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Original article

The use of non-vitamin K antagonists in the treatment of pulmonary thromboembolism: nationwide experience from Serbia 2011-2019

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Abstract

Introduction. Pulmonary embolism (PE) is one of the major cause of hospitalization and morbidity. All studies that compared efficacy and safety of novel oral anticoagulants (NOACs) to vitamin K antagonists (VKAs) in the treatment of PE, have showed that all NOACs were equally effective as VKAs, but superior in safety.

Materials and Methods. This retrospective study included 1095 of patients from the Serbian Academic Pulmonary Embolism Registry (SAPERE) with a confirmed diagnosis of PTE treated in Military Medical Academy Belgrade, Institute for Pulmonary Diseases and Institute for Cardiovascular Diseases Vojvodina, Clinical Center Niš, Kragujevac, Banja Luka, General Hospital Pančevo, Clinical Hospital Center Zemun and Zvezdara.

Results. Of the 863 total patients, NOACs were therapeutic choice in 452 (52.4%) of patients.The most preferred NOAC in Military Medical Academy was Rivaroxaban, which was therapeutic choice in 117 (33.8%) of patients in this institution. On the other hand, VKAs were administered in 103 (88.0%) of patients treated in University Clinical Center Kragujevac. The use of different type of OACs was greatly influenced by the year of PE diagnosis. From 2018, VKAs are drastically less used for the treatment of PE, while the use of Rivaroxaban and Apixaban is slowly rising. The use of OACs was also influenced by the initial treatment with/without thrombolysis, value of Creatinin Clearence (CrCl) on admission, history of previous major or non-major bleeding, presence of active malignancy and HAS-BLAD score value.

Conclusion. In Serbia, VKAs are still predominantly used in the treatment of PE, however, decision of the type of OAC (VKAs or NOACs) used in the treatment of this patient population greatly varies between health institutions from Serbia.

Kew words pulmonary embolism, NOACs, bleeding, malignancies

Introduction

Venous thromboembolism (VTE) holds third place in the spectrum of cardiovascular diseases, with an increasing incidence with aging[1,2]. The most common form of VTE, pulmonary embolism (PTE) is a major cause of hospitalization and morbidity, with a presentation ranging from sudden death to an incidental finding[3]. Recurrence of PTE is also one of the major problems with the highest risk in the first 12 months after the initial event and the rate of recurrence ranging from 8.6-10.1% in the first 6 months[4]. Therefore anticoagulation therapy represents one of the corner stones of the treatment of PTE[5].

In the last decade, non-vitamin K antagonists (NOACs), such as Dabigatran, Rivaroxaban and Apixaban have found their place in the treatment of patients with VTE. Between 2009 and 2013, 6 different studies examined NOACs (Dabigatran, Rivaroxaban, Apixaban and Edoxaban) in a total of 27,023 patients[6]. All studies which compared efficacy and safety of NOACs to VKAs in the treatment of PTE (RE-COVER and RE-COVER II investigated Dabigatran, EINSTEIN-DVT and EINSTEIN-PE, investigated Rivaroxaban and AMPLIFY apixaban) have shown that all of the abovementioned NOACs were equally effective as VKAs, but superior in safety with a lower occurrence of the clinically significant and major bleedings[7-12]. Furthermore, a lot of other beneficial features of NOACs have been demonstrated, indicating a clear advantage of their use over VKAs, such as the rapid onset of action, no need for routine monitoring of coagulation parameters, administration in fixed doses, etc.[13]

With the introduction of NOACs, their use in the treatment of PTE is rapidly increasing, however important

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data from low income countries are still missing. Therefore the aim of this study was to assess the use of NOACs and VKAs in patients with PTE who were treated at various institutions from Serbia from 2011 until 2019.

