ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
ΘΡΟΜΒΩΣΗ ΚΑΙ ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ

Μεταπτυχιακή Διπλωματική Εργασία

"ΘΡΟΜΒΟΕΜΒΟΛΙΚΟΣ ΚΙΝΔΥΝΟΣ ΚΑΙ ΑΝΤΙΠΗΚΤΙΚΗ ΑΓΩΓΗ ΣΕ ΑΣΘΕΝΕΙΣ ΠΟΥ ΕΜΦΑΝΙΖΟΥΝ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΕΠΕΙΤΑ ΑΠΟ ΧΕΙΡΟΥΡΓΙΚΗ ΕΠΕΜΒΑΣΗ"

υπό

ΠΟΛΥΞΕΝΗΣ Ι. ΟΙΚΟΝΟΜΟΥ

Ειδικευόμενης Καρδιολογίας

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«Θρόμβωση και Αντιθρομβωτική Αγωγή»

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Τίτλος εργασίας στα αγγλικά:

"The risk of thromboembolism in patients presenting with atrial fibrillation after non-cardiac surgery and anticoagulation treatment."

ΕΥΧΑΡΙΣΤΙΕΣ

Για την εκπόνηση της συγκεκριμένης εργασίας θα ήθελα να ευχαριστήσω:

την οικογένειά μου, και ιδίως το σύζυγό μου, *Απόστολο Παξινό*

τους συναδέλφους και φίλους *Στέφανο Στεφάνου, Χρήστο Στεφάνου, Ορέστη Τσώνη*

καθώς και το φίλο κι επιστήμονα *Ευάγγελο Δημητρίου*

για την πολύτιμη συνεισφορά τους και τη στήριξή τους καθ' όλη τη διάρκεια του έργου

Abstract

Atrial fibrillation (AF) is the most common arrhythmia complicating surgery, however, its pathophysiologic mechanism in the postoperative setting is not fully understood. It has been established that it increases the risk of stroke and long-term mortality. Current evidence is lacking and so far postoperative atrial fibrillation is treated as non-valvular, non-surgical atrial fibrillation, complicating everyday clinical practice and challenging decision making. In our research we studied a population of 481 postoperative patients and tried to detect those with new onset AF. We aimed to evaluate their thromboembolic risk and examine how treatment strategy was designed, which parameters were taken under consideration and what an optimal approach would be like.

Key words: non cardiac surgery, atrial fibrillation, postoperative, anticoagulation, thrombotic risk, bleeding risk, treatment.

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GENERAL PART

Chapter 1. Introduction

1.1 Definition of Post Operative Atrial Fibrillation

Post operative atrial fibrillation (POAF) is defined as new-onset AF in the postoperative course[6,21] and is the most common arrythmia complicating surgery. [16,26,27] It is recognized by no discernible P waves and an irregularly irregular rhythm on any ECG tracing.[4,6] The median time of POAF diagnosis is 32 days[5,23], most episodes presenting between the second and fourth postoperative day.[1,4]

POAF following cardiothoracic surgery incidence ranges from 30% to 50%[1,5,31,36] However, it is a frequent complication of noncardiac surgery too, occurring in 0.8% -29% of patients within the first 7 days postoperatively (peak incidence the first two days), depending on the type of the surgical procedure,[11,27,31] and 5-10% after vascular or large abdominal surgeries specifically.[1,19,39]

AF imposes an increased morbidity and mortality burden, increasing the risk of stroke by five-fold within the first postoperative month[5,14] and accounting for about 50% of cardioembolic strokes.[16,25] Besides being a troubling clinical problem, POAF affects the length of hospital stay and increases healthcare expenses.[1,4,5,7,26,32,36]

POAF usually resolves spontaneously and may be subclinical.[3,22,25,31,36] Nevertheless, clinically important new onset AF may cause angina, congestive heart failure and haemodynamic instabillity, or even require either a rate or rhythm control strategy.[1, 18,26, 29,31,36]Given the fact that many episodes are transient, [19,26,39] detection is more possible during prolonged ECG monitoring.[3]

The term AFOTS (Atrial Fibrillation Occuring Transiently with Stress) has also been used to describe AF as a transient phenomenon in a stressful setting (including surgery) that can resolve when the causal factor is reversed.[3,5,22,26]

However, an AFOTS episode could itself indicate a first appearance of permanent AF, signaling the degeneration of the patients' atrial substrate, which, in turn, increases the inducibility of the arrhythmia.[3,11,14,32,38]

1.1.1 Pathophysiology

Postoperative AF is often a progressive and self-preserving arrythmia with complex pathophysiology that is not fully elucidated.[2,7,16]

In Cardiothoracics, surgical maneuvers on the heart, local inflammation, and atrial stretch, may contribute to atrial electrophysiological alterations favoring the development of POAF.[2,7,5,19,21] In non-cardiothoracic surgery, where no such manipulation of the cardiac muscle is involved, the pathophysiological mechanism causing the arrhythmia is more intricate and multifactorial, involving increased sympathetic drive, systemic inflammatory response, electrolyte and metabolic disturbances, hypoxia, and fluid imbalance (hypervolemia).[19,21,26,28] These factors have a serious impact on the atrial substrate and eventually derange the organized atrial activity into fibrillatory.[5,8,19,21,29]

Conceptually, triggering events and predisposing (underlying) conditions interact, favoring arrhythmogenesis and thromboembolism in more susceptible subjects.[3,8,21,29,31]

Predisposed subjects are those with multiple systemic diseases as represented by a higher $CHADS_2VAS_2C$ score (history of hypertension, diabetes mellitus, valvular disease, left ventricular dysfunction, obesity, sleep apnea, increased age, impaired renal function and alcohol consumption)[16,24,31], as well as patients who underwent a pulmonary, vascular, or abdominal surgery.[2,18,36,37] Some studies report that advanced age, hypertension, and more complicated diseases, as are congestive heart failure and vascular disease, can even predict POAF.[5,36,37]

New-onset AF after surgery can also be correlated with postoperative complications, such as “leaks” or fluid collections, infection, anemia, ischemia, autonomic dysfunction (e.g secondary to pain, blood loss, or drug withdrawal), or other cardiac and pulmonary dysfunction.[3,5,8,21] On the other hand, in some cases there is no such obvious underlying mechanism.[5]

More interestingly, outside cardiac surgery, a POAF episode may simply indicate an increased predisposition to thromboembolism.[23,38] Long-term risk is strongly associated with non-cardiac POAF.[1,22,27]

Despite the fact that AFOTS is usually eliminated by resolution of the underlying pathology,[3,21] it is not quite clear yet, if it tends to recur in the future.[3,14,21]

1.1.2 Epidemiology

It has been established that POAF occurrence differs according to the surgical procedure performed.[5,32] Rates after cardiac surgery reach up to 50% for certain procedures,[5,32,33,36,37] while incidence of after non cardiac surgery is about 3–10%.[19,21,39] However, data concerning new-onset POAF after general surgery is limited.[5,6] It seems to develop more often after major, urgent and thoracic surgery, ranging from 1 to 35%.[3] It affects approximately 12%-30% of patients after abdominal surgery,[5,6,8] 17.6% of patients after intrathoracic esophagectomy,[5] while in colorectal surgery the incidence of AFOTS ranges between 9 and 14%.[3] In surgical procedures that involve the biliary tract, the pancreas, and upper gastrointestinal system, malignancies not included, postoperative atrial fibrillation had the lowest rates at 4.8%, 5.2%, and 5.6%, respectively.[5]

Nevertheless, the frequency of new onset AF after surgery is most likely underestimated, as continuous rhythm monitoring is not routinely used in all postoperative patients.[3,8,30]

A prospective study from *Guenancia et.al* reported the highest incidence of AFOTS in literature in ICU patients monitored with an ambulatory device continuously for a week. The monitors recognized at least one episode of AF in 44% of the patients, lasting at least 30 s. Clinicians were able to recognize only two-thirds of cases.[3,30]

1.1.3 Recurrence

Many episodes of POAF are self-terminating and subclinical and a large proportion of patients present asymptomatic during follow-up,[1,15] which may lead to the assumption that small paroxysmal episodes remain undetected and the overall incidence is underestimated.[38]

Nevertheless, since the arrhythmia appears for the first time, it increases the risk of recurrence by four to five-fold in the following 5 years.[1,314,33,38] Postoperative patients complicated by AF precipitants such as infection, thyroid malfunction, pulmonary or pericardial disease, the recurrence rates were even higher in the first 5-6 years of follow-up, reaching a proportion of 44%.[3,14]

Additionally, patients with underlying “silent” atrial myopathy, in whom surgical stress is just the triggering event for AF manifestation are more likely to recur and present with a

thromboembolic event as well.[11,39] Recurrent strokes represent 12% of thrombotic complications annually[15] and POAF patients are twice as likely to present with one in the first postoperative year.[19]

As far as noncardiac surgery for malignancies is concerned, POAF seems to recur at high rates and this can be attributed to carcinogenesis and paraneoplastic syndromes, which cause chronic inflammatory response.[17]

1.1.4 Risk of thromboembolism in AF after non cardiac surgery

The long term risk of thromboembolic complications, is understudied in the non-cardiac POAF population, in contrast to those with AF outside of the operative setting.[22,23,27] The existence, however, of additional risk factors or preexisting cardiovascular disease (reflected by a high CHA2DS2-VASc score) cause a long term risk for thromboembolism at least as high as in patients with non-operative, non- valvular AF.[2,15, 23,24] According to the Framingham study investigators, the systemic embolism risk in subclinical POAF, is similar with that noticed in clinical atrial fibrillation[25] Other studies have shown that patients with postoperative AF present a higher risk of early and long-term stroke (62% and 37% respectively), as well as higher mortality rates in comparison to those without postoperative AF.[1,11,22,27,39] Even subclinical-device detected- AF has long ago been suspected to correlate with the -so called- cryptogenic strokes.[25]

In some studies, the manifestation of even a single 6-minute lasting episode of subclinical POAF was enough to increase the risk of subsequent stroke or other systemic embolism, mortality, and length of stay.[22,25,29]

POAF also increases the risk for myocardial ischemia (myocardial infarction and death in the first postoperative year)[23], congestive heart failure, bacterial lung infections and, consequently, longer hospital stay.[1,23,26,28] Surprisingly, it has been reported in literature that the risk of myocardial infarction appears to be higher than that of stroke, which may also imply that underlying predisposing risk factors of patients who developed POAF (and not the arrhythmia alone), are responsible for ischemic brain complications.[23]

On the other hand, the POISE trial (including a 8351 patients undergoing noncardiac surgery and comparing beta-blocker vs. placebo) showed that new-onset clinically

significant AF increased the risk of stroke within the first month postoperatively. Reevaluation of the periprocedural risk factors did not change the risk of stroke in the first month after surgery.[26]

Even if the initial arrhythmia is successfully converted to sinus rhythm, patients are twice as likely to have a stroke in the first postoperative year,[19] giving the patient a poor prognosis, including severe neurological deficits and recurrence.[15]

Taking into account the large number of noncardiac surgical procedures performed worldwide, the transient nature of POAF and the long-term burden it imposes, the necessity for continuous monitoring needs to be further investigated.[2,15,22]

Moreover, considering oral anticoagulation (OAC) treatment to AF patients after non cardiac surgery as in patients with non-operative AF, seems rational and is tempting for clinicians.[11,23] However, this conclusion may be rushed, since evidence data for post discharge OAC is lacking.[2,23]

1.1.5 Treatment

Currently, there is no robust trial evidence to guide management of new-onset POAF patients, in order to prevent thromboembolism after non cardiac surgery.[11,15,27,31] Whether oral anticoagulation is a safe and long term effective strategy for these subjects needs to be further investigated,[1,15,27,31,33] since the exact prevalence of POAF patients who eventually develop permanent atrial fibrillation is not clear yet.[23] So far, uncertainty remains regarding the thromboembolic risk of POAF as well, because of its transient and reversible nature in the setting of surgical stress. [11,15] Some studies support that under these circumstances it is not sure whether POAF actually increases stroke rates and conceptually, whether long term anticoagulation is needed.[14,15] Moreover, it is not established how many strokes are actually of cardioembolic origin and whether anticoagulation helps prevent them.[23,31]

Controversy also exists about the duration of POAF episodes. Most guidelines agree initiating OAC in AF patients with AF persisting longer than 48 hours, while the benefit of anticoagulation remains controversial when POAF is shorter in duration.[1,12,14,15,26]

The UK National Institute of Health and Care Excellence (NICE) recommendations suggest treating postoperative AF in the same way as AF of any other origin.[19,20]

Anticoagulation in the POAF population is complex and challenging.[15,27] In the postoperative period the balance between hypercoagulable state and increased risk of bleeding is fragile,[8] which can lead to adverse cardiovascular outcomes, disability, and death.[8,15,27] When deciding for OAC, it should be made with caution, preferably involving patients' preferences and considering long –term benefit.[8,26]

The CHA_2DS_2VASc and HAS-BLED scores are recommended for assessing the thromboembolic and bleeding risk respectively.[1,12,15,35,37] However, both of them have been designed for assessing AF patients with non-valvular atrial fibrillation outside the operative course.[11,12,13]

Patients at high risk for thromboembolism are more benefited from OAC, than those with a lower CHA_2DS_2VASc score.[1,11,15] However, that also entails a higher bleeding risk, because of common predisposing risk factors and commorbidities.[15] Long term anticoagulation for preventing thromboembolism should always be balanced against the potential of major bleeding,[11,15,24,34,35] considering that 15% of patients on such medicine manifest a bleeding complication during follow-up.[15]

A study reports, that in the presence of other comorbidities (as represented by a higher CHA_2DS_2VASc rating), no anticoagulation at 30days post-surgery increases the risk of stroke as the patient's score increases.[15] Furthermore, stroke risk insisting beyond 12 months following noncardiac surgery, does not support the theory of POAF being a benign condition with no need of oral anticoagulation for a long period after surgery.[27] On the contrary, it suggests that oral anticoagulation in the postoperative setting may confer not only stroke prevention, but vascular benefits as well.[23]

Despite all controversies, things seem to be different and clearer for patients developing atrial fibrillation after noncardiac surgery for malignancies, who should receive anticoagulation for long-term period postoperatively.[17]

As far as oral anticoagulation is concerned, direct new oral anticoagulants are preferable to Vitamin K antagonists, because of their better inherent pharmacological properties, provided that no mechanical valve or severe renal dysfunction is present.[1] They are not,

however, recommended for immediate postoperative use, because of the difficulty in reversing their activity, in case of major bleeding.[8] Postoperative bleeding varies according to the surgical procedure performed and the surgeon should always participate in decision making.[8]

The majority of patients, does not require immediate anticoagulation, but when initiated, OAC should be continued for 4–6 weeks, even when atrial fibrillation converts to sinus rhythm postoperatively.[8]

1.2 Similar studies

Atrial fibrillation has been recognized as is an independent risk factor associated with a five-fold increase in stroke is established since 1991 in the *Framingham study,* that examined a population of 5,070 patients, during 34 years of medical follow-up. [10]

From 1996 to 2015, Danish authors *Butt H. J., et.al.,* studied the risk of thromboembolic events in POAF patients after non-cardiac surgery accessing nationwide data. They concluded that the risk of thromboembolism in this population is as high as in non-surgical, non-valvular atrial fibrillation and was significantly reduced with anticoagulation treatment.[2]

Elharram, et al run a retrospective analysis of 22.007 patients that presented new onset AF following non cardiac surgery. Their analysis aimed to determine the impact of oral anticoagulation on the incidence thromboembolic, as well as major bleeding events.[15]

Compared to the Danish nationwide registry-based study, *Elharam et al* report that POAF patients not receiving OAC were in lower thromboembolic risk than matching patients with non-valvular non-surgical AF, contrary to what is reported by *Butt H. J., et al,*[2,15] and, therefore, suggesting that the optimal management of POAF patients, should not be guided by what we already know about preexistent non valvular AF.[2,11,15]

Heywood et al studied a population of 2967 patients, that underwent abdominal surgery and, more specifically, gastrointestinal and hepatobiliary. A proportion of 6% older than 65 years were likely to develop AF within 90 days postoperatively, having also lower survival rates. Preexisting heart failure, hypertension, and vascular disease increase the risk of POAF even more.[5]

Another clinical research from Higuchi S., et. al., included patients who underwent non-cardiac surgeries for malignancies. Authors present POAF as a frequently recurring complication and realized that anticoagulation may have contributed to lower rates of stroke in men with CHA2DS2 -VASc score of ≥1 and women with a score ≥ 2.[17]

Alonso-Coello, et. al., undertook a substudy from the PeriOperative ISchemic Evaluation (POISE) trial and identified age and surgery as independent risk factors, predicting the development of new onset AF. They also found out that only a small proportion of POAF patients gets discharged on anticoagulation treatment, regardless of a high $CHADS_2VA_2SC$ score.[18]

Conen D., et al followed 18.000 POAF patients for 1 year after non-cardiac surgery to find that they were associated with higher stroke risk, as well as poor cardiovascular prognosis, including myocardial infarction.[23]

Healey S. J, et. al. studied subclinical atrial tachyarrhythmias (AF included) in 2580 patients and followed them up for 2.5 years. They concluded that subjects with subclinical episodes in the past 3 months had higher stroke or systemic embolism rates than those with no arrhythmia detected.[25]

SPECIFIC PART (CLINICAL RESEARCH)

Chapter 2. Methods

2.1 Purpose of review

The purpose of the literature review was to highlight the incidence frequency of non-cardiac postoperative new-onset atrial fibrillation, as well as the stroke risk and mortality burden it imposes in the long term. Atrial fibrillation's significance lies in its potential adverse outcomes and its appearance in the postoperative setting is understudied. Furthermore, evidence regarding management of POAF patients is lacking, so similar studies were searched, in order to understand current clinical strategies that help evaluate the thromboembolic risk of this patient category and define a proper anticoagulation treatment.

2.2 Patients' inclusion and elimination criteria

In our study we included patients that underwent non cardiac surgical procedures, pertaining to orthopedic, urological and abdominal, regardless if they were inpatients' surgeries or urgent ones. Postoperative patients after cardiac surgery were excluded. Furthermore, we aimed to focus on major, more stressful surgeries, so we excluded minor procedures, such as eye, ear, breast, obstetrical and skin/ subcutaneous surgeries.

2.3 Methodology of the study and data extrapolation

For the general review part of the study three major search engines, namely PubMed, EMBASE, and MEDLINE were searched for articles that matched any combination of the following key words: [non cardiac surgery] OR [atrial fibrillation] AND [postoperative] OR [thrombotic risk] AND [anticoagulation] OR [treatment] AND [bleeding risk]. Only papers in English were included, focusing on the thromboembolic risk of non-cardiac postoperative patients and their optimal anticoagulation treatment. As long as the clinical research part of the study is concerned, two hospital centers were involved, in which no cardiac or other thoracic surgeries are performed. The time interval in which we examined postoperative patients was from May 2021 till August 2021.

Patients programmed for orthopedic, abdominal, or urological surgery were examined on a regular basis preoperatively, and again immediately after surgery, and on the first two days after surgery, besides those who presented with an urgent clinical complication or symptom, such as shortness of breath, palpitations, tachycardia, chest pain or acute hemodynamic instability. Examination in asymptomatic patients included auscultation, and ECG. Continuous cardiac monitoring was possible only for patients that underwent a large bowel surgery, abdominal surgery for malignancy, or those who had a difficult intubation and became unstable during surgery.

For those who were diagnosed with atrial fibrillation, we completed a form with patient's basic social (e.g family of friends, ability for regular follow-up) and medical characteristics (e.g possible predisposing factors) and the type of surgery. Data was stratified using the CHA_2DS_2-VASc score to predict each patient's risk for thrombotic complications and the HASBLED score to evaluate the bleeding risk. Using surgeon's opinion, we estimated the thrombotic and bleeding risk of each surgical procedure, as well as the postoperative bleeding possibility of the surgical field. Antithrombotic treatment was decided through a multidisciplinary approach and adjusted to patient's kidney function, according to the current guidelines.

2.4 Definitions

Atrial fibrillation was defined as an irregularly irregular cardiac rhythm in auscultation as well as pulse sensation and was confirmed by the absence of discernible p waves, besides the abnormal QRS intervals.

Patients at high thromboembolic risk were considered those with a CHA_2DS_2VASC score [Congestive heart failure=1pt, Hypertension=1pt, Age ≥75 years=pts, Diabetes mellitus=1pt, Stroke=2pts, Vascular disease=1pt, Age 65-74 years=1pt, Sex category (female)=1pt][1] ≥1 or ≥2 for men and women respectively.

Postoperative patients with a HASBLED [uncontrolled Hypertension=1pt, Abnormal liver/kidney function=1pt for each, Stroke=1pt, Bleeding history or predisposition=1pt, Labile INR=1pt, Elderly/age> 65=1pt, Drugs or excessive alcohol drinking=1pt][1] score

of 3 or more were defined as at high bleeding risk and antithrombotic treatment was reduced to the half dosage.

Anticoagulation was also half-reduced to patients with abnormal renal function and more specifically when glomerular filtration rate was lower than 50ml/min/1.73m^2, using the MDRD method.

Antithrombotic parenteral treatment included subcutaneous injections of weight adjusted Low Molecular Weight Heparin, mostly enoxaparin, besides the cases where the surgeon had already provided a prophylactic treatment with other heparins (usually tinzaparin or bemiparin), so the initial dosage and substance were modified accordingly.

2.5 Statistical analysis

For the present study a paired t-test was performed, as the small sample of patients did not allow any further statistical testing. According to the paired t-test the null hypothesis that the HCT value during admission equals to the HCT value postoperatively is rejected at 5% level of significance. More specifically, the mean value of HCT during admission is statistically higher than the mean of HCT postoperatively. The mean difference equals to 4.175 (s.e.=1.12) units.

Stata 16.0 was used to perform the analysis. The level of significance is set to 5%.

Chapter 3. Results

3.1 Patient data description

In this study we examined a total of 481 surgical patients. 325 underwent abdominal surgeries, 72 were orthopedic procedures and the rest 84 were urological. 12 of the postoperative patients developed new-onset atrial fibrillation after surgery. Of those, 8 were abdominal surgeries (2 for cancer, 2 for bowel obstruction and 1 diaphragmatic hernia), 2 were urological (both for malignancies) and 2 orthopedic procedures, one for hip fracture reconstruction, and a total arthroplasty. Most patients were women and patients' age ranged from 54 to 94 years.

The majority of patients had an elevated CHA_2D_2SVASC score and all of them were provided anticoagulation treatment, both in the acute phase of the arrhythmia and at

discharge, as well. Seven of them were diagnosed on the second postoperative day, so therapeutic dosages were immediately initiated. For the rest of them, diagnosis was made either in the first 6 hours postoperatively, or while already taking a prophylactic dose of heparin (i.e as in the case of the orthopedic surgeries, where immobilization is part of the recovery). Those patients were on reduced, weight adjusted LMWH at first and therapeutic dosage continued on the first or second 24hours, according to surgeon's choice, regarding the hemostatic status of the field. None of the surgeons preferred per os treatment in the acute phase of the arrhythmia. In fact, the majority was discharged on heparin, mostly because of the fear of anastomotic "leaks" or long-term bleeding complications. Patients were advised to seek for further treatment consultation by a cardiologist after the first 20-30 days postoperatively.

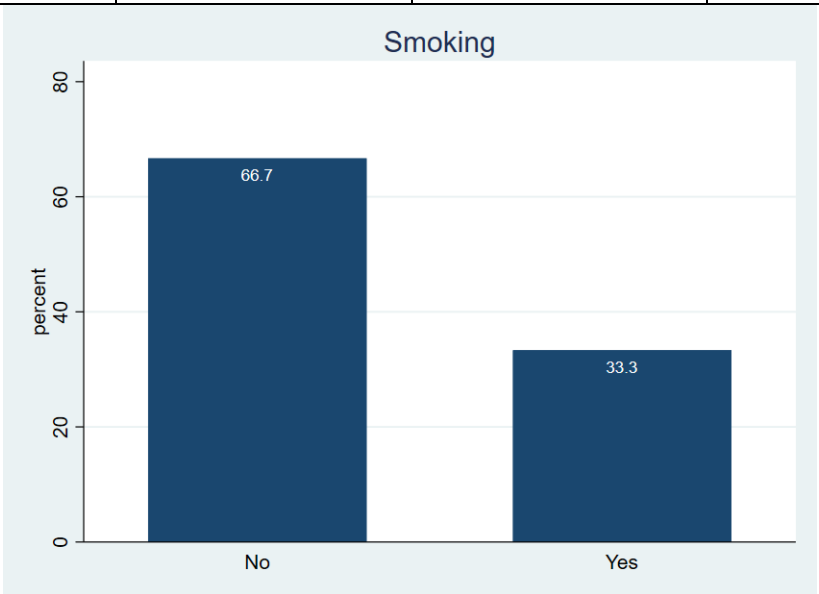
In single case of a young female subject with hypertension as a single risk factor, a reduced therapeutic dose of rivaroxaban 15 was prescribed at discharge for no obvious reason for 30 days. During follow up sinus rhythm was maintained for a long postoperative period (as confirmed by successive portable follow-up monitoring devices) and anticoagulation was discontinued after the first postoperative month. Bleeding complicated only one of our postoperative patients, that underwent a urological surgery for cauterization of bladder papillomas, with a history of mechanical mitral valve, already receiving vitamin K antagonist (VKA) before surgery. Surgeon's choice was bridging with LMWH before initiating the VKA, however bleeding through the urinal catheter delayed the per os treatment further. In the end, enoxaparin was discontinued and VKA alone was initiated, luckily without any thrombotic complications or further bleeding. Hospital stay was, however, significantly prolonged. In the acute phase of the arrhythmia all cardiologists advised for initiation of enoxaparin subcutaneously. However, the final therapy was defined by the surgeon alone.

3.2 Result composition

Smoking	Freq.	Percent	Cum.
No	8	66.67	66.67
Yes	4	33.33	100.00
Total	12	100.00	

Table 1. Smoking

	Gender		
Smoking	Male	Female	Total
No	1	7	8
Yes	3	1	4
Total	4	8	12



Alcohol	**Freq.**	**Percent**	**Cum.**
Never	8	66.67	66.67
Socially	4	33.33	100.00
Total	12	100.00	

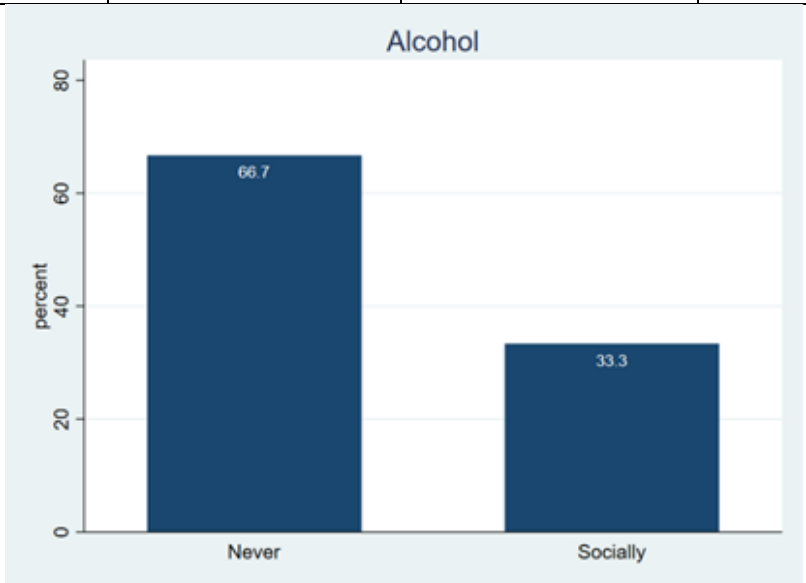


Table 2. Alcohol

Surgery	Freq.	Percent	Cum.
Bladder cancer resection	1	8.33	8.33
Cauterization of bladder papillae	1	8.33	16.67
Diaphragmatic hernia repair	1	8.33	25.00
Emphysematous cholecystitis-peritonitis	1	8.33	33.33
Open cholecystectomy	1	8.33	41.67
Separated hip fracture-total arthroplasty	2	16.67	58.33
Partial gastrectomy - stomach Ca	1	8.33	66.67
Postoperative abdominal hernia	1	8.33	75.00
Sigmoidectomy	1	8.33	83.33
Small bowel perforation, peritonitis, septic shock	1	8.33	91.67
Small intestinal intussusception	1	8.33	100.00
Total	12	100.00	

Table 3. Surgery

Type of surgery	Freq.	Percent	Cum.
Abdominal	8	66.67	66.67
Orthopedic	2	16.67	83.33
Urological	2	16.67	100.00
Total	12	100.00	

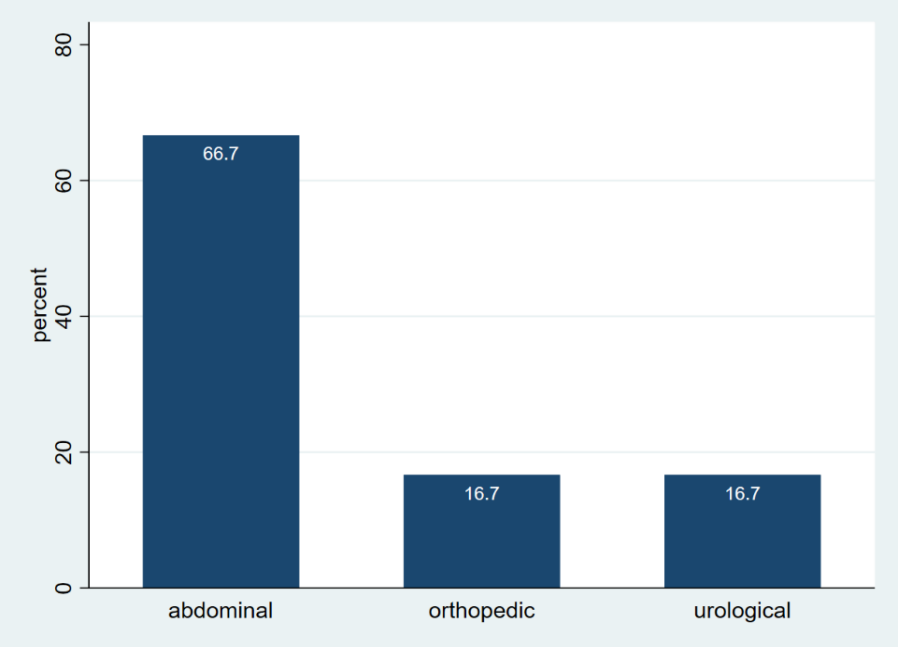
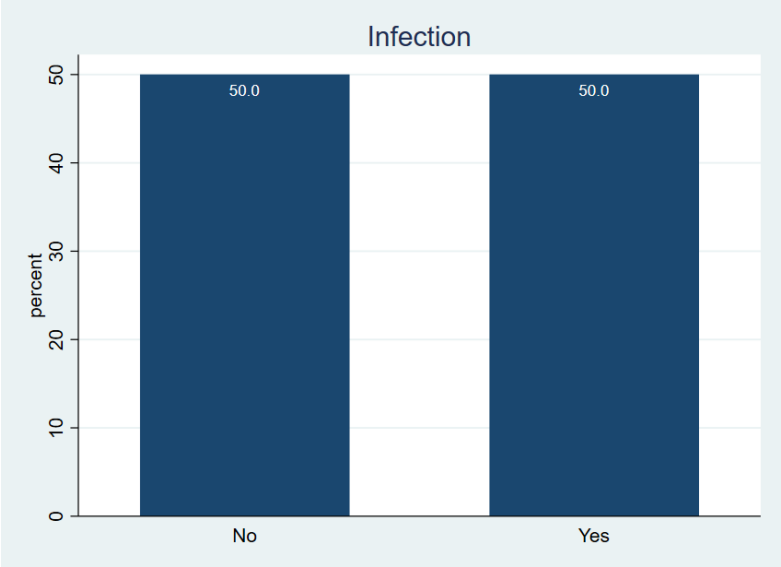


Table 4. Type of surgery

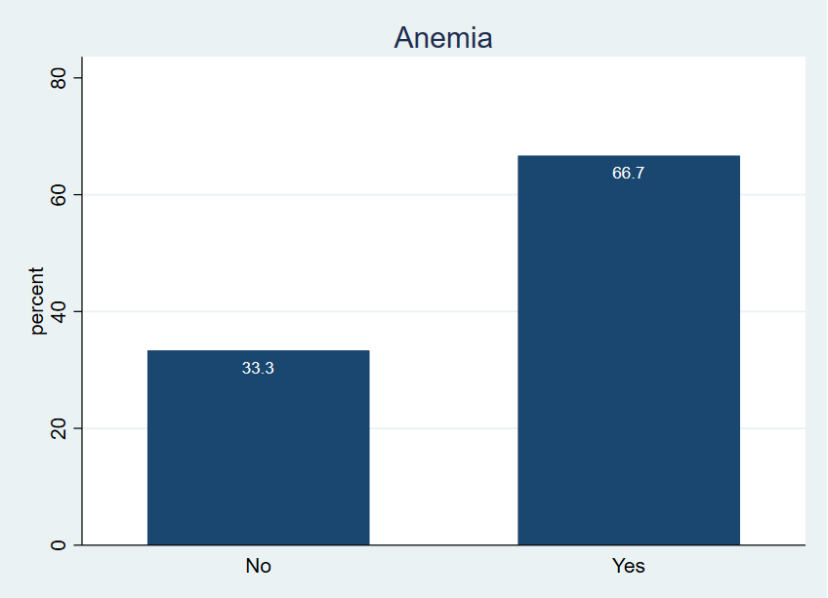
Infection	Freq.	Percent	Cum.
No	6	50.00	50.00
Yes	6	50.00	100.00
Total	12	100.00	

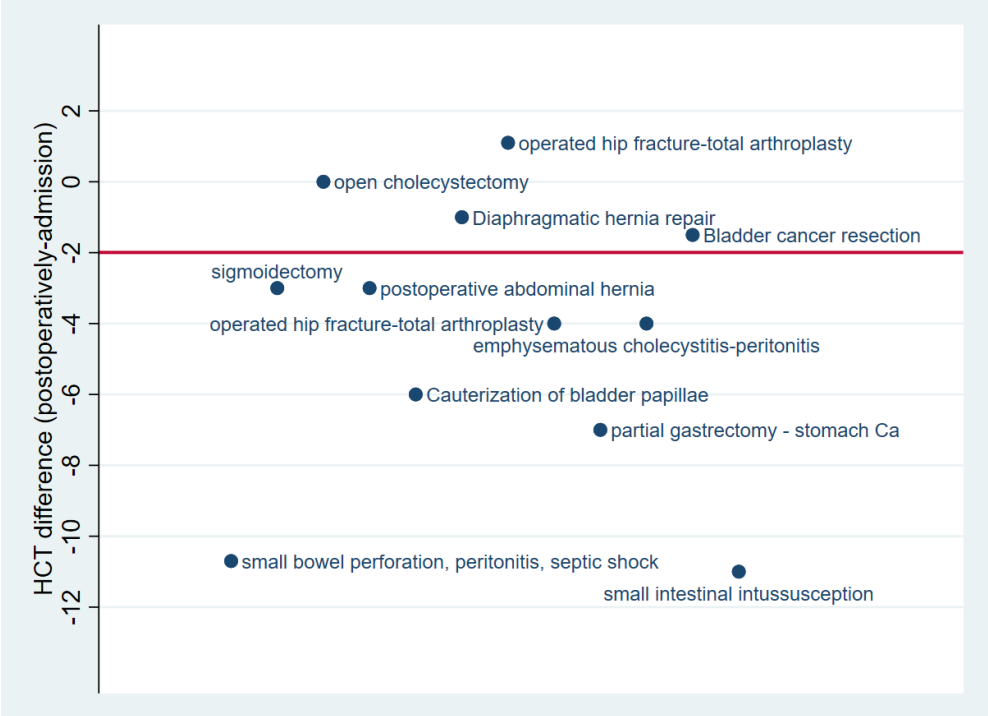
Table 5. Infection



Anemia	Freq.	Percent	Cum.
No	4	33.33	33.33
Yes	8	66.67	100.00
Total	12	100.00	

Table 6. Anemia





Difference of HCT between admission and postoperatively. A value lower than -2 is considered as anemia.

Thrombotic Risk			
	Freq.	Percent	Cum.
Low	3	25.00	25.00
Moderate	4	33.33	58.33
High	5	41.67	100.00
Total	12	100.00	

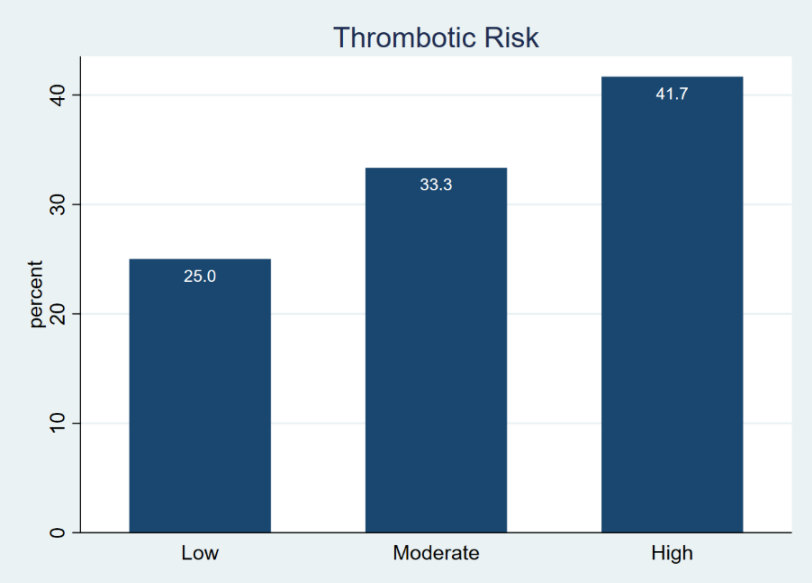
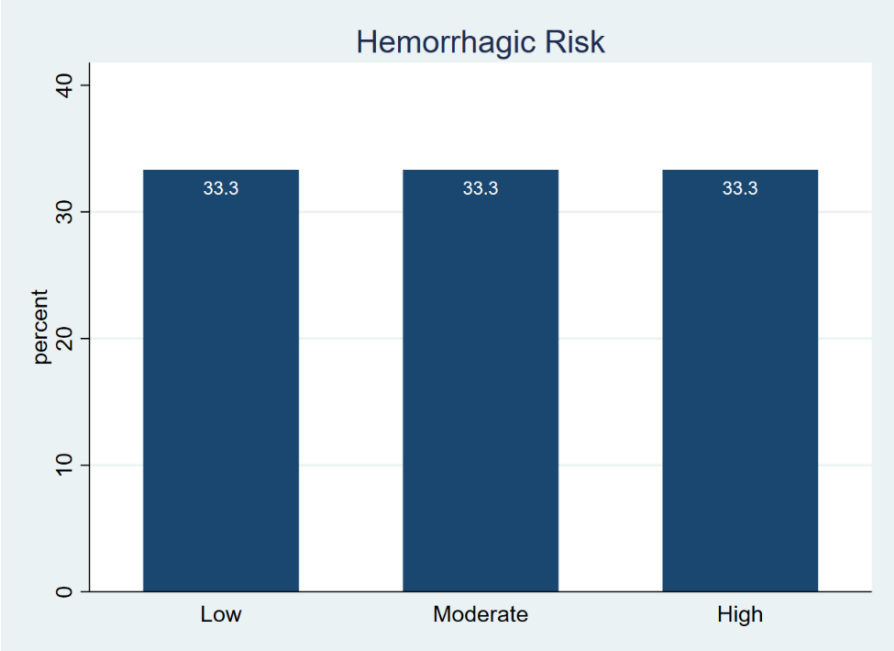


Table 7. Thrombotic risk of surgery (total)

Hemorrhagic Risk			
	Freq.	Percent	Cum.
Low	4	33.33	33.33
Moderate	4	33.33	66.67
High	4	33.33	100.00
Total	12	100.00	

Table 8. Hemorrhagic risk of surgery (total)



Surgery	**Thrombotic Risk**	**Hemorrhagic Risk**
Postoperative abdominal hernia	Low	Low
Open cholecystectomy	Low	Low
Diaphragmatic hernia repair	Low	Moderate
Small intestinal intussusception	Moderate	Low
Sigmoidectomy	Moderate	Moderate
Emphysematous cholecystitis-peritonitis	Moderate	Moderate
Cauterization of bladder papillae	Moderate	High
Small bowel perforation, peritonitis, septic shock	High	Low
Partial gastrectomy - stomach Ca	High	Moderate
Separated hip fracture-total arthroplasty	High	High
Bladder cancer resection	High	High

Table 9. Type of surgery/ bleeding/ thromboembolism

Antithrombotic drugs (acute phase of arrhythmia)	Freq.	Percent	Cum.
enoxaparin 6000iu o.d first 6hrs	1	8.33	8.33
bemiparin 5mg o.d	1	8.33	16.67
enoxaparin 6000iu o.d	2	16.67	33.33
enoxaparin 6000iu b.i.d	3	25.00	58.33
enoxaparin 8000iu b.i.d	3	25.00	83.33
enoxaparin 8000iu o.d first 6 hrs	1	8.33	91.67
tinzaparin 14.000iu o.d	1	8.33	100.00
Total	12	100.00	

Table 10. Anticoagulation/ acute phase

Antithrombotic drugs (discharge)	Freq.	Percent	Cum.
Enoxaparin 6000iu b.i.d	3	25.00	33.33
Enoxaparin 8000iu b.i.d	4	33.33	66.67
Dabigatran 150mg b.i.d	1	8.33	75.00
Acenocoumarol	1	8.33	83.33
Rivaroxaban 15mg o.d	1	8.33	91.67
Rivaroxaban 20mg o.d	2	16,66	100.00
Total	12	100.00	

Table 11. Anticoagulation/discharge

Comparison of the mean of HCT during admission and postoperatively

	Mean	Std. Error	95% Confidence Interval
HCT (admission)	37.14	1.26	(34.36 , 39.92)
HCT (postoperatively)	32.97	1.65	(29.33 , 36.60)
Difference	4.175	1.12	(1.71 , 6.64)
H_0: HCT (admission) = HCT (postoperatively)		p-value = 0.0034	

According to the paired t-test the null hypothesis that the HCT value during admission equals to the HCT value postoperatively is rejected at 5% level of significance. More specifically, the mean value of HCT during admission is statistically higher that the mean of HCT postoperatively. The mean difference equals to 4.175 (s.e.=1.12) units.

Chapter 4. Discussion

Our study is a brilliant example of how difficult it is to detect postoperative atrial fibrillation episodes, especially when continuous rhythm monitoring is not available. We confirm that most episodes occurring in this setting were asymptomatic and the majority

of them were randomly discovered. We were not able to capture the duration of the arrhythmia either.

Moreover, patients with more predisposing risk factors, as represented by a higher CHA_2DS_2VASC score, were more likely to develop AF after surgery than those who did not, as were the patients that were complicated with infection (mostly of the lungs), and anemia. Some of those patients had symptomatic episodes of AF and usually complained of palpitations, dyspnea, or chest discomfort. Furthermore, POAF occurred with higher incidence rates in patients that underwent a major abdominal surgery, either for malignancy or bowel obstruction, as well as women. Anticoagulation treatment was decided according to the currently existing guidelines about non valvular, non-surgical AF. However, no common strategy seemed to exist and, further, the thrombotic and bleeding risk could not be precisely balanced. Dosage adjustments had to be made by experience and surgeon's preferences.

Limitations of our study

Our study is restricted by several limitations. First of all, continuous cardiac electrocardiography was not available, so the duration and number of events could not be captured. Secondly, patients were examined immediately after surgery and again on the first two postoperative days, so whether AF persisted at discharge is not known. Moreover, many cases may have been missed and the number of POAF patients we detected cannot be considered statistically important. In addition, not all patients came back for a follow up within the first postoperative month to check if the arrhythmia recurred. Furthermore, since the preoperative cardiological screening involves a superficial ECG, the preexistence of baseline paroxysmal AF cannot be known. The two hospital centers that were involved in the study perform only abdominal, orthopedic and urological surgeries, so no general conclusion about non-cardiac surgery can be extracted.

Chapter 5. Conclusions

POAF is a common arrhythmia presenting in the stressful setting of surgery. It has been associated with elevated stroke risk as well as increased long-term morbidity and prolonged hospital stay. It is still not completely understood whether POAF is an arrhythmia occurring transiently with stress (also known as AFOTS) or if an even short-lasting episode preludes permanent or recurring AF, indicating a complex underlying pathophysiology.

Surgical patients represent a special and demanding population with many predisposing risk factors favoring the development of fibrillatory atrial activity and diagnosis is of great importance. However, detection especially without continuous monitoring and given the transient character of the arrhythmia, is challenging and many cases may be missed.

Unfortunately, the exact thromboembolic risk of POAF or is not fully elucidated and data guiding the optimal anticoagulation treatment is lacking. Moreover, recurrence incidence of POAF is quite unclear and treatment duration cannot be decided with safety in the absence of more data regarding the surgical population. Therapists so far base their decision making on guidance about non valvular atrial fibrillation outside the postoperative setting. Under these circumstances, no specific or safe treatment can be decided and clinical practice is encumbered. Further studies that consider the eminent characteristics of postoperative atrial fibrillation patients alone are needed.

Chapter 6. Summary

In conclusion, POAF is the arrhythmia that more often complicates non cardiac surgery. Its nature and future recurrence possibility is not completely understood but it imposes a great risk of stroke and long-term mortality. In our study, patients that underwent a large abdominal surgery, surgery for malignancies, those who already have predisposing risk factors and those who presented with infection, anemia or similar distress after surgery had higher incidence rates. Since the thrombotic risk of POAF patients cannot be exactly determined with current evidence data, all patients were treated with anticoagulation, weighing embolism towards the risk of bleeding. Cooperation between surgeons and

cardiologists was the key to a successful postoperative management, as defining a treatment strategy in this understudied population is quite challenging in everyday clinical practice. Further evidence and management guidance is needed, as surgical patients represent a very special group of patients, requiring close attention and careful handling.

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