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The anticoagulant treatment dilemma in pulmonary embolism associated to cancer

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Abstract

English:

Pulmonary embolism (PE) is defined by the obstruction of pulmonary arteries by thrombi or emboli (malignant, grease, air). Most frequently, thrombi arise from deep veins of lower limbs. Pulmonary embolism is a medical emergency with a high death risk. Early mortality is high, sudden death occurs in about a quarter of the patients. On long term, it can lead to post-embolic pulmonary hypertension and recurrent pulmonary embolia. The high risk of death in acute phase and on long-term depends on the severity of the acute phase, on the recurrence, and on the co-morbidities. PE can be the first manifestation of on occult malignancy, or it may complicate an already diagnosed cancer.
We present a retrospective analysis on PE associated to malignancy, on 106 patients, with classic anticoagulant treatment (low weight molecule heparin and/or antivitamin K agents) or novel oral anticoagulants (NOAC) and compare the early and late mortality associated to PE and anticoagulant treatment. Our observations note a higher percentage of recurrences but significantly lower mortality in patients treated with NOAC as compared to classic treatments.

Keywords

pulmonary embolism • malignancy • recurrent pulmonary embolism • anticoagulant treatment

Dilema tratamentului anticoagulant în trombembolismul pulmonar asociat cancerului

Rezumat

Romanian:

Tromboembolismul pulmonar (TEP) se definește prin obstrucția arterelor pulmonare cu trombi, emboli: tumorali, grăsoși, aer. Trombi sunt proveniți mai frecvent din sistemul venos profund al membrelor inferioare. Tromboembolismul pulmonar este o urgență medicală cu risc de deces. Mortalitatea precoce este mare, aproximativ un sfert din pacienți mor subit, pe termen lung poate determina hipertensiune pulmonară tromboembolică; embolie pulmonară recurentă. Riscul crescut de mortalitate atât în faza acută cât și pe termen lung, este dependent atât de severitatea formei acute, recurența emboliei cât și de afecțiunile asociate. Embolia pulmonara poate fi prima manifestare a unei malignitati oculte subiacente sau poate reprezenta o complicatie a unei malignitati cunoscute.
Prezentăm o analiză retrospectivă a cazurilor de TEP asociat cancerului pe un grup de 106 pacienți, tratați cu schema clasică de anticoagulant (heparină cu greutate moleculară mică și/sau antagoniști de vitamina K) sau cu anticoagulante orale noi (NOAC) pentru a compara mortalitatea precoce și tardivă asociată TEP și tratamentului anticoagulant. Observațiile noastre constată mai multe recurențe dar o mortalitate semnificativ scăzută la pacienții tratați cu NOAC față de terapia clasică.

Cuvinte-cheie

trombembolism pulmonar • malignitate • trombembolism recurent • anticoagulante

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General aspects

The main cause of pulmonary embolism (PE) is the deep vein thrombosis of the lower limbs, in approximately 70% of patients diagnosed with PE (1,2).
PE can be classified as "induced" or "non-induced" (3,4):

- "Induced" PE – following surgery, prolonged immobilization, trauma, pregnancy, malignancies.
- "Non-induced" PE – in all other situations (3,4).

The risk for PE is greatest in the first 12 months after a diagnosis of malignancy, afterwards the risk decreases progressively, being similar to general population after about 10 years. The high risk for PE in the first 12 months is associated to treatments: chemotherapy and surgery (5,6). Based on the higher risk for PE in patient treated with chemotherapy as compared to healthy population, Khorona AA et al proposed a score to evaluate this risk (Table 1). The score comprises 5 elements, for each 0 to 2 points can be allocated. With a score of 0, the risk for PE is less than 1%; a score of 1-2 points is associated to a 2% risk, and a score equal to or higher than 3 is associated to a risk of 7% (7).
Acute phase anticoagulant treatment aims improvement of symptoms, preventing the thrombosis progression, preventing death (8). Long term anticoagulant treatment aims prevention of thrombo-embolic recurrences and of post-embolic pulmonary hypertension (3).
In patients with PE and associated malignancies it is preferred the use of low molecular weight heparins (LMWH) in the first 3-6 months after the acute event, because their superiority in preventing recurrences as compared to antivitamin K agents (AKA), with a similar risk for bleeding and mortality. Ongoing anticoagulation after 6 months since the acute event is important, considering the 3 times higher risk for thrombo-embolic recurrences in this patients' vs general population (9,10).
Louzada designed a score aiming to help stratify the risk of recurrence in patients with a first PE event and associated malignancy (6,9,10) (Table 2).