Methods

Study design

This retrospective study included patients from the Serbian Academic Pulmonary Embolism Registry (SAPERE) with a confirmed diagnosis of PTE treated in Military Medical Academy Belgrade, Institute for Pulmonary Diseases Sremska Kamenica, Clinical Center Niš, Clinical Center Kragujevac, Clinical Center Banja Luka, General Hospital Pančevo, Clinical Hospital Center Zemun and Cardiology Clinic Zvezdara. SAPERE registry was formed in 2011, and for the next several years has been managed by the Military Medical Academy Belgrade. In 2015, Institute for Pulmonary Diseases Sremska Kamenica has started contributing, in 2018 Clinical Center Zemun, Clinical Center Niš, Clinical Center Banja Luka, Clinical Center Kragujevac and finally General Hospital Pančevo in 2019. In the previous period, Clinical Center Zvezdara also contributed to the development of the registry, but currently they are not participating in data collection.

Patient population

This study included 1095 consecutive patients with pulmonary thromboembolism, confirmed using multidetector CT pulmonary angiography (MDCT-PA) enrolled during the period from January 2011 – November 2019. However, the data regarding anticoagulation therapy is missing for 232 patients and therefore these patients were not included in the analysis and the total number of patients was 863. The study was approved by each facility's Institutional Review Board and the permission for conducting the study was obtained. All patients gave written consent and the study was conducted according to the Helsinki Declaration.

Treatment

Risk stratification to low, intermediate and high risk PTE was done according to the latest available ESC guidelines[5]. All patients received standard anticoagulant therapy: intravenous unfractionated heparin (UFH) or a subcutaneous weight-adjusted dose of low-molecular-weight heparin (LMWH), followed by an oral anticoagulant (such as Warfarin or Acenocoumarin) or novel, direct oral anticoagulants: Dabigatran, Rivaroxaban or Apixaban. Edoxaban is not a registered drug in Serbia and therefore it was not used. Patients with high and intermediate-high risk PTE were treated with thrombolytic therapy. The initial use of thrombolytic therapy in intermediate-high risk PTE group was not in accordance with ESC guidelines but was used as a standard practice in included hospitals[14]. The protocol for lytic therapy which was used was in accordance with the ESC guidelines, or protocol for the recombinant tissue plasminogen activator (rTPA) as previously described[14,15]. So called slow-protocol for lytic therapy was used predominantly in intermediate-high risk group of patients. Bleeding events were assessed by using the International Society of Thrombosis and Haemostasis criteria[16,17].

Variables

The following parameters were recorded when the PTE was diagnosed: sex, age, body weight, presence of active cancer (defined as newly diagnosed malignancy or malignancy already treated by surgery, chemotherapy, radiation therapy, hormones, separately or in combination), previous major or non-major bleeding, major bleeding in the first 90 days and creatinine clearance (CrCl) by using Cockcroft-Gault formula[18]. HAS-BLED scor was used for the stratification of bleeding risk[19].
The primary end-points were overall hospital death and PE related death rates. Secondary end-points were the rate of major and fatal bleeding events.

Statistical analysis

Mean ± standard deviations (SD) were used for expression of the continuous variables. We presented categorical variables as numbers and frequency percentages. Continuous variables was compared by using the unpaired t-test or the Mann-Whitney U test. Comparison of categorical variables was done by the $\chi 2$-test or one-way ANOVA test. P value less than 0.05 was considered as statistically significant.

Results

From the total number of 863 patients included in our analysis, 40.1% (346) of patients were enrolled at Military Medical Academy in Belgrade, 13.6%[117] were from University Clinical Center Kragujevac, 11.5%[) were from Institute of Pulmonary Diseases Vojvodina and Clinical Center Novi Sad, 10.3% (89) were from University Clinical Center Niš, 7.2% (62) were from University Clinical Center Banja Luka, 7% (61) patients from Cardiology Clinic Zvezdara in Belgrade, 5.7% (49) patients were enrolled from Clinical Hospital Center Zemun and 4.6% (40) patients from General Hospital Pančevo (Figure 1.). Figure 1. also shows the use of anticoagulants (VKAs and different NOACs) in various health care institutions in Serbia. A large number of patients were treated in Military Medical Academy, where NOACs, as a treatment of choice for PTE, were used more than VKAs. Out of the total number of 863 patients, NOACs were the therapeutic choice in 452 (52.4%) of patients.The most preferred NOAC in Military Medical Academy was Rivaroxaban, which was a therapeutic choice in 117 (33.8%) of patients in this institution. On the other hand, VKAs were administered in 103 (88.0%) of patients treated in the University Clinical Center Kragujevac.

