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Real-life trends of anticoagulant prescribing practices for pulmonary embolism – results of a single-center study based on the experience of a multi-profile clinical hospital

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Abstract: Acute pulmonary embolism (APE) is one of the main causes of cardiovascular deaths and anticoagulant treatment plays a key role in preventing recurrent episodes, chronic thromboembolic pulmonary hypertension (CTEPH), and deaths. The aim of this study is to assess the real-life trends and to determine factors associated with the choice of anticoagulation therapy in patients with APE. This is a single center prospective open study. We followed 178 consecutive patients admitted to the tertiary clinical center with APE proven with computed tomography (CT) scan within period of 24 months. A total number of 178 patients with APE were enrolled in the study. 48.9% of subjects were hospitalized in cardiology department. As a prolonged anticoagulant therapy 35.7% of study cohort received direct oral anticoagulants (DOACs), 35.1% LMWH, and 29.2% vitamin K antagonists (VKA), respectively. No statistically significant differences were found between the departments regarding frequency of prescribing anticoagulants (p=0.15). The multivariable analysis showed that oral anti-coagulants (OACs) were less likely to be prescribed than LMWH in patients with malignancy, history of major bleeding, serious medical condition and altered mental status. OACs were preferred over LMWH in symptoms of deep vein thrombosis (DVT). VKA were significantly less likely to be chosen than DOACs in

patients with history of orthopaedics procedure. After six months anticoagulation therapy was discontinued in 24.3% of patients. Concluding, the form of anticoagulant therapy was associated with the presence of chronic diseases. LMWH was prescribed in high bleeding risk patients more frequently.

Keywords: anticoagulation, low molecular weight heparin, direct oral anti-coagulants, pulmonary embolism, vitamin K antagonists

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Introduction

Acute pulmonary embolism (APE) is a major cause of morbidity and mortality, and therefore, requires prompt evaluation, diagnosis, and treatment [1]. To date, anticoagulation using low molecular weight heparin (LMWH), or vitamin K antagonists (VKA) has been the mainstay of treatment in the subset of patients in whom APE does not compromise hemodynamics. On the other hand, in patients with APE and shock, thrombolysis is the therapy of choice [2]. The management patterns of APE have significantly changed since the introduction of direct oral anticoagulants (DOACs) [3,4]. Anticoagulation treatment should be administered immediately in all patients with a confirmed diagnosis of APE and in patients with a high or intermediate clinical probability of APE who are waiting for diagnostic tests results. Prompt anticoagulation can only be achieved with parenteral anticoagulants such as unfractionated heparin (UFH), LMWH, and fondaparinux as a bridge to VKA or DOAC [5]. Poor-quality anticoagulation may contribute to a higher risk of in-hospital complications, recurrent PE episodes, chronic thromboembolic pulmonary hypertension (CTEPH), worsening quality of life, and deaths [6,7]. In patients with APE who are hemodynamically stable DOACs are the recommended form of anticoagulant treatment [8]. DOACs have a rapid onset of activity, no lab monitoring is required, and the risk of interactions with other drugs is quite low, which makes new anticoagulants convenient alternative to standard therapy. However, the cost of this treatment is quite high. The objective of this study was to determine factors associated with the choice of anticoagulant therapy.

Patients and Methods

We present analysis of single center trends in anticoagulation therapy of APE assessed prospectively conducted in Central Research Hospital Ministry of Interior and Administration, multi-profile clinical hospital. The study group was partially composed of patients included in the ZATPOL-2 study, a prospective registry conducted in 20 cardiology

departments in Poland [9]. However, due to the intention to provide a detailed assessment of the method of diagnosis and treatment of APE in our center and its compliance with current recommendations, the study period was extended to 2 years. Inclusion criteria in this study were age at least 18 years and APE confirmed by CT. Exclusion criteria were diagnosis of APE without imaging confirmation and chronic PE. Collected data for further analysis were as follow: demographics, admission details, symptoms of APE, comorbidities, VTE risk factors, bleeding risk factors, previous anticoagulation treatment, laboratory tests results, imaging tests results, in-hospital therapy, home treatment and treatment 6 months after discharge. Ethical approval for this analysis was obtained from the local ethical committee (no. 44/PB/2013).

Statistical Analysis

Data gathered in the study was presented using the descriptive methods. In descriptive statistics for categorical variables, the number and percentage of occurrence were reported. The distribution of continuous variables was first tested for normality using the Shapiro-Wilk test, then for normality distributed variables mean and standard deviation (SD) were reported, otherwise median with the 25^{th} and 75^{th} percentiles (Q1 and Q3) were provided. Fisher exact test was used to compare the distribution of categorical variables between groups. To identify factors that affect anticoagulant therapy choice uni- and multivariable logistic regression models were used. To select final multivariable model, the stepwise regression backward elimination procedure with the minimization of the Akaike criterion was used and the procedure started from the set of variables for which the p-value of the Wald's test in the univariable analysis was less than 0.05. Odds ratio (OR) with 95% confidence intervals and Wald's test p-value were reported. A statistical significance level was set at 0.05. No data imputation methods for missing data were applied. Statistical analysis was performed using R statistical software version 3.1.2 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-porject.org/.)

Results

Characteristics of study group

Within 24 months a total number of consecutive 178 patients with proved APE in CT scan were enrolled in the study. Nearly half of the cohort were women (49.2%). The median of age was 69.0 [IQR 57.0-80.8] years. 48.9% of subjects were hospitalized in cardiology departments, while the rest of the study group in other clinical departments (Table 1).

Table 1. Characteristics of the study group.

Parameter	**Number (n) / P**ercent (%)
Age (median [IQR]) [years]	69.0 [57.0-80.8]
Women / men	87 (49.2) / 90 (50.8)
Dyspnea with exertion	120 (67.8)
Dyspnea at rest	76 (42.9)
Pleuric chest pain	36 (20.3)
Substernal chest pain	18 (10.2)
Haemoptysis	16 (9.0)
Fever	27 (15.2)
Syncope	47 (26.6)
Tachycardia	71 (39.9)
Hypotension/shock	15 (8.4)
Cough	51 (28.7)
DVT symptoms	45 (25.4)
Coronary artery disease	37 (20.9)
Atrial fibrillation	31 (17.5)
Pior ischemic stroke	4 (2.3)
Prior hemorrhagic stroke	1 (0.6)
Chronic pulmonary disease	17 (9.6)
Active cancer	34 (19.1)
Diabetes	41 (23.2)
Arterial hypertension	110 (62.1)
Prior major bleeding	8 (4.5)
Chronic liver disease	10 (5.6)
Orthopaedics procedure within 3 months	11 (6.2)
Gynaecologic procedure within 3 months	1 (0.6)
Surgical procedurę within 3 months	13 (7.3)
Trauma	12 (6.8)
Limb trauma with plaster	10 (5.6)
Lower limbs paralyses	7 (4.0)
Prior VTE	28 (15.7)
Family history of trombophilia	5 (2.8)
Congestive heart failure class III/IV NYHA	12 (6.8)
Immobility > 3 days	22 (12.4)
Central line	3 (1.7)
Oral contraceptions	5 (2.8)
Obesity	40 (22.6)
Long journey within 8 weeks	4 (2.3)
Serious medical condition	13 (7.3)
Low-risk PE	55 (30.9)
Moderate-risk PE	77 (43.3)
High-risk PE	15 (8.4)
Non-high-risk PE	31 (17.4)
Hospitalization in cardiology department	87 (48.9)
Hospitalization in other department	91 (51.1)

Abbreviations: DVT, deep vein thrombosis; VTE, venous thromboembolism; NYHA, New York Heart Association; PE, pulmonary embolism; VTE, venous thromboembolism.

Nearly 70% of patients complained of dyspnea with exertion, 42.9% reported dyspnea at rest and 28.7% had cough. The most common comorbidity was hypertension (62.1%), diabetes (23.2%), and coronary artery disease (20.9%). Obesity was identified in 22.6%, whereas malignancy in 19.1% and previous episode of VTE in 15.7% (Table 1). Idiopathic APE was recognized in 65% of subjects. Low-risk APE was diagnosed in 34.3%, moderate-risk in 57.3% and high-risk APE in 8.4%, respectively. In cardiology departments 9.2 % patients were with high-risk APE, 58.6% with moderate-risk, and 32.2% with low-risk APE. Whereas, in other departments 56% of patients were diagnosed with moderate-risk APE and 36.3% with low-risk, respectively. Only 7.7% subjects were at high-risk of early death in those departments.