Table 1. Score for evaluation of the risk for PE associated to chemo-therapy (adapted after 7)

Variables	Points
Malignancy localization - Very high risk (stomach, pancreas) - High risk (lung, lymphoma, gynecologic area, urologic area	 2 1
Pre-chemotherapy thrombocytes ≥ 350 x 10^9/ L	1
Hemoglobin < 10 g/dl, or use of erythropoietin growth factors	1
Pre-chemotherapy leukocyte count > 11 x 10^9 / L	1
Body mass index ≥ 35 kg/ m^2	1

After the acute event, anticoagulant treatment should be continued until the malignancy is considered cured. It should also be considered the risk for recurrence, the risk for bleeding, and the patient's preferences (3,12).
The recurrence of thrombo-embolic events is associated to increased mortality on long term. Some studies suggest that an increased dose of LMWH is needed in cancer patients at the second thrombo-embolic event, in order to decrease mortality (13).
Novel oral anticoagulants (NOAC – apixaban, rivaroxaban, edoxaban, dabigatran) were directly compared in a study, the data suggesting similar efficiency on the recurrence risk and mortality. This study also proved the superior safety profile of edoxaban and apixaban, both having the lowest risk for bleeding (14,15).
Current guidelines recommend the treatment scheme in table 3 for the long term (first 3 months) treatment of deep vein thrombosis or PE associated to cancer.
In cancer patients, LMWH are preferred over AKA because there is evidence to support their higher efficiency (16,17). There is also evidence of a higher risk for recurrence in oncology patients treated with AKA. Sometimes it is difficult to maintain a therapeutic interval in cancer patients on AKA. LMWH are preferred in patients with difficulties in oral drugs administration (ex: vomiting) and are easier to adjust in case of invasive interventions and in patients developing thrombocytopenia. In patients with venous thromboembolism (VTE) and cancer, the risk for recurrence is lower in patients treated with LMWH than AKA.
The comparative risk for VTE recurrence in patients treated with NOAC versus LMWH was not assessed, but based on

Table 2. Risk score for PE recurrence in malignant patients and previous PE (modificed after 10,11)

Parameter	Points	Clinical probability	Points
Female gender	+1	Low (≤ 0)	-3 to 0
Lung cancer	+1		
Breast cancer	-1	Increased (≥1)	1 to 3
TNM stage 1			
Histroy of venous thrombosis			

Table 3. Indications of anticoagulant treatment in patients with deep vein thrombosis or PE associated to cancer (14).

Anticoagulant treatment	Indication class
1. LMWH LMWH preferred over AKA	2B
2. AKA	2B
3. NOAC (rivaroxaban, apixaban, edoxaban, dabigatran)	2C

indirect comparisons, LMWH may be more efficient than NOAC in patients with VTE and cancer (16).
The VTE risk reduction was not directly compared between various NOAC, but based on indirect comparisons, the effect is similar in all NOACs (18). The risk for bleeding, and especially brain bleeding, is lower with NOAC than with AKA (18,19,20,21,22).
In the absence of direct comparisons between NOACs and with no convincing evidence that a NOAC is superior to another, there is no specific preference for a particular drug.
The followings are the risks for recurrence of VTE:

- VTE induced by non-surgical factor (estrogenic treatments, pregnancy) – estimated recurrence at 5 years is 15%.
- Unprovoked VTE, also called idiopathic (in the absence of criteria for induced VTE or presence of cancer) – estimated recurrence at 5 years is 30% (23,24).
- VTE associated to cancer – annual risk for recurrence is 15%, 5 years recurrence risk was not estimated due to high cancer mortality (25,26).