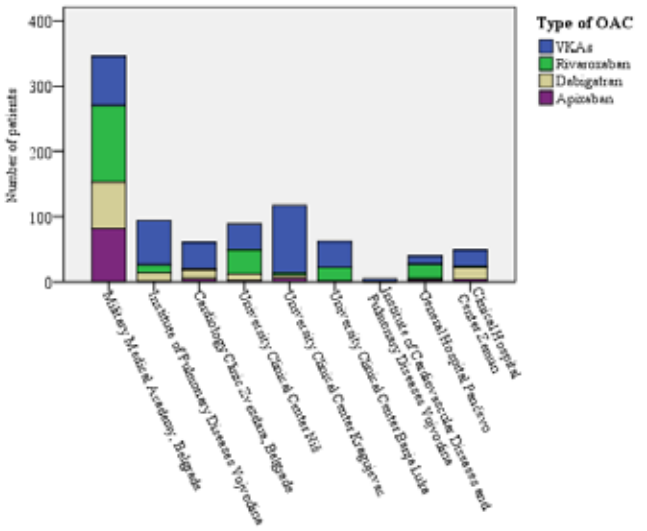

Figure 1. The use of NOACs vs. VKAs in different health institutions in our country

The baseline characteristics of patients are shown in Table 1. Out of the total number of 863 patients, 448 (51,9%) were female. When it comes to relation to gender, there was no significant difference between the use of NOACs and VKAs (p=0.154). The mean age of patients was 62.54 ± 15.44 years, while patients receiving VKAs were significantly older than patients treated with Rivaroxaban (p=0.004). In all groups due to choice of anticoagulation, mean BMI was above the normal range.
Out of the total number of 863 patients (Our study showed that), NOACs were therapeutic choice in 452 (52.4%) of patients, while VKAs were used in 411 patients. Out of NOACs, Rivaroxaban was most frequently used NOAC with 19.7%, followed by Dabigatran with 133 patients and Apixaban was used in 103 patients (9.4%).

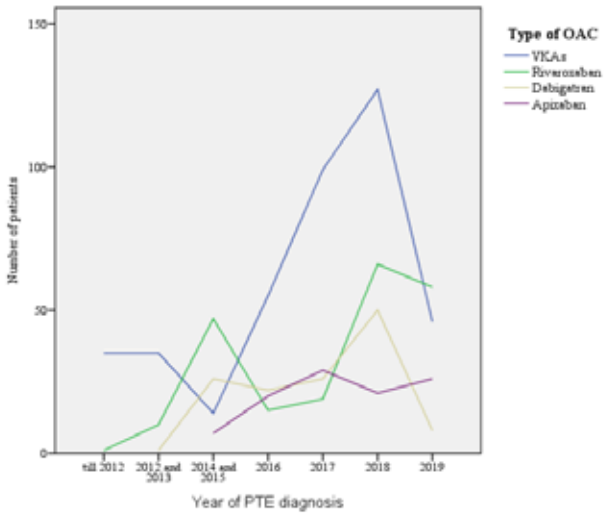

Figure 2. The use of different OACs in relation to the year of PTE diagnosis

The use of a different type of OACs was greatly influenced by the year of PTE diagnosis, with higher use of VKAs until 2013 and a peak in the use of VKAs in 2018, while Rivaroxaban was used more than VKAs in 2014 and 2015 (p<0.000, χ2 test) . From 2018, VKAs have been drastically less used for the treatment of PTE, while the use Rivaroxaban and Apixaban is slowly rising (Figure 2.).

