoracic surgery coverage,

Table 2 Morbidity and mortality in anatomic vs. wedge resection patients

Variable	Anatomic (n=300), N (%)	Wedge (n=237), N (%)	P value
POAF	28 (9.3)	1 (0.4)	<0.001
30-day complications*	43 (14.3)	13 (5.5)	0.001
Pneumothorax requiring intervention	22 (7.3)	8 (3.4)	0.047
Air leak requiring intervention	3 (1.0)	2 (0.8)	0.852
Atelectasis requiring bronchoscopy	6 (2.0)	1 (0.4)	0.109
Length of stay, days, median [range]	4 [1–38]	1 [0–48]	<0.001
Chest tube duration, days, median [range]	3 [0–58]	1 [0–127]	<0.001
30-day readmission	25 (8.3)	14 (5.9)	0.282
30-day mortality	1 (0.3)	2 (0.8)	0.431

*, Clavien-Dindo classification system grade III/IV. POAF, post-operative atrial fibrillation.

inconsistent telemetry use, and loss to follow-up.

As expected, other non-AF postoperative complications occurred significantly more in the anatomic resection patients as compared to wedge resections. Anatomic resection patients had a longer LOS and longer CT duration, but 30-day readmission and mortality were not different between groups.

POAF risk factors: univariate and multivariable analyses

On univariate analysis, patients who developed POAF were significantly older, more likely to have undergone a thoracotomy, and have an anatomic resection as compared to those who did not develop POAF (*Table 3*). Patients who developed POAF were also more likely to have undergone surgery for a primary malignancy, have a longer operative time, and lymph node dissection (both overall and for hilar (N1) and mediastinal (N2) nodal dissection). There were no differences in gender, preoperative comorbidities, PFTs, or location of resection between those who did and did not develop POAF.

Given that only 1 patient in the wedge resection group developed POAF, a further statistically meaningful analysis including these patients was not possible. Consequently, we evaluated risk factors for POAF in the anatomic resection group (*Table 4*). In this group, patients who developed POAF were significantly older and had a higher percentage of age ≥ 65 years. There was a trend toward higher rates of thoracotomy, lower lobe resection, and longer operative time but these were not statistically significant.

On multivariable analysis, development of POAF was

associated with age ≥ 65 (*Table 5*). In our patient population, surgical approach, longer operative time and lobe resected did not have an independent associated risk of POAF. This model yielded a c-statistic of 0.79.

Discussion

There is consistent evidence that chemoprophylaxis reduces the rate of POAF after anatomic lung resection (2,26,30–33). In this study, we observed that implementation of a new amiodarone order set following anatomic lung resection was easy to administer, well-tolerated, safe, and led to a reduction in the rate of POAF as compared to both institutional historic rates and previously published rates of POAF without prophylaxis (1–3). Moreover, our rate was comparable to other published studies that use more complex and prolonged amiodarone prophylaxis regimens (30–33). While wedge resection patients were not intended to receive amiodarone prophylaxis, limited data exist on the utility or need for prophylaxis following wedge resection alone. As the indications for a wedge resection continue to evolve (8–13), we must define the burden of POAF to avoid unnecessary medication exposure. POAF occurred in only a single wedge resection patient. Based on our data, we determined that our novel amiodarone order set is safe and efficacious for anatomic resections and that POAF prophylaxis following wedge resection is unnecessary.

Previous authors have demonstrated lower morbidity and mortality following wedge resection as compared to anatomic resection (16,17,19,21). However, the absence of

Table 3 Perioperative risk factors associated with POAF

Variable	POAF (n=29), N (%)	No POAF (n=508), N (%)	P value
Age (years, mean ± SD)	70.5±7.9	62.0±13.5	<0.001
≥65 years	23 (79.3)	237 (46.7)	0.001
Gender			
Male	12 (41.4)	265 (52.2)	0.258
Past medical history			
Paroxysmal AF*	1 (3.5)	29 (5.7)	0.606
MI	1 (3.5)	26 (5.1)	0.689
COPD	10 (34.5)	120 (23.6)	0.184
Body mass index			0.618
≤18	1 (3.5)	17 (3.4)	
18–30	22 (75.9)	343 (67.5)	
≥30	6 (20.7)	148 (29.1)	
Pre-operative PFTs [#] , mean ± SD			
FEV1 % predicted	82.7±21.6	80.5±20.7	0.570
DLCO % predicted	76.0±16.9	80.1±20.6	0.294
Preoperative medication use			
Statin	13 (44.8)	184 (36.2)	0.350
Beta blocker	5 (17.2)	48 (9.4)	0.171
Calcium channel blocker	1 (3.4)	12 (2.4)	0.518
Surgical approach			<0.001
Thoracotomy (“open”)	10 (34.5)	56 (11.0)	
Robotic-assisted VATS	12 (41.4)	184 (36.2)	
VATS	7 (24.1)	268 (52.8)	
Side of procedure			0.944
Left	13 (44.8)	227 (44.7)	
Right	16 (55.2)	279 (54.9)	
Bilateral	–	2 (0.4)	
Location of procedure ^a			0.343
Lower lobe	15 (51.7)	195 (38.4)	
Middle lobe	1 (3.5)	31 (6.1)	
Upper lobe	13 (44.8)	282 (55.5)	
Resection type			<0.001
Anatomic	28 (96.6)	272 (53.5)	
Wedge	1 (3.5)	236 (46.5)	

Table 3 (continued)

Table 3 (continued)

Variable	POAF (n=29), N (%)	No POAF (n=508), N (%)	P value
Surgical pathology			0.010
Benign disease	2 (6.9)	138 (27.2)	
Metastatic disease	2 (6.9)	75 (14.8)	
Primary malignancy	25 (86.2)	295 (58.1)	
NSCLC	24	287	
Other ^b	1	8	
Operative time (min, mean ± SD)	294±80	202±93	<0.001
Lymph node sampling ^c	28 (96.6)	309 (61.0)	<0.001
Hilar (N1) dissection	28 (96.6)	279 (55.3)	<0.001
Mediastinal (N2) dissection	28 (96.6)	285 (56.4)	<0.001

* , patients with paroxysmal AF who were not in normal sinus rhythm on the day of surgery were excluded; [#], for the No POAF group, excludes FEV1 & DLCO data missing in 58 patients (7 anatomic, 51 wedge); only DLCO data missing in 14 patients (8 anatomic, 6 wedge); ^a, anatomic location determined by largest lobe removed; ^b, other includes small cell lung cancer, lymphoma, mesothelioma, and a combined neuroendocrine tumor with NSCLC; ^c, hilar (N1): lymph node dissection up to the ipsilateral hilar lymph nodes, Mediastinal (N2): lymph node dissection up to the ipsilateral mediastinal lymph nodes or more. POAF, post-operative atrial fibrillation; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; PFT, pulmonary function test; FEV1, forced expiratory volume in 1 second; DLCO, diffusion lung capacity for carbon monoxide; VATS, video-assisted thoracic surgery; NSCLC, non-small cell lung cancer.

discrete data on POAF following wedge resection alone, particularly in the contemporary minimally invasive era, limits the ability to ascertain the need for prophylaxis. The STS guidelines do not specify what type of lung resection warrants prophylaxis and there is a paucity of current data on the rate of POAF following wedge resections. Studies from more than ten years ago show a wide variability, ranging from 4% to 25% (6,7,22,23). While 7 wedge resection patients inadvertently received amiodarone prophylaxis in our study, it is unlikely this significantly alters our findings. Based on our results, we have re-educated all thoracic surgery providers at our institution that prophylaxis for wedge resection patients is not necessary. To inform national guidelines, data from other centers will be needed.

We observed a reduction in the rate of POAF after anatomic resection as compared to historic institutional rates when using our amiodarone order set. We acknowledge that this finding must be interpreted with caution. A historic analytic cohort could not be established due to intermittent thoracic coverage, unreliable use of telemetry and significant loss to follow up prior to 2015. There was a similar proportion of patients ≥65 in both groups and the historic cohort did not receive any POAF prophylaxis. However, there were significantly more open

surgery cases in that group. Ultimately, the rate of POAF in the historical group was likely underestimated secondary to inconsistent telemetry use and lack of electronic record keeping. Unfortunately, this does limit the strength of our conclusions. Regardless, results from our study corroborate previous reports and our rate of POAF is in-line with other studies of amiodarone prophylaxis after anatomic resection (2,30-32).

To our knowledge, this is the first report of POAF outcomes using this specific amiodarone regimen, and there remains no national consensus on optimal administration of amiodarone for prophylaxis. The STS guidelines suggest dosing 1,050 mg by continuous infusion over the first 24 hours postoperatively followed by 400 mg tablets taken twice daily for 6 days. The AATS recommends a 150–300 mg IV bolus over 1 hour, followed by a 10–50 mg/hour IV continuous infusion over 24 hours (4,5). We elected to use a practical combination of both recommendations: a 300mg IV loading bolus over 1 hour in the PACU followed by a 400 mg tablets three times daily for 3 days. This regimen allowed for excellent compliance as patients were initially recovering from surgery and the early transition to tablets had minimal side effects. Limiting the IV infusion is also less

Table 4 Perioperative risk factors associated with POAF in anatomic lung resections

Variable	POAF (n=28), N (%)	No POAF (n=272), N (%)	P value
Age (years, mean \pm SD)	70.1 \pm 7.8	64.6 \pm 9.8	0.004
\geq 65 years	22 (78.6)	130 (47.8)	0.002
Gender			
Male	12 (42.9)	128 (47.1)	0.671
Past medical history			
Paroxysmal AF*	1 (3.6)	11 (4.0)	0.903
MI	1 (3.6)	19 (7.0)	0.490
COPD	10 (35.7)	75 (27.6)	0.363
Body mass index			0.552
\leq 18	1 (3.6)	4 (1.5)	
18–30	21 (75.0)	191 (70.2)	
\geq 30	6 (21.4)	77 (28.3)	
Pre-operative PFTs [#] , mean \pm SD			
FEV1 % predicted	82.3 \pm 21.9	79.8 \pm 18.2	0.508
DLCO % predicted	75.7 \pm 17.2	80.3 \pm 19.1	0.229
Preoperative medication use			
Statin	12 (42.9)	113 (41.5)	0.893
Beta blocker	5 (17.9)	23 (8.5)	0.103
Calcium channel blocker	1 (3.57)	6 (2.21)	0.649
Surgical approach			0.052
Thoracotomy (“open”)	10 (35.7)	46 (16.9)	
Robotic-assisted VATS	12 (42.9)	150 (55.2)	
VATS	6 (21.4)	76 (27.9)	
Side of procedure			0.466
Left	13 (46.4)	107 (39.3)	
Right	15 (53.6)	165 (60.7)	
Location of procedure ^a			0.083
Lower lobe	15 (53.6)	89 (32.7)	
Middle lobe	1 (3.6)	20 (7.4)	
Upper lobe	12 (42.9)	163 (59.9)	
Surgical pathology			0.955
Benign disease	1 (3.6)	13 (4.8)	
Metastatic disease	2 (7.1)	18 (6.6)	
Primary malignancy	25 (89.3)	241 (88.6)	
NSCLC	24	236	
Other ^b	1	5	

Table 4 (continued)

Table 4 (continued)

Variable	POAF (n=28), N (%)	No POAF (n=272), N (%)	P value
Operative time (min, mean ± SD)	301±77	269±78	0.105
Lymph node sampling ^c	28 (100.0)	266 (98.2)	0.469
Hilar (N1) dissection	28 (100.0)	247 (91.5)	0.108
Mediastinal (N2) dissection	28 (100.0)	248 (91.9)	0.117
Chest tube duration, days, median (range)	4 [1–34]	3 (0–58)	0.113

^{*}, patients with paroxysmal AFib who were not in normal sinus rhythm on the day of surgery were excluded; [#], for the No POAF group, excludes FEV1 & DLCO data missing in 7 patients; only DLCO data missing in 8 patients; ^a, anatomic location determined by largest lobe removed; ^b, other includes small cell lung cancer, lymphoma, mesothelioma, and a combined neuroendocrine tumor with NSCLC; ^c, hilar (N1): lymph node dissection up to the ipsilateral hilar lymph nodes, Mediastinal (N2): lymph node dissection up to the ipsilateral mediastinal lymph nodes or more. POAF, post-operative atrial fibrillation; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; PFT, pulmonary function test; FEV1, forced expiratory volume in 1 second; DLCO, diffusion lung capacity for carbon monoxide; VATS, video-assisted thoracic surgery; NSCLC, non-small cell lung cancer.

Table 5 Multivariable analysis of risk factors associated with POAF in anatomic lung resections

Variable	Odds ratio	95% CI	Adjusted ^a odds ratio	95% CI	P value
Age (≥65 years) ^b	4.00	1.57–10.19	5.41	1.47–19.85	0.011
Surgical approach (VATS) ^c	0.37	0.16–0.84	0.50	0.14–1.85	0.302
Operative time (per 15 minutes) ^d	1.07	0.99–1.16	1.05	0.94–1.17	0.379
Location of resection ^e					
Upper lobe	Ref	Ref	Ref	Ref	
Middle lobe	0.68	0.08–5.50	1.17	0.13–10.73	0.888
Lower lobe	2.29	1.03–5.10	2.28	0.80–6.47	0.121

^a, adjusted for age, surgical approach, operative time, and location of resection; ^b, 2 categories: ≥65 years relative to <65 years; ^c, 2 categories: open relative to video-assisted thoracic surgery (including robotic-assisted); ^d, duration (continuous): odds ratio given for 15-minute increments; ^e, anatomic location determined by largest lobe removed. POAF, post-operative atrial fibrillation.

problematic for nursing, complies with hospital policies for floor level admissions, decreases the risk of peripheral infusion-related complications such as thrombophlebitis (34,35), and allows for expedited discharge. We did not have any major adverse events associated with the use of amiodarone. All of our patients were able to tolerate amiodarone orally, but if that is not possible, other studies have reported alternative administration via nasogastric tube (31).

During the study period, there was a transition in order set inclusion for patients on preoperative BB/CCBs. The STS and AATS POAF prevention guidelines recommend continuing a preoperative BB, but it is unclear if that should also exclude patients from receiving additional prophylaxis. In our study, a small number of anatomic

resection patients were on a preoperative BB/CCB and none were on amiodarone. Initially, these patients continued their medications while simultaneously receiving the amiodarone order set. However, 6 months prior to the end of the study period a patient experienced asymptomatic transient heart block. Following this event patients on preoperative BBs (n=3) or CCBs (n=1) were continued on these medications and not given amiodarone. None of these 4 patients experienced POAF. We are unable to determine if preoperative BB/CCB use significantly affected our results, though these medications were used in only ~13% of patients in both the wedge and anatomic lung resection groups. Further study is needed in a larger cohort to help clarify this issue.

Some argue against the use of amiodarone after anatomic

lung resection, citing issues of clinical relevance and safety (14,36). Two randomized controlled trials (RCTs) comparing no prophylaxis to using amiodarone did not report an increased incidence of POAF at discharge between groups (30,31). However, these and other retrospective studies have been confounded by under-reporting of POAF, excluding cases that occur after another pulmonary complication or not using telemetry monitoring (14,32). Inclusion of asymptomatic POAF and using conservative definitions of POAF is clinically important, as authors have demonstrated that POAF following non-cardiac surgery is associated with an increased long-term risk of ischemic stroke (37). In our study, POAF was clinically relevant, as several patients who developed POAF experienced hemodynamic instability that required intensive care unit transfer and two patients underwent cardioversion. At follow up, 2 patients remained in AF. With regard to safety, the two most recent RCTs utilizing amiodarone prophylaxis in POAF after anatomic resection showed a sizable reduction in POAF (<15%) with no major adverse events associated with amiodarone (30,31). Our rate of POAF following anatomic resection was less than 10% and we had no major adverse events associated with the use of amiodarone. POAF prevention is effective, clinically relevant and safe.

The occurrence of POAF after wedge resection was too rare to allow for inclusion of resection type in multivariable analysis. This will be an area for future study, as wedge resection surgery is becoming more popular and stratifying POAF risk will be needed. As segmentectomy becomes more commonly performed, it will be interesting to see if this also affects POAF compared with lobectomy. For anatomic resections, we modeled perioperative risk factors for developing POAF. Analysis revealed that age ≥ 65 was the only independent predictor in these patients. This is in-line with previous findings (3,24-26). Authors have theorized that POAF following lung resection occurs secondary to inflammation, and this may be amplified during longer surgery (25,38,39). On univariate analysis, anatomic resection patients had a significantly longer duration of surgery, which may have led to more inflammation and thus a higher rate of POAF. However, increased operative time was not associated with POAF in our cohort of anatomic resections. Mediastinal lymph node dissection has been associated with POAF as well (15,16). While many wedge resection patients underwent a mediastinal lymph node dissection in our study, none of these patients experienced POAF and it was not an independent risk factor in our anatomic resection patients. Interestingly, surgical approach

via open thoracotomy was also not independently associated with a higher risk of POAF on multivariable analysis.

The findings of our study should be considered in the context of several limitations. First, this is a single institution, retrospective review and our results may not be generalizable to a broader patient population. POAF occurred in only one patient who did not undergo lymph node dissection, which limits the ability to independently assess this as a risk factor. In addition, selection bias on who received amiodarone could have influenced our results. Approximately 11% of anatomic resection patients ≥ 65 did not receive amiodarone and a similar percentage < 65 did receive it. Also, 3% of wedge resection patients received amiodarone, which may have prevented POAF in that group. It is unclear if this was from incorrect ordering or potentially surgeon bias as all 7 were ≥ 65 years of age. Nevertheless, if all of these patients would have developed POAF, the rate in the wedge cohort would have been only 3.4%, which in our opinion still does not warrant prophylaxis in this group. The incidence of POAF in wedge resections may also have been confounded by a decreased detection rate, as they had a shorter postoperative LOS. Lastly, we were unable to establish a pre-order set analytic cohort for direct comparison in the anatomic resection patients. This limited our ability to draw any definitive conclusions on the reduced rate of POAF seen in our anatomic resection patients that received the amiodarone order set. Despite these limitations, our study addresses a knowledge gap in the incidence of POAF following wedge resection alone and highlights the safety and efficacy of a novel amiodarone order set that is easy to administer.

Conclusions

This study demonstrates the feasibility and efficacy in employing a well-tolerated and practical POAF prophylactic amiodarone order set in anatomic lung resection patients. The occurrence of POAF following wedge resection is too rare to warrant prophylaxis. Results from this study can be used to inform national guidelines for further refinement for POAF prevention.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-180>). JDP reports personal fees from Intuitive Surgical, Inc., outside the submitted work, but has no ongoing relationship. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Institutional Review Board at Dartmouth College and Dartmouth-Hitchcock Medical Center (IRB# 31040) and was granted a waiver of consent given its retrospective nature.

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