Men have a higher risk for recurrence of about 75% (1.75 times) as compared to women. Patients with positive D-dimers at 1 month after stopping anticoagulant treatment have a recurrence risk almost double as compared to those with negative D-dimers (14).
In patients with deep vein thrombosis or PE and active cancer, with no increased risk for bleeding, long term anticoagulant therapy, over 3 months, is recommended (with no scheduled stopping date).
Limited data are available regarding the subsegmental PE, but there is enough evidence to show the efficiency and safety of anticoagulant therapy in patients with massive PE (obstruction of pulmonary artery bifurcation or in one of the main pulmonary arteries) or lobar PE. This evidence can justify the use of the same therapy also in patients with subsegmental PE. The risk for progressive or recurrent PE is high enough to justify anticoagulation in patients with subsegmental PE (27,28,29).
Some studies suggest that there were no records of recurrent subsegmental PE in patients in whom proximal PE was excluded and were not receiving anticoagulants (27,28). Still, another retrospective analysis claims that subsegmental PE had a similar risk for recurrence in the first 3 months of anticoagulant treatment as in patients with higher level PE (30).
There is moderate quality data suggesting that LMWH are more efficient than AKA in patients with VTE and cancer. Consequently, the switch to LMWH with complete dose is often made in case of inexplicable recurrent VTE in patients on AKA or NOAC. If the recurrence appears in patients on LMWH, the dosage of LMWH can be increased. If the dose was diminished before (ex: with 25% after 1 month of treatment), it is indicated to resume the initial dose. If the patient has a complete LMWH dose, this can be increased with 25%. Also, if the patient receives LMWH once daily, switch to twice daily can be made (14).
The most important intrinsic risk factor for recurrent VTE during anticoagulant treatment is active cancer, an inexplicable recurrence indicating an undiagnosed underlying disease. One of the causes for recurrent VTE in cancer patients is cancer treatment (chemotherapy, surgery) (14).
A retrospective observational study noticed an acceptable recurrence risk (8.6%) and major bleeding (1.4%) over 3 months of follow-up in 70 cancer patients with recurrent VTE under anticoagulant treatment, who either switched from AKA to LMWH (23 patients), either increased LMWH dose with 25% (47 patients) (13). If there is no way to precent VTE recurrence under anticoagulant treatment, and the intensity of anticoagulation cannot be increased because of the risk of bleeding, a filter can be inserted in vena cava to prevent PE (31). Still, there is insufficient evidence to support the benefit of a vena cava filter under these circumstances, and AT10 panel considers this as a last resort option.
In patients with recurrent VTE under therapeutic AKA dosage or NOAC, it is suggested to switch to LMWH at least temporarily (indication 2C).
Long term LMWH treatment is preferred for VTE and cancer, but NOAC are no longer considered inferior to AKA (14).
Expertise for choosing one NOAC over another exists for non-cancer patients. In cancer patients, there is insufficient data to justify the choice of a specific NOAC, or the choice of a NOAC over AKA, because of the following:

- There are no direct comparisons of different NOACs.
- NOAC were not compared to AKA in large series of patients with VTE and cancer.
- Indirect comparisons didn't give convincing results for the selection of a certain class of anticoagulants.

Clinical study

The aim of the study was the direct comparison between different NOACs and the comparison between NOAC and classic anticoagulant treatments (LMWH, AKA) in terms of efficiency, bleeding risk and recurrence.
In our study we included 106 patients with PE and active cancer with different localizations and clinical stages. Fifty-eight patients (54.72%) were women. Patients were between 29 and 94 years old, most of them between 61 and 81 years (66.04%); mean age was 69.22 years ± 9.47. Most patients (56.60%) were living in urban areas.
Staging was noted in 79 patients (74.53%), most of them in stage 4 (58.23%) (Table 4). In 27 patients, PE was the first manifestation of malignancy.