Table 1. Characteristics of the patients at the baseline

			VKAs	Rivaroxaban	Dabigatran	Apixaban	p-value (among 4 groups)
Age (mean±SD)			64.2±15.0#	59.85±15.6	60.63±15.4	63.89±16.2	p=0.002[b]
Sex (male no. %)			190 (45.8)	102 (24.6)	76 (18.3)	47 (11.3)	p=0.154[a]
BMI (mean±SD)			27±4#	28.5±5.4	27.7±5	28±6	p=0.021[b]
Malignancy (yes: numb.%)			40 (48.8)	18 (22)	9 (11.0)	15 (18.3)	p=0.207[a]
Thrombolysis (yes; numb.%)			73 (30.4)	87 (36.3)	40 (16.7)	40 (16.7)	p<0.001[a]
CrCl < 60mL/min/1.73m^2 (yes:numb.%)			137 (56.9)	36 (15.7)	30 (13.0)	27 (11.7)	p<0.001[a]
CrCl < 30mL/min/1.73m^2 (yes; numb.%)			23 (63.9)	5 (13.9)	5 (13.9)	3 (8.3)	p=0.173[a]
Risk of early mortality	High (no.%)		46 (54.8)	23 (27.4)	7 (8.3)	8 (9.5)	p=0.185[a]
	Intermediate-high (no.%)		105 (43.2)	61 (25.1)	43 (17.7)	34 (14.0)	
	Intermediate-low (no.%)		84 (44.0)	54 (28.3)	35 (18.3)	18 (9.4)	
	Low (no.%)		176 (51.0)	78 (22.6)	48 (13.9)	43 (12.5)	
HASBLED score (no.%)		0	100 (11.6)	69 (8.0)	36 (4.2)	25 (2.9)	p=0.018[a]
		1	150 (17.4)	90 (10.4)	51 (5.9)	30 (3.5)	
		2	96 (11.1)	44 (5.1)	37 (4.3)	31 (3.6)	
		3	53 (6.1)	12 (1.4)	7 (0.8)	15 (1.7)	
		4	9 (1.0)	1 (0.1)	2 (0.2)	1 (0.1)	
		5	3 (0.4)	0 (0)	0 (0)	1 (0.1)	
Previous bleeding (yes; numb. %)			15 (28.3)	13 (24.5)	11 (20.8)	14 (26.4)	p=0.001[a]
ASA or other drugs associated with bleeding (yes/numb.%)			94 (43.1)	45 (20.6)	38 (17.4)	41 (18.8)	p=0.001[a]

Statistical test used: [a]-χ2 test; [b]-One-way ANOVA (post hoc Bonferonni); For statistical significance was considered p<0.05; #Statistical significance in relation to Rivaroxaban; ¶ Statistical significance in relation to Dabigatran; ‡ Statistical significance in relation to Apixaban;

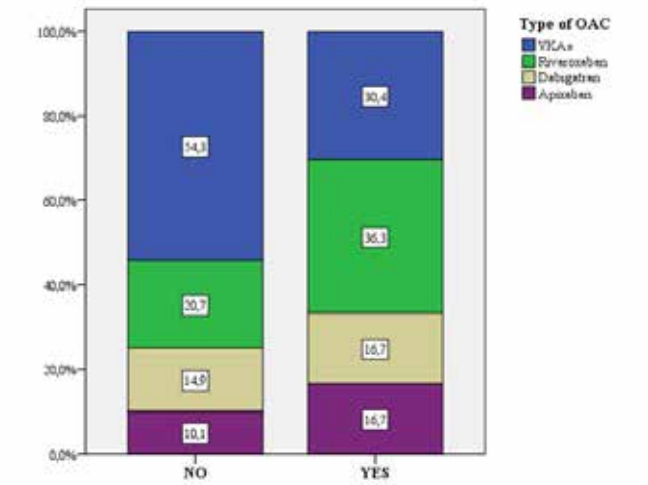

Figure 3. Use of NOACs vs. VKAs in patients initially treated with/without throbolysis

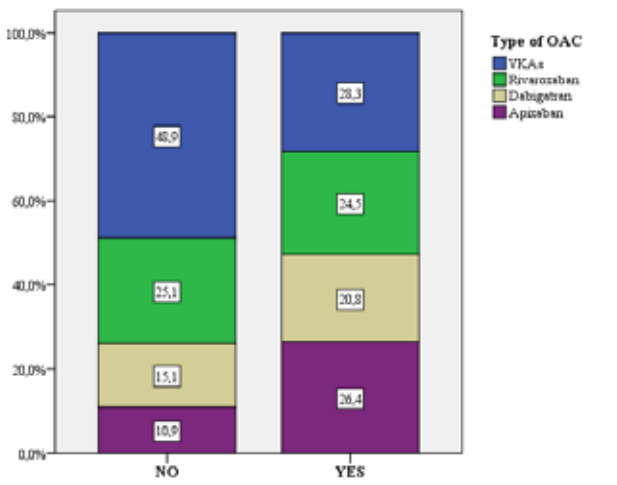

Figure 5. Use of NOACs vs. VKAs in regard to previous major or non-major bleeding

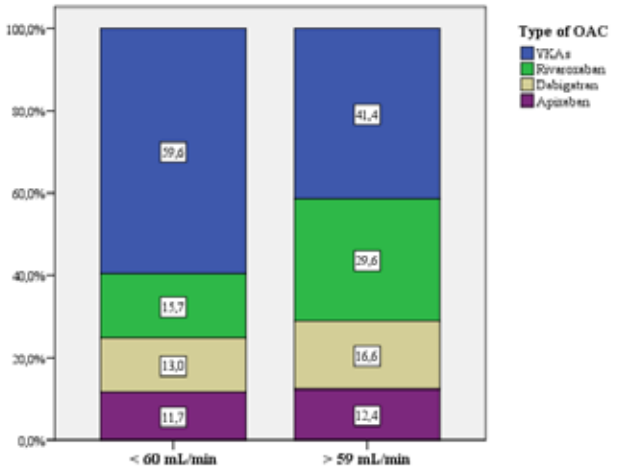

Figure 4. Use of NOACs vs. VKAs in patients with CrCl more or less than 60mL/min/1.73m^2

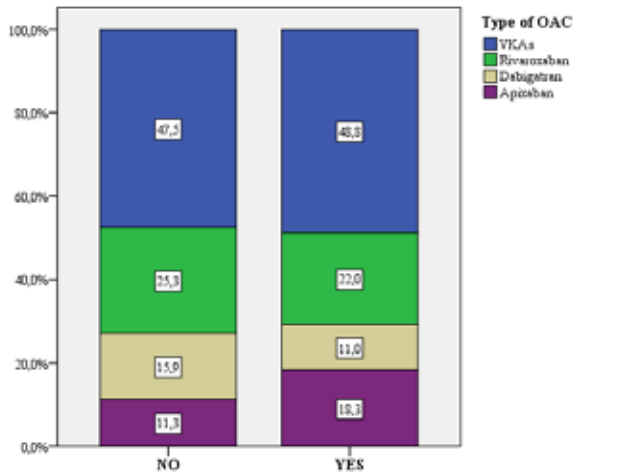

Figure 6. Use of NOACs vs. VKAs in regard to presence of active malignancy

When we classified patients according to the risk of early mortality due to PTE, the frequency of administration of NOAC and VKAs was statistically independent of the early mortality risk categories (p=0.185). In high-risk patients, VKAs was administered in 46 patients, Rivaroxaban in 23 patients, Dabigatran in 7, and Apixaban in 8 patients (Table 1.)

According to the data from our registry, thrombolytic therapy was administered to 240 (27.8%) patients. Statistical analysis revealed that the initial treatment with thrombolytic therapy and the choice of oral anticoagulant treatment were dependent characteristics with more NOACs used in patients that received thrombolytic therapy (p<0.001) (Figure 3).

Out of the total number of 863 patients included in this analysis, CrCl was evaluated on admission in 827 patients. In patients with CrCl <60mL/min/1.73m^2 VKAs were used significantly more than NOACs. Rivaroxaban was the second option for the treatment of those patients with 15.7%, Dabigatran with 13% and Apixaban with 11.7%. In a group of patients with CrCl <30mL/min/1.73m^2 (n=36) VKAs were also the treatment of choice, but without significant difference among gropus. Patients with PTE and CrCl >59 mL/min/1.73m^2 were also more often treated with VKAs, but with much lesser proportion (41.4%), while 29.6% of patients received Rivaroxaban (Figure 4. and Table 1.).

Out of the total number of 863 patients, 218 was using acetil-salicil acid (ASA) or some other drug associated with bleeding risk. In those patients the use of any NOAC drug was significantly higher than VKAs (p=0.001). However, VKAs were still predominant when compared to specific NOAC drug (Rivaroxaban, Apixaban and Dabigatran).

History of previous bleeding was obtained in 859 patients, out of which 53 (6.2%) patients had previous bleeding. In patients with previous major or non-major bleeding, there was an equal distribution of the use of different OACs (Figure 5.).

In 82 patients (9.5%) there was active malignancy present. Among these patients, VKAs were predominantly used in 40 patients, Rivaroxaban in 18 patients, Dabigatran in 9 and Apixaban in 15 patients. In these patients there was no significant difference in the frequency of use of NOACs or VKAs (p=0.207) (Figure 6.).

When we calculated HAS-BLED score for patients in our registry, VKAs were significantly more used among all clusters of patients followed by Rivaroxaban and Dabigatran, while Apixaban was least used in all clusters of patients (Figure 7.).

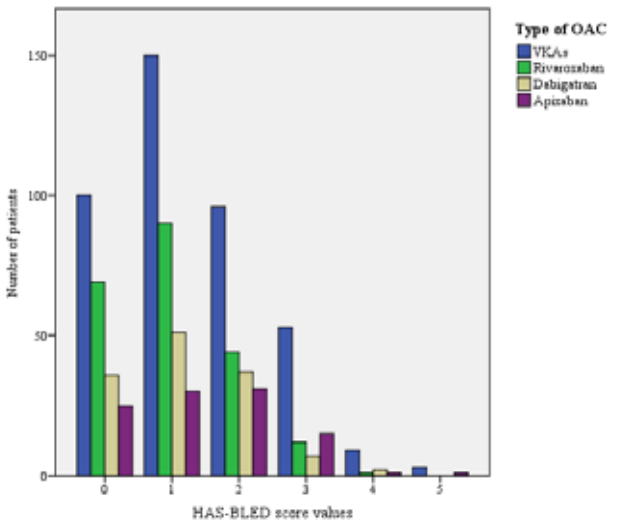

Figure 7. The use of NOACs vs. VKAs in correlation with value of HAS-BLED score

Discussion

The observational studies have a great ability for the assessment of implementing a new therapeutic approaches in an appropriate patient population, such as our, SAPERE registry. In this analysis, we have shown that VKAs are still predominantly used in the treatment of PTE, in low income country, such as Serbia. However, the decision of the type of OAC used (VKAs or NOACs) in the treatment of this patient population greatly varies between institutions, with Rivaroxaban predominantly used in Military Medical Academy and VKAs in Clinical Center Kragujevac. Also, the use of OACs in the treatment of PTE was largely influenced by the year of PTE diagnosis, with the greatest proportion of patients treated with VKAs in the year when SAPERE registry started, but when Rivaroxaban and Dabigatran were registered for PTE treatment in Serbia in 2012, NOACs soon became the treatment of choice and the use of VKAs drastically fell. When other institutions from Serbia started enrolling patients, we realized that their choice for OAC was predominantly VKAs as we can see, with the peak of their use in 2018, alongside Rivaroxaban and Dabigatran.

The real incidence of PTE is hard to estimate, although it has been shown a rising patterne from 24 to 65 cases per 100 000 persons in 25 years (from 1985 to 2009)[3,20-21]. There is an equal distribution of the incidence of PTE between male and female sex, however with a trend towards higher incidence in females, such as in our registry[22]. This higher incidence in females correlates with higher mortality of females after PTE, as shown in the large World Health Organization Mortality Database for Europe[23]. One of the possible explanations lies in the higher risk of thromboembolic events in females, even after full adjustment, as described in the Swedish nationwide study[24]. However, the data regarding influence of female sex on the risk of thromboembolic is not consistent, the data from Danish registries showed that females did not confer a higher risk for thromboembolic risk[25]. However, in a meta-analysis, it has been shown that there were small differences in NOACs efficacy and safety between male and female patients[26].

The choice of initial treatment of patients with PTE is greatly influenced by the risk of early PTE-related mortality, since it correlates with the choice of initial treatment regimen[27]. Based on the presence of early PTE-related mortality risk indicators (hemodynamic instability, PESI/sPESI score, values of cardiospecific enzymes, signs of right ventricular dysfunction), patients with PTE are classified into 1 of 4 categories: high, intermediate-high, intermediate-low and low risk of early mortality[27]. Thus the data from available RCTs and observational studies showed that NOACs are effective and safe as VKAs in treating patients with PTE and at some point even superior, however the data from our registry showed that in our health care institutions the use of VKAs is still dominant among patients with PTE, independently of the early PTE-related mortality risk stratification[28].

The presence of renal dysfunction and chronic kidney disease (CKD) significantly increase the risk of recurrence of VTE and the rate of glomerular filtration has a predictive role in intrahospital all-cause and PTE-related mortality rates, as shown in the previous report from this registry[29,30]. Although the use of NOACs is associated with a less major bleeding events in patients with atrial fibrillation (AF) and CKD, the data from our registry shows that VKAs are still predominantly used in the population of patients with eGFR lower than 60 mL/min/m^2.[31]

The use of thrombolysis and NOACs in the treatment of PTE has been proven safe and effective in moderate and severe PTE[32]. Previously published results also suggest that NOACs can result in shorter hospitalization and favorable first 3-month outcomes[33]. Results from our registry show that after thrombolysis the preferable choice of OAC was NOACs with 69.7% vs VKAs with 30.4%, while the most frequently used NOAC was Rivaroxaban, while Dabigatran and Apixaban were equally distributed in the population of patients with PTE treated with thrombolysis. On the other hand, the data from our registry shows that in patients that were not treated with thrombolysis after PTE, VKAs still hold the majority of OAC choice.

The data on previous bleeding events before PTE also influenced the choice of OAC, with a higher proportion of patients treated with NOACs in whom there was previous bleeding with higher use of Apixaban in this patient population. This coincides with a different meta-analysis that shown that NOACs are safer than VKAs in patients with AF and VTE[34]. Also, higher use of Apixaban in this patient population correlates with lower major and non-major bleeding rates associated with Apixaban use in patients with VTE[35]. In one meta-analysis, Dabigatran and Edoxaban in lower doses, did not show efficacy as other NOACs[36]. Also, concomitant use of other agents associated with bleeding resulted in higher use of NOACs in our registry, however VKAs are still predominantly used in patients receiving drugs that is associated with bleeding. Despite that fact, it is interesting that the use of Apixaban was doubled when we com-

pared presence of other agents that could lead to bleeding vs. without those agents, while the use of Rivaroxaban fell from 26.5% in patients that were not using bleeding agents to 20.6% in patients treated with concomitant bleeding agents. One meta-analysis has suggested that NOACs may be better choice compared to VKAs, when there is an inevitable need for concomitant use of anticoagulant and antithrombotic drug. (37). Even though we are witnessing a higher focus of research on cancer and thromboembolic risk, there is a huge gap in this area. The data from our registry shows that after PTE in cancer patients, VKAs still hold the majority of anticoagulant treatment, followed by Rivaroxaban and Apixaban. The meta-analysis that included key phase III clinical trials showed that by applying NOACs in this population that there recurrent VTE and bleeding events were reduced[38]. Also, it has been shown that NOACs are as effective as low-molecular weight heparin at preventing recurrent VTE, as suggested by Al-Samkari et al.[39]
The data from our registry shows that VKAs are still predominantly used among patients with higher HAS-BLED score, even though previous researches have shown that use of VKAs in these patients is associated with grater risk of major bleeding events[40]. Nevertheless, VKAs are also the treatment of choice in patients with HAS-BLED score less than 3, as we have shown in our registry. These results may be a result of lower income from Serbia, because as we have previously discussed NOACs have far better safety than VKAs, especially in patients that are in at high risk of bleeding.

Conclusions

VKAs are still predominantly used in the treatment of PTE, in low income country, such as Serbia. However, the decision of the type of OAC used (VKAs or NOACs) in the treatment of this patient population greatly varies between institutions from Serbia. The data from our registry shows that NOACs are only predominantly used in the subpopulation of patients that were treated with thrombolysis, patients with the previous history of bleeding, eGFR higher than 59 mL/min/1.73m^2 and in patients that were receiving other drugs that are associated with bleeding. However, in patients that were in higher bleeding risk, assessed by HAS-BLED score, VKAs are still predominantly used.

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Sažetak

Upotreba novih oralnih antagonista u lečenju plućne tromboembolije: iskustva iz Srbije 2011-2019

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Uvod. *Plućna embolija (PE) jedna je od glavnih uzroka hospitalizacije i morbiditeta. Sve studije koje su poredile efikasnost i bezbednost novih oralnih antikoagulanasa (NOAK) u odnosu na vitamin K antagoniste (VKA) u lečenju PE, pokazale su da su svi NOAK podjednako efikasni, ali i bezbedniji u odnosu na VKA.*

Materijal i metode. *Ovo retrospektivno istraživanje obuhvatilo je 1095 pacijenata iz Srpskog Akademskog PE Registra (SAPERE) sa potvrđenom dijagnozom plućne embolije, lečenih u Vojno-medicinskoj Akademiji (Beograd), Institutu za plućne bolesti Vojvodina, Institutu za kardiovaskularne bolesti Vojvodina, Kliničkom centru Niš, Kliničkom centru Kragujevac, Kliničkom centru Banja Luka, Opštoj bolnici Pančevo, Kliničko-bolničkom centru Zemun i Kliničko bolničkom centru Zvezdara.*

Rezultati. *Od ukupno 863 pacijenata, NOAK su bili terapijski izbor kod 452 (52.4%) pacijenata. Rivaroksaban je najviše primenjivan u Vojno-medicinskoj Akademiji i to kod 117 (33.8%) pacijenata. Sa druge strane, VKA su primenjivani kod 103 (88.0%) pacijenata lečenih u Kliničkom centru Kragujevac. Odabir različitih antikoagulanasa veoma je zavisio od godine u kojoj je postavljena dijagnoza plućne embolije. Od 2018.-te godine, VKA su drastično manje primenjivani za lečenje plućne embolije, dok upotreba Rivaroksabana i Apiksabana polako raste. Odabir antikoagulansa zavisio je i od inicijalne primene trombolize, vrednosti klirensa kreatinina na prijemu, podataka o postojanju prethodnog krvarenja, prisustva aktivnog maligniteta i vrednosti HAS-BLED skora.*

Zaključak. *U Srbiji, VKA se još uvek dominantno koriste za lečenje plućne embolije. međutim odluka o odabiru vrste antikoagulantne terapije (NOAK ili VKA) za lečenje ove populacije pacijenata veoma varira među zdravstvenim institucijama u našoj zemlji.*

Ključne reči: plućna embolija, ne-vitamin K antagonisti, krvarenje, maligniteti