

POSTOPERATIVE ATRIAL FIBRILLATION PROPHYLAXIS AND LUNG RESECTION – OUR EXPERIENCE WITH 608 CONSECUTIVE PATIENTS

Vjekoslav Karadža, Dinko Stančić-Rokotov, Jasna Špiček Macan, Nevenka Hodoba,
Nevenka Kolarić and Sanja Sakan

Jordanovac Department of Thoracic Surgery, Zagreb University Hospital Center, Zagreb, Croatia

SUMMARY – Postoperative atrial fibrillation is a common complication after lung resection. It is burdened by increased mortality and morbidity, prolonged hospitalization, and higher resource utilization in thoracic surgery patients. Therefore, some kind of pharmacological prophylaxis is recommended. In our patients, diltiazem, a calcium antagonist, is administered. We collected data on all 608 patients having undergone lung resection (no less than lobectomy) between November 2012 and May 2015. This period included patients having received diltiazem during their postoperative stay in our Intensive Care Unit and surgical ward, and those that did not receive it. Patients having had atrial fibrillation before the surgery and patients with cardiac pacemaker were excluded from the trial. Other patients were divided into three groups: patients with some kind of antiarrhythmic therapy before and continued after the surgery; patients with diltiazem prophylaxis; and patients without any antiarrhythmic prophylaxis. The data collected were statistically analyzed. We found no statistically significant difference in the incidence of postoperative atrial fibrillation among the groups ($p < 0.05$).

Key words: *Diltiazem; Atrial fibrillation; Thoracic surgery*

Introduction

According to the literature, postoperative atrial fibrillation (POAF) (or equivalent supraventricular arrhythmia) is a common complication after pulmonary and esophageal surgery, with the incidence between 12% and 44%^{1,2}. Some risk factors have been identified, correlation with perioperative mortality and morbidity has been demonstrated, and prophylactic and therapeutic guidelines have been developed^{1,2}. POAF is associated with hemodynamic instability, heart failure, thromboembolic events, higher resource utilization and, possibly, increased mortality¹. The precise mechanism of POAF development is not well understood¹. The risk factors include history of smoking, obesity, advancing age, atrial dilatation, myocardial

ischemia, volume overload, history of heart failure, increased adrenergic and vagal tone, and surgical procedures associated with local or systemic inflammation^{1,2}. The extent of pulmonary resection is of importance as a risk factor, with the highest rates of incidence noted after pneumonectomies, extrapleural pneumonectomies and lung transplantations². Lobectomies and pneumonectomies are recognized as high risk procedures with POAF incidence above 15%¹. Among drugs recommended for the prophylaxis of POAF and equivalent postoperative arrhythmias is diltiazem, a calcium antagonist^{2,3}. It has few side effects and, with respect to known contraindications, it is well tolerated, especially in patients with chronic obstructive pulmonary disease (COPD)².

Patients and Methods

This observational study was performed at Jordanovac Department of Thoracic Surgery, Zagreb University Hospital Centre, Zagreb, Croatia. Data from med-

Correspondence to: *Vjekoslav Karadža, MD*, Jordanovac Department of Thoracic Surgery, Zagreb University Hospital Center, Jordanovac 104, HR-10000 Zagreb, Croatia
E-mail: vkaradzja@xnet.hr, anestezijska.tk3@kbc-zagreb.hr
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Table 1. Extent of lung resection

Frequency table		
Lung resection	n	%
PD	26	4.4
PS	56	9.5
BID	27	4.6
BSD	16	2.7
LID	77	13.1
LSS	121	20.5
LIS	82	13.9
LSD	149	25.3
LMD	35	5.9
Total	589	100.0

PD = right pneumonectomy; PS = left pneumonectomy; BID = right inferior bilobectomy; BSD = right superior bilobectomy; LID = right inferior lobectomy; LSS = left superior lobectomy; LIS = left inferior lobectomy; LSD = right superior lobectomy; LMD = right middle lobe resection

Table 2. Incidence of atrial fibrillation (AF)

Frequency table		
AF	n	%
Yes	77	13.1
No	512	86.9
Total	589	100.0

Table 3. Prophylaxis groups

Frequency table		
Atrial fibrillation prophylaxis	n	%
Diltiazem	221	37.5
Preoperative antiarrhythmic therapy	132	22.4
None	236	40.1
Total	589	100.0

ical records of all patients having undergone pulmonary resection procedures with a high risk of POAF¹ (lobectomies, bilobectomies and pneumonectomies) between November 2012 and May 2015 were included in the study. It was the time of introducing diltiazem for atrial fibrillation (AF) prophylaxis in our patients, thus including patient data before and during the introduction of diltiazem prophylaxis. The following data were collected: patient age, sex, the American

Society of Anesthesiologists Physical Status (ASA status), comorbidity (coronary disease, arterial hypertension, other cardiac diseases and arrhythmias, preoperative chemotherapy, preoperative irradiation, hypo-/hyperthyroidism, diabetes mellitus, renal insufficiency, alcoholic cirrhosis, concomitant malignancy), relevant preoperative drug therapy, lung resection type (extent, intrapericardial, extrapleural), use/no use of thoracic epidural analgesia (TEA), use/no use of POAF prophylaxis (and if, what kind), presence/absence of postoperative fibrillation and equivalent arrhythmia, and the highest ventricular response recorded during POAF. The choice of risk factors and collected data was determined by the data available from medical records. All patients had spent at least one night, most of them two or more nights, in the Intensive Care Unit (ICU) before they were admitted to thoracic surgery ward. Patients were divided into three groups: group A included patients with no POAF prophylaxis; group B included patients with diltiazem prophylaxis; and group C included patients with preoperative antiarrhythmic therapy (mostly beta-blockers, a few propafenone or amiodarone) that was continued postoperatively. Diltiazem was included in therapy, if there were no contraindications, on the day of surgery or the first postoperative day (according to clinical circumstances) and continued after transfer from ICU to surgical ward. A patient was included in group B if the 24-hour diltiazem dose was at least 60 mg (usually it was between 60 mg and 240 mg *per os* divided in 2-4 doses). All patients were treated equally according to the ICU and surgical ward perioperative treatment protocol. All patients gave their informed consent for participation in the study. Statistical analysis and data analysis were done by the licensed STATISTICA 6.1 StatSoft Inc. 1983-2003 (serial number AGA304B211928E61) software. The sample was presented by descriptive statistics and frequency tables. Correlation between the highest recorded ventricular frequency of AF and other parameters was tested by the analysis of variance (ANOVA) and t-test for independent samples. Correlation between the incidence of AF and other parameters was presented in contingency tables and tested by χ^2 -test. Results of statistical analysis were presented graphically and numerically (in tables). Statistical testing was performed at the level of significance of 95% ($\alpha=0.05$).

Results

There were 608 patients undergoing lung resection greater or equal to lobectomy during the period of 31 months. As 15 patients with chronic AF and four pa-

tients with some kind of pacemaker were excluded, there remained 589 patients with lung resection for further analysis (Table 1). Seventy-seven of these 589 patients developed POAF (13.1%) (Table 2). There were 82 pneumonectomies with 19 (23.17%) cases of

Table 4. Postoperative atrial fibrillation prophylaxis and incidence

2-way summary table: frequencies observed				
AF	AF prophylaxis: diltiazem	AF prophylaxis: preoperative antiarrhythmic therapy	AF prophylaxis: none	Total
Yes	27	16	34	77
%	35.06%	20.78%	44.16%	
No	194	116	202	512
%	37.89%	22.66%	39.45%	
Total	221	132	236	589

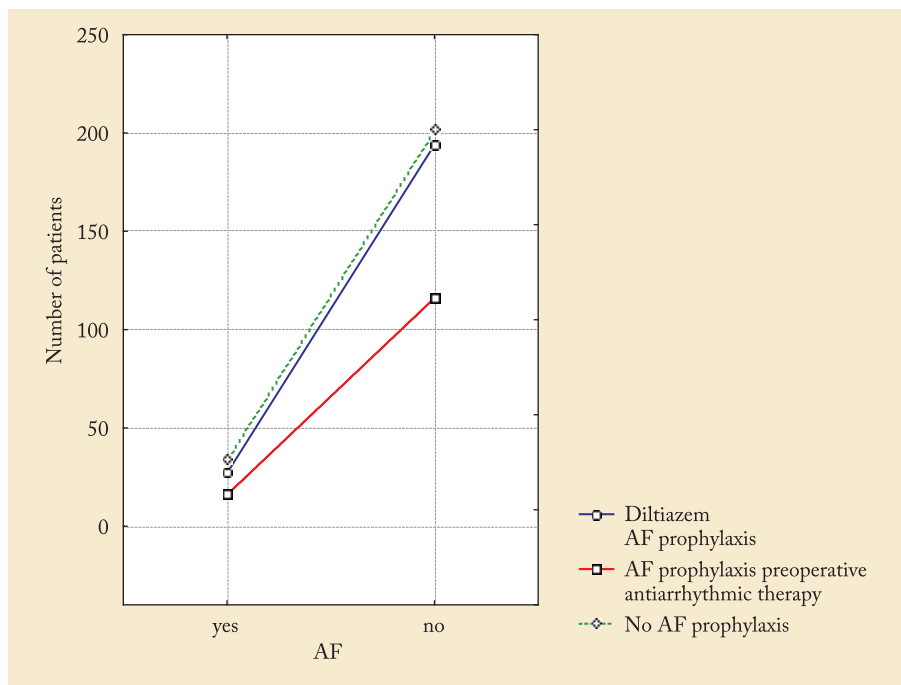
AF = atrial fibrillation

Table 5. Statistics: POAF and POAF prophylaxis (AF)

Statistics: AF(2) x AF prophylaxis(3)			
	χ^2 -test	df	p
Pearson χ^2 -test	0.617	2	0.734

POAF = postoperative atrial fibrillation; AF = atrial fibrillation

POAF. According to their AF prophylaxis, these 589 patients were divided into 3 groups: group A, 236 patients without prophylaxis; group B, 221 patients with diltiazem prophylaxis; and group C, 132 patients with continued preoperative antiarrhythmic therapy (Table 3). POAF was recorded in 34 (14.41%) group



POAF = postoperative atrial fibrillation; AF = atrial fibrillation

Fig. 1. POAF prophylaxis and incidence.

Table 6. POAF prophylaxis and POAF as the highest ventricular response recorded (here: AF frequency)

AF prophylaxis	N	AF frequency Mean	AF frequency SD	AF frequency SE	AF frequency -95% CI	AF frequency +95% CI
Total	77	149.6234	22.79430	2.597651	144.4497	154.7970
Diltiazem	27	148.1481	20.48208	3.941778	140.0457	156.2506
Preoperative antiarrhythmic therapy	16	146.2500	14.24313	3.560782	138.6604	153.8396
None	34	152.3824	27.54502	4.723932	142.7714	161.9933

POAF = postoperative atrial fibrillation; AF = atrial fibrillation; SD = standard deviation; SE = standard error

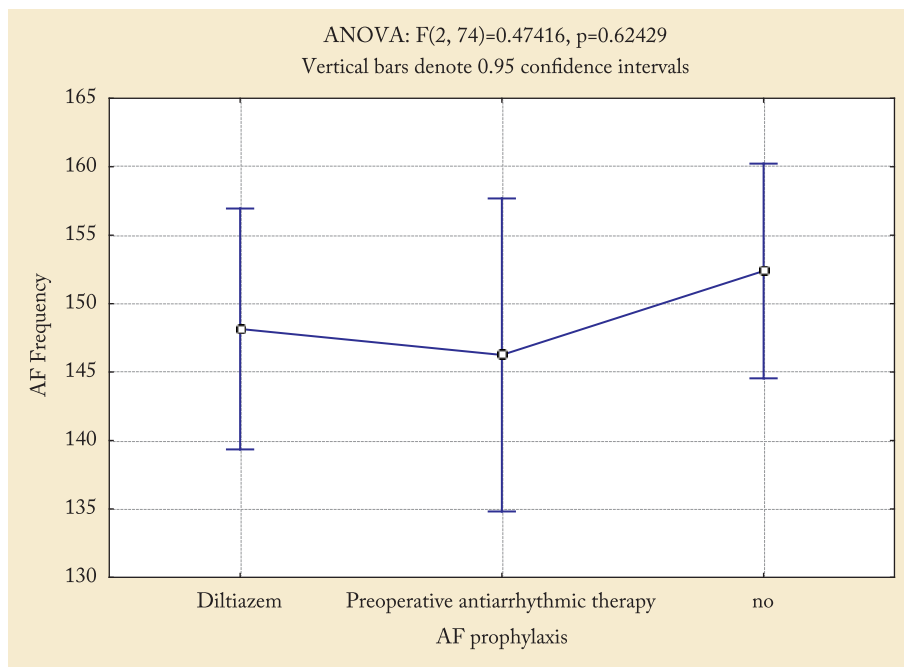


Fig. 2. Testing of the highest ventricular frequency observed and POAF prophylaxis.

A patients, 27 (12.22%) group B patients and 16 (12.12%) group C patients. The highest ventricular response in AF was recorded in each patient, with median 160 (range 91-230) in group A, 150 (range

Table 7. Age groups

Frequency table		
Age group (yrs)	n	%
≤55	110	18.7
65-74	190	32.3
56-64	248	42.1
≥75	41	7.0
Total	589	100.0

Table 8. Age groups and POAF (AF)

2-way summary table: frequencies observed			
Age group (yrs)	AF yes	AF no	Total
≤55	9	101	110
%	8.18%	91.82%	
56-64	27	221	248
%	10.89%	89.11%	
65-74	30	160	190
%	15.79%	84.21%	
≥75	11	30	41
%	26.83%	73.17%	
Total	77	512	589

POAF = postoperative atrial fibrillation; AF = atrial fibrillation

Table 9. Statistics: age groups and POAF (AF)

Statistics: age group(4) x AF(2)			
	χ^2 -test	df	p
Pearson χ^2 -test	11.41967	3	0.00966

POAF = postoperative atrial fibrillation; AF = atrial fibrillation

110-210) in group B and 148 (range 125-170) in group C. The χ^2 -test showed no statistically significant difference in the incidence of AF among patients with different AF prophylaxis ($p>0.05$) (Tables 4 and 5, Fig. 1). Analysis of variance (ANOVA) yielded no statistically significant difference among patients with different AF prophylaxis with respect to the highest ventricular frequency. Patients without prophylactic antiarrhythmic drugs had higher ventricular frequency during AF but this difference was not statistically significant ($p>0.05$) (Table 6, Fig. 2). Analysis of correlation of particular risk factors with POAF yielded sta-

Table 10. Sex distribution of study patients

Frequency table		
Sex	n	%
Male	389	66.0
Female	200	34.0
Total	589	100.0

Table 11. Sex and POAF incidence (AF)

2-way summary table: frequencies observed			
Sex	AF yes	AF no	Total
Male	60	329	389
%	15.42%	84.58%	
Female	17	183	200
%	8.50%	91.50%	
Total	77	512	589

POAF = postoperative atrial fibrillation; AF = atrial fibrillation

Table 12. Statistics: sex and POAF (AF)

Statistics: sex(2) x AF(2)			
	χ^2 -test	df	p
Pearson χ^2 -test	5.573	1	0.018

POAF = postoperative atrial fibrillation; AF = atrial fibrillation

tistically significant correlation ($p<0,05$) for age (Tables 7, 8 and 9), sex (Tables 10, 11 and 12), pneumonectomy versus other resections (Tables 13, 14, 15 and 16), generalized atherosclerotic disease (in our study, it was defined as comorbidity including history of myocardial infarction or cerebrovascular insult, diagnosis of coronary disease and peripheral vascular disease) (Tables 17, 18 and 19), and ASA status (Tables 20, 21 and 22). Considering other states and comorbidities,

Table 13. Lung resection extent and POAF (AF)

2-way summary table: frequencies observed			
Lung resection	AF yes	AF no	Total
PD	3	23	26
%	11.54%	88.46%	
PS	16	40	56
%	28.57%	71.43%	
BID	2	25	27
%	7.41%	92.59%	
BSD	3	13	16
%	18.75%	81.25%	
LID	8	69	77
%	10.39%	89.61%	
LSS	16	105	121
%	13.22%	86.78%	
LIS	9	73	82
%	10.98%	89.02%	
LSD	16	133	149
%	10.74%	89.26%	
LMD	4	31	35
%	11.43%	88.57%	
Total	77	512	589

POAF = postoperative atrial fibrillation; AF = atrial fibrillation; PD = right pneumonectomy; PS = left pneumonectomy; BID = right inferior bilobectomy; BSD = right superior bilobectomy; LID = right inferior lobectomy; LSS = left superior lobectomy; LIS = left inferior lobectomy; LSD = right superior lobectomy; LMD = right middle lobe resection

Table 14. Statistics: lung resection extent and POAF (AF)

Statistics: lung resection(9) x AF(2)			
	χ^2 -test	df	p
Pearson χ^2 -test	14.71278	8	0.06499

POAF = postoperative atrial fibrillation; AF = atrial fibrillation

Table 15. *Pneumonectomies and POAF (AF)*

2-way summary table: frequencies observed			
	AF yes	AF no	Total
PD + PS	19	63	82
%	23.17%	76.83%	
Other	58	449	507
%	11.44%	88.56%	
Total	77	512	589

POAF = postoperative atrial fibrillation; AF = atrial fibrillation; PD = right pneumonectomy; PS = left pneumonectomy

Table 16. *Statistics: pneumonectomies and POAF*

Statistics: PD + PS(2) x AF(2)			
	χ^2 -test	df	p
Pearson χ^2 -test	8.547484	1	0.00346

POAF = postoperative atrial fibrillation; AF = atrial fibrillation; PD = right pneumonectomy; PS = left pneumonectomy

Table 17. *Generalized atherosclerotic disease (GAD)*

Frequency table:		
GAD	n	%
Yes	78	13.2
No	511	86.8
Total	589	100.0

Table 18. *Generalized atherosclerotic disease and POAF*

2-way summary table: frequencies observed			
GAD	AF yes	AF no	Total
Yes	16	62	78
Row %	20.51%	79.49%	
No	61	450	511
Row %	11.94%	88.06%	
Total	77	512	589

GAD = generalized atherosclerotic disease; POAF = postoperative atrial fibrillation; AF = atrial fibrillation

Table 19. *Statistics: generalized atherosclerotic disease and POAF*

Statistics: GAD(2) x AF(2)			
	χ^2 -test	df	p
Pearson χ^2 -test	4.379084	1	0.03639

GAD = generalized atherosclerotic disease; POAF = postoperative atrial fibrillation; AF = atrial fibrillation

Table 20. *ASA status*

Frequency table		
ASA status	n	%
<ASA III	237	40.2
≥ASA III	352	59.8
Total	589	100.0

ASA status = American Society of Anesthesiologists Physical Status

Table 21. *ASA status and POAF incidence (FA)*

2-way summary table: frequencies observed; marked cells had counts >10			
	AF	AF	Row
<ASA III	18	219	237
Row %	7.59%	92.41%	
≥ASA III	59	293	352
Row %	16.76%	83.24%	
Total	77	512	589

ASA status = American Society of Anesthesiologists Physical Status; POAF = postoperative atrial fibrillation; AF = atrial fibrillation

Table 22. *Statistics: ASA status and POAF incidence (FA)*

Statistics: ASA status(2) x AF(2)			
	χ^2 -test	df	p
Pearson χ^2 -test	10.47239	1	0.00121

ASA status = American Society of Anesthesiologists Physical Status; POAF = postoperative atrial fibrillation; AF = atrial fibrillation

statistical analysis did not show statistical significance, e.g., thoracic epidural analgesia (Tables 23, 24 and 25), arterial hypertension (Tables 26, 27 and 28) and prior chemotherapy (Tables 29, 30 and 31), or the entities were too rare in our patients to be included in the analysis, e.g., diabetes mellitus, renal insufficiency and Teolin therapy.

Discussion

The search for the ideal antiarrhythmic for POAF prophylaxis is far from finished. Avoidance of β blockade withdrawal in patients on chronic therapy with these medications is the simple and most effective preventive measure^{1,2,4}. As with AF therapy, there is no ideal drug or method for POAF prevention in other patients. Magnesium supplementation is usually rec-

Table 23. Thoracic epidural analgesia (TEA)

Frequency table		
TEA	n	%
Yes	286	48.6
No	303	51.4
Total	589	100.0

Table 24. TEA and POAF (FA)

2-way summary table: frequencies observed			
TEA	AF yes	AF no	Total
Yes	36	250	286
%	12.59%	87.41%	
No	41	262	303
%	13.53%	86.47%	
Total	77	512	589

TEA = thoracic epidural analgesia; POAF = postoperative atrial fibrillation; AF = atrial fibrillation

Table 25. Statistics: TEA and POAF (FA)

Statistics: TEA(2) x FA(2)			
	χ^2 -test	df	p
Pearson χ^2 -test	0.1153593	1	0.73412

TEA = thoracic epidural analgesia; POAF = postoperative atrial fibrillation; AF = atrial fibrillation

ommended¹ and regularly administered in our patients. Some of the established antiarrhythmics such as amiodarone have questionable safety, especially in patients with pneumonectomy and COPD^{1,2,5}. Diltiazem has been established as a prophylactic antiarrhythmic drug with moderate success^{1,2}. It is recommended early postoperatively, especially in COPD patients, and is usually well tolerated³. Diltiazem is a nondihydropyridine calcium channel antagonist (class IV Vaughan Williams agent)⁶. As AF prophylaxis, we administer it in oral form. In our study, we found no statistically significant difference between patient groups with and without diltiazem prophylaxis, suggesting that in our patients, POAF occurred as a complication of lung resection comparably often with and without diltiazem prophylaxis. So, we could not confirm the report by Amar *et al.* on diltiazem therapy and its significant

Table 26. Arterial hypertension

Frequency table		
Arterial hypertension	n	%
Yes	272	46.2
No	317	53.8
Total	589	100.0

Table 27. Arterial hypertension and POAF incidence

2-way summary table: frequencies observed			
AH	AF yes	AF no	Total
Yes	40	232	272
%	14.71%	85.29%	
No	37	280	317
%	11.67%	88.33%	
Total	77	512	589

AH = arterial hypertension; POAF = postoperative atrial fibrillation; AF = atrial fibrillation

Table 28. Statistics: arterial hypertension and POAF

Statistics: AH(2) x AF(2)			
	χ^2 -test	df	p
Pearson χ^2 -test	1.185774	1	0.27619

AH = arterial hypertension; POAF = postoperative atrial fibrillation; AF = atrial fibrillation

POAF rate reduction³. Our speculation that patients with diltiazem prophylaxis generally have somewhat slower ventricular response during POAF (median 150; without any prophylaxis, median 160), which could have some protective properties *per se*, was not confirmed by statistical analysis. Maybe the most problematic part of the study was the uneven dosage of diltiazem postoperatively, especially on day 0; also, underdosing was probably quite common due to hemodynamic instability of patients at that time. However, Hiran *et al.*² in their guidelines suggest that diltiazem prophylaxis *per os* be initiated in recovery room at a dose of 30-60 mg every 6 hours, depending on the patient related factors and with "hold parameters", and we did so accordingly. There is also the issue of the oral route of taking the drug and its gastrointestinal resorption in the early postoperative course. In our study, the incidence of POAF was 13.1%, which is consistent