In most patient score Khorana 1-2 was registered (65.09%), and score 3 in 26.42%.

In most cases, localization of PE was in lobar arteries (66.98%); in 22.64% PE in main arteries was noted (Table 5).

PE as initial diagnosis (at the same time with the diagnosis of cancer) was recorded in 35.85% of cases, followed by post-chemotherapy PE (26.42%) and post-surgery PE (18.87%).

In our study most patients had a unique site of cancer (89.62%), the most frequent was the lung (26.41%). Uro-genital sites were 23.58%, and digestive sites 22.64%.

Classic anticoagulant treatment (LMWH associated or not with AKA) was administered in59.43% of patients, and NOAC (apixaban, rivaroxaban and dabigatran) in 40.57% (p=0.006) (Table 6).

We noticed in our study that the prevalence of complications increases with the more advanced stage, with 0% in stage 1 and 21.74% in stage 4.

We didn't record any bleeding or recurrence in stage 1 patients. The highest percentage of bleedings was recorded in patients in stage 4 (13.04%), but insignificantly higher than stages 2 or 3 (11.11%, p=0.875, and respectively 9.52%, p=0.682).

Table 4. Stage distribution (106 patients)

Stage	No	%
1	3	3.80
2	9	11.39
3	21	26.58
4	46	58.23
Total	79	100

Table 5. Distribution of PE localization

	No	%
PE in lobar arteries	71	66.98
PE in main pulmonary arteries (massive)	24	22.64
PE in segmental/subsegmental arteries	11	10.38

Table 6. Distribution of PE treatment

	No	%
Classic treatment	**63**	**59.43**
LMWH	34	32.08
LMWH + AKA	29	27.36
NOAC treatment	**43**	**40.57**
Apixaban	29	27.36
Rivaroxaban	9	8.49
Dabigatran	5	4.72

PE complications were recorded in 21 patients (19.81%): bleeding consisted in 12.26%, and recurrences 7.55%.

Recurrences were noted only in stages 3 and 4 (4.76% vs 8.70%, p=0.572).

The risk for complications in patients in stages 3 and 4 is 2.3 times higher than in patients in stages 1 and 2 (RR=2.328, 95%CI: 0.3349-16.1859, z=0.854, p=0.393). The risk for bleeding is 1.4 times higher (RR=1.433, 95%CI: 0.1966-10.4405, z=0.355, p=0.723), and the risk for recurrences is 1.9 times higher (RR=1.941, 95%CI: 0.1146-32.8717, z=0.459, p=0.646).

Most complications were recorded in cancer patients with PE in lobar arteries (21.31%), but without significant difference as compared to PE in main arteries od segmental arteries (16.67%, p=0.633, respectively 18.18%, p=0.115).

The risk for complications in cancer patients with PE in lobar arteries is 1.3 times higher than patients with PE in main arteries (RR=1.268, 95%CI: 0.4658-3.4497, z=0.464, p=0.643), and 1.2 times higher than those with PE in segmental arteries (RR=1.162, 95%CI: 0.3068-4.4012, z=0.221, p=0.825).

The prevalence of complications was highest in patients with PE at initial diagnosis (18.42%), not significantly different from PE post-chemotherapy (14.29%, p=0.659), PE post-chemotherapy + post-surgery (11.11%, p=0.604), and PE post-surgery (15%, p=0.745). Bleedings were more frequent in patients with PE post-chemotherapy (14.29%), but also present in patients with PE post-chemotherapy + post-surgery (11.11%, p=0.811), PE post-surgery (10%, p=0.611), and PE as initial diagnosis (1.16%, p=0.896) (Table 7).

In cancer patients, bleeding were more frequently encountered in patients with a classic treatment, but without significant differences (15.87% vs 6.98%, p=0.173).

In patients with classic treatment the bleeding risk is 2.3 times higher as compared to NOAC treatment (RR=2.275, 95%CI: 0.665-7.788, z=1.309, p=0.190).