The median length of hospital stay was 9 [IQR 7.0-13.5] days. In cardiology departments median time of hospitalization was 9 [IQR 6.0-12.5] days and in other departments 10 [IQR 7.0-15.0] days, respectively.

During the hospital observation bleeding complications occurred in 7 (3.9%) subjects, of which in 3 (3.4%) patients in cardiology departments and in 4 (4.4%) in other departments. Respiratory failure was diagnosed in 3.9% of the study cohort (2.3% in cardiology departments vs. 5.5% in other departments). In-hospital mortality rate was 6.7%. Six patients died in cardiology departments (6.9%) and the same number in other departments (6.6%).

Pulmonary embolism treatment

In a group of high-risk PE acute phase treatment included thrombolysis used in 6.7% of patients, UFH and LMWH used in 46.7% of patients each. Embolectomy was performed in 21.4% of high-risk subjects due to the lack of improvement after previously applied treatment. Most of the patients with moderate-risk APE received LMWH (93.1%) as initial treatment, whereas UFH was administered only in 4.9% of them. DOAC (rivaroxaban) was started on the first day of treatment in 1% of moderate-risk patients. One moderate-risk subject (1%) did not receive any kind of anticoagulation due to contraindications. Due to the worsening condition of the patients, thrombolysis was used in 1% of subjects and embolectomy was performed in 4.9%, respectively. Similarly, in a group of low risk nearly all patients received LMWH (98,9%). 1.6% of low-risk patients received DOAC (rivaroxaban) as initial treatment. In cardiology department in a group of high-risk patients fibrinolysis was used in only one subject (12.5%). Treatment with UFH was initiated in 37.5% of them and half of the patients received LMWH, respectively. Meanwhile, in other departments in

unstable patients fibrinolysis was not used at all, UFH was administered in 57.1% subjects and LMWH in 42.9% respectively. In 42.9% patients in other departments surgical embolectomy was performed.

In patients with moderate-risk APE in cardiology departments fibrinolytic agent was administered in one patient (2%), UFH in 3%, LMWH in 91%, DOACs (rivaroxaban) in 2% respectively. One moderate-risk subject (2%) did not receive any kind of anticoagulation. Two patients (3%) underwent surgical embolectomy. In other departments UFH received 5.9% of patients, LMWH 94.1% respectively. In 5.9% of subjects, surgical embolectomy was performed. In other clinical departments, fibrinolysis or rivaroxaban were not used in acute phase treatment.

In patients diagnosed with low-risk APE only one subject (3.6%) in the cardiology department received rivaroxaban as initial treatment. The rest of the group was treated with LMWH.

As a prolonged anticoagulant therapy, 35.1% of the study cohort received LMWH, 35.7% DOACs (rivaroxaban) and 29.2% VKA, respectively. No statistically significant differences were found between the departments regarding the frequency of prescribing anticoagulants (p=0.15). After six months anticoagulation therapy was discontinued in 24.3% of patients.

Factors associated with choice of prolonged anticoagulant treatment.

The multivariable analysis of factors influencing the choice of OACs instead of LMWH showed that OACs were less likely to be prescribed than LMWH in patients with malignancy, history of major bleeding, serious medical condition, and altered mental status. OACs were preferred over LMWH in symptoms of DVT and odds for oral anticoagulant use instead of LMWH use increased with an increase in hematocrit value (Table 2). The analysis performed to identify factors that affect the choice of VKA over the DOACs as a prolonged anticoagulant treatment showed that the only factor that has significant effect is prior orthopaedics procedure. VKA were significantly less likely to be prescribed than DOACs in patients with history of orthopaedics procedure (OR 0,12; 95%CI: 0.01-0.66, p=0.046). Neither type of department nor severity of APE affected the choice of anticoagulant therapy.

Discussion

This study evaluates anticoagulant prescription practices for APE across different clinical departments in tertiary clinical center. In our research, the most common treatment

prescribed at discharge was rivaroxaban, which is like that observed in another Polish study. In a single-center study by Paczyńska et al. it was reported that 39% of analyzed group received rivaroxaban as chronic therapy [10]. In PREFER IN VTE registry, one month after discharge 61.8% of subjects were treated with VKA, 22% with DOACs and 16.9% with LMWH, respectively. Authors of that report suggested that a small proportion of patients receiving DOACs was a result of older age, comorbidities, and high bleeding risk in the study cohort [11]. We did not find any differences between the departments regarding frequency of prescribing anticoagulants. However, a survey conducted among 365 US physicians of different specialties showed that cardiologists were more likely to choose rivaroxaban as initial treatment in APE (p=0.004) [12]. A potential explanation for the lack of differences in prescribing anticoagulant agent between specialties in our research may be the fact that DOACs were officially recommended in guidelines for APE management 19 months from the beginning of the ZATPOL-2 registry. In the last five months of our study, we did not notice any increase in DOACs prescribing, which may indirectly indicate the adherence to recommendations. That also explains why we did not report the use of other DOACs such as dabigatran, apixaban and edoxaban. Rivaroxaban was approved by EMA in APE treatment in 2012, whereas dabigatran and apixaban in 2014 and edoxaban in 2015.

Table 2. Multivariable logistic regression model for choice of long-term anticoagulant therapy in patients with acute PE: use of OACs over LMWH.

Parameter	**Odds ratio (95%CI)**	**P-value**
Symptoms of DVT	6.35 (1.80 – 28.50)	0.008
Malignancy	0.03 (0.01 – 0.08)	<0.001
Prior major bleeding	0.04 (0.00 – 0.35)	0.011
Serious medical condition	0.12 (0.01 – 0.72)	0.028
Altered mental status	0.12 (0.01 – 0.75)	0.029
Hematocrit	1.08 (0.99 – 1.18)	0.092

Abbreviations: DVT, deep vein thrombosis; LMWH, low molecule weight heparin; OACs, oral anticoagulants.

In our study malignancy, history of major bleeding, serious medical condition and altered mental status were identified as predictors of LMWH prescription over OACs. Several facts could explain these findings. Firstly, those factors were identified as bleeding risk indicators in several previous studies [13-15]. Secondly, patients with comorbidities mentioned above were usually excluded from clinical trials. The lack of clinical evidence of OACs safe use in specific group of patients might have affected physicians' choice of anticoagulant therapy. In Canadian retrospective review the use of DOACs in the acute and

chronic phase of cancer-related APE prior Hokusai-VTE trail was 1% and 2%, respectively [16]. Thirdly, treatment with LMWH is simple, quite cheap, and convenient, so in case of bleeding complication anticoagulant effect is easily reversible. Our study was conducted before introduction of idarucizumab and andexanet alpha.

The only identified predictor of DOAC prescription over VKA was prior orthopaedics procedure within 3 months. DOACs were firstly approved in VTE prevention after orthopaedics procedures, what may explain our finding. Dault et al. in single-center study reported that DOACs were prescribed more frequently than VKA in patients with VTE, who were < 65 years old, diagnosed with DVT without APE and hospitalized in emergency departments [17]. In PREFER in VTE registry DOACs were used more often in younger subjects without renal impairment and low bleeding risk. In French multicenter registry malignancy and chronic kidney disease were identified as factors associated with non-prescription of DOACs [18].

To the best of our knowledge this is the first study evaluating factors associated with choice of anticoagulant therapy in Polish patients with APE. The limitation of our research is that it was a single-center analysis. Our results need to be confirmed in international multicenter studies. This report is based on the registry, so some data might have been missed due to incomplete patients' documentation. Another limitation might be a small proportion of high-risk APE patients. We did not conduct a survey among doctors working in our hospital regarding their preferences for anticoagulant therapy.

Conclusions

DOACs are the most common form of prolonged therapy in patients with APE. Malignancy, prior major bleeding, serious medical condition and altered mental status are associated with less frequent prescription of OACs than LMWH. Prior orthopaedics procedure within 3 months is a factor of choosing DOACs over VKA in long-term treatment in patients with APE. Type of department and severity of APE is not related to the choice of chronic anticoagulation.

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