Table 29. Prior chemotherapy

Frequency table		
CHT	n	%
Yes	127	21.6
No	462	78.4
Total	589	100.0

CHT = chemotherapy

Table 30. Prior chemotherapy and POAF incidence

2-way summary table: frequencies observed; marked cells had counts >10			
CHT	AF yes	AF no	Total
Yes	14	113	127
%	11.02%	88.98%	
No	63	399	462
%	13.64%	86.36%	
Total	77	512	589

POAF = postoperative atrial fibrillation; AF = atrial fibrillation; CHT = chemotherapy

Table 31. Statistics: prior chemotherapy and POAF incidence

Statistics: CHT(2) x AF(2)			
	χ^2 -test	df	p
Pearson χ^2 -test	0.5984023	1	0.43919

POAF = postoperative atrial fibrillation; CHT = chemotherapy

with literature data², where it is reported to be 12%-44%. If we exclude pneumonectomies, then our POAF incidence was 11.4%. As most of our patients were transferred from the ICU on postoperative day 2, we can speculate that there were much more unnoticed and asymptomatic POAF episodes on surgical ward. We confirmed literature reports on patient age, sex, pneumonectomy (especially intrapericardial and extrapleural extensions) and generalized atherosclerotic disease (i.e. coronary disease) as risk factors^{1,2} (statistically significant results). Some other risk factors could not be confirmed due to the relatively low number of affected patients in our sample (hyperthyroidism, cardiac diseases other than coronary disease, arrhythmias, diabetes mellitus, etc.)^{1,2}. We believe that there were more patients with these risk factors, but it was not

recorded in their medical documentation. It should be noted that we found a statistically significant correlation between ASA status and POAF, but not between epidural analgesia/anesthesia and POAF. ASA status, as stated in the literature, correlates with perioperative mortality "even better than other classifications of mortality and morbidity"^{7,8}. TEA is considered to exert some protective effect against POAF⁹. Arterial hypertension was not confirmed as a risk factor for POAF, in contrast to the 2014 American Heart Association Atrial Fibrillation Guidelines and relevant literature^{1,2,4}. Preoperative chemotherapy, indicated as a risk factor for postoperative cardiovascular events¹⁰, does not seem to increase the risk of POAF. To establish more definitive conclusions, additional study in a bigger sample and including more and better defined risk factors is needed.

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Sažetak

PROFILAKSA POSLJIEOPERACIJSKE ATRIJSKE FIBRILACIJE I RESEKCIJA PLUĆA – NAŠA ISKUSTVA SA 608 UZASTOPNIH BOLESNIKA

V. Karadža, D. Stančić-Rokotov, J. Špiček Macan, N. Hodoba, N. Kolarić i S. Sakan

Poslijeoperacijska atrijska fibrilacija je česta komplikacija resekcije pluća. Ona dovodi do povišenog pobola i smrtnosti, produljenog bolničkog liječenja i povećane potrošnje sredstava u torakokirurških bolesnika. U skladu s tim, savjetuje se neki oblik farmakološke profilakse. U naših bolesnika odabrani lijek je kalcijev antagonist diltiazem. Skupili smo podatke o svih 608 bolesnika podvrnutih resekciji pluća (ne manjoj od lobektomije) u razdoblju između studenog 2012. i svibnja 2015. Ovo razdoblje uključuje bolesnike koji su primali diltiazem tijekom njihova poslijeoperacijskog boravka u Jedinici intenzivnog liječenja i na kirurškom odjelu te bolesnike koji ga nisu primali. Bolesnici s atrijskom fibrilacijom prije operacije i bolesnici s elektrostimulatorom srca isključeni su iz obrade. Ostali bolesnici podijeljeni su u tri skupine: skupinu liječenu nekim antiaritmikom prije operacije koji su nastavili svoju terapiju i nakon operativnog zahvata, skupinu na profilaksi diltiazemom i skupinu bez profilakse. Skupljeni podaci su statistički analizirani. Nismo našli statistički značajnu razliku između skupina u incidenciji poslijeoperacijske atrijske fibrilacije ($p < 0,05$).

Ključne riječi: *Diltiazem; Atrijska fibrilacija; Torakalna kirurgija*