Bleeding risk in cancer patients treated with LMWH is 3.4, respectively 2.1 times higher than patients treated with apixaban, and rivaroxaban respectively (RR=3.412, 95%CI: 0.786-14.812, z=1.638, p=0.101, respectively RR=2.118, 95%CI: 0.303-14.806, z=0.756, p=0.450).

Bleeding risk in cancer patients treated with rivaroxaban is 1.4 times higher as compared to patients treated with LMWH + AKA (RR=1.403, 95%CI: 0.321-6.130, z=0.450, p=0.653).

Table 7. Prevalence of bleeding correlated to treatment (classic/NOAC)

Treatment	Bleeding risk
Classic treatment	15.87%
1. LMWH	23.53%
2. AKA	6.9%
NOAC	6.9%
1. Apixaban	6.9%
2. Rivaroxaban	11.11%
3. Dabigatran	0

In our study group, the Louzada score ranged between 1 and 3 in most patients (62.26%0).

Recurrences were recorded only in patients with post-surgery PE and initial PE (5% vs 5.26%, p=0.966) (Table 8).

Recurrences were not seen in patients with segmental PE, and the percentage of recurrences was insignificantly higher in lobar arteries PE versus main arteries PE (9.86% vs 4.17%, p=00.388).

The risk of recurrences in cancer patients with lobar arteries PE is 2.4 times higher than in patients with PE in the main arteries (RR=2.366, 95%CI: 0.3066-18.2628, z=0.826, p=0.409), and 2.5 times higher than those with PE in segmental arteries (RR=2.500, 95%CI: 0.1525-40.9791, z=0.642, p=0.521).

The recurrences were more frequent in patients on classic anticoagulant treatment, without significant differences (9.52% vs 4.65%, p=0.354).

We didn't record any recurrence in patients treated with apixaban.

The risk for recurrence in patients treated with rivaroxaban, and dabigatran respectively, is 1.3, respectively 2.3 times higher than patients on LMWH (RR=1.259, 95%CI: 0.148-10.710, z=0.211, p=0.833, respective RR=2.267, 95%CI: 0.289-17.772, z=0.779, p=0.436).

The risk for recurrence is not higher in patients treated with rivaroxaban as compared to those treated with LMWH + AKA (RR=1.074, p=0.948), and the risk for recurrence in patients treated with dabigatran is 1.9 times higher than patients on LMWH + AKA (RR=1.933, 95%CI: 0.248-15.087, z=0.629, p=0.529).

In our group, 60 patients died (56.60%), with a higher percentage of late mortality (17.92% vs 38.68%, p<0.001) (table 9).

In patients in stages 1 and 2, mortality was 33.33%, significantly lower than in patients in stages 3 and 4 (73.13%, p=0.007); early deaths were 16.67%, and 22.39% respectively (p=0.659), and late deaths were 16.67%, and 40.75% respectively (p=0.030).

Most fatalities occurred in cancer patients with PE in main arteries (66.67%), but insignificantly more than in patients with lobar or segmental arteries PE (52.11%, p=0.217, and 63.64%, p=0.863, respectively).

Early deaths were registered in 27.27% of patients with PE in segmental arteries, just a little higher than PE in lobar or main arteries (15.49%, p=0.337, and 20.83%, p=0.678 respectively).

Late deaths were recorded in 45.84% of patients with PE in the main arteries, slightly higher than in patients with PE in lobar or segmental arteries (36.62%, p=0.426, respectively 36.36%, p=0.605) (table 10).

Among cancer patients with classic anticoagulant treatment, mortality was significantly higher than in patients on NOAC (69.84% vs 37.21%, p<0.001). This difference was noted also in early mortality (28.57% vs 2.33%, p<0.001), but not in the late mortality (41.27% vs 34.88%, p=0.509).

No early death was registered in patients treated with apixaban and dabigatran.

In comparison to cancer patients treated with apixaban, the death risk is 2.4 times higher in patients treated with LMWH (RR=2.369, 95%CI: 1.328-4.227, z=2.921, p=0.004), and it is 2.1 times higher in those treated with LMWH + AKA (RR=2.111, 95%CI: 1.155-3.860, z=2.427, p=0.015).

The death risk in patients treated with rivaroxaban is 1.2 times higher than in patients on LMWH + AKA (RR=1.187, 95%CI: 0.766-1.839, z=0.768, p=0.443), but the risk is not higher in comparison to those treated with LMWH only (RR=1.058, 95%CI: 0.707-1.583, z=0.273, p=0.785).

Early death risk is 4.2 times higher in cancer patients treated with LMWH as compared to patients treated with rivaroxaban (RR=4.235, 95%CI: 0.645-27.811, z=1.503, p=0.133), and 1.6 times higher in patients treated with rivaroxaban as compared to those on LMWH + AKA (RR=1.611, 95%CI: 0.165-15.768, z=0.410, p=0.682).

Table 9. Lethality index

	No	%
Earl death (< 30 days)	19	17.92
Late death (> 3 months)	41	36.68
Total	60	56.60

Table 8. Prevalence of recurrences according to treatment: classic/ NOAC

Treatment	Risk for recurrence
Classic treatment	**9.52%**
1. LMWH	8.82%
2. AKA	10.34%
NOAC	**4.65%**
1. Apixaban	0
2. Rivaroxaban	11.11%
3. Dabigatran	20%

Table 10. Lethality index in correlation with the anticoagulant treatment, classic vs NOAC

Treatment	Early death	Late death	Total
Classic treatment	28.57%	41.27 %	69.84%
1. LMWH	47.06 %	26.47%	73.53%
2. AKA	6.90%	58.62%	65.52%
NOAC treatment	2.33 %	34.88%	37.21%
1. Apixaban	0%	31.03%	31.03%
2. Rivaroxaban	11.11%	66.67%	77.78%
3. Dabigatran	0%	0%	0%

Late death risk is 1.2 times higher in patients treated with apixaban as compared to those on LMWH (RR=1.172, 95%CI: 0.538-2.557, z=0.400, p=0.689), and 2.5 times higher in those treated with rivaroxaban (RR=2.519, 95%CI: 1.218-5.206, z=2.493, p=0.013).
Late death risk is 1.9 times higher in patients treated with LMWH + AKA as compared to those on apixaban (RR=1.889, 95%CI: 1.013-3.521, z=2.001, p=0.045), while in those treated with rivaroxaban there is a similar late death risk as in patients on LMWH + AKA (RR=1.137, 95%CI: 0.6545-1.979, z=0.455, p=0.649).
Total mortality (early and late) in cancer patients treated with classic anticoagulant treatment was significantly higher than in patients treated with NOAC (69.84% vs 37.21%, p<0.001). The same was noted for early mortality (28.57% vs 2.33%, p<0.001), while for late deaths the difference was not significant (41.27% vs 34.88%, p=0.509).
In comparison to cancer patients on NOAC, in patients on classic treatment the death risk is 1.9 times higher (RR=1.877, 95%CI: 1.2323-2.8590, z=2.933, p=0.003), the risk for early death is 12.3 times higher (RR=12.286, 95%CI: 1.7030-88.6299, z=2.488, p=0.013), and the risk for late death is 1.2 times higher (RR=1.183, 95%CI: 0.7150-1.9574, z=0.654, p=0.513).

Discussion

In patients with pulmonary embolism and associated malignancies, anticoagulation with LMWH is preferred for the first 3-6 months after the acute event, due to the observed superiority on preventing the thromboembolic recurrences as compared to AKA, without an inferiority in respect to the risk for bleeding and mortality. Continued anticoagulation after 6 months since the acute event is important, considering the risk for thromboembolic recurrences, up to 3 times higher than general population (9,10).
The risk for recurrence of VTE in patients treated with NOAC as compared to LMWH was not evaluated, but based on indirect observations, LMWH could be more efficient than NOAC in patients with VTE and cancer (16).
If an inexplicable recurrent VTE was noted in patients on correct AKA dosage or on NOAC, a switch can be made to complete dose of LMWH. If the recurrence of thromboembolic event occurred in patients treated with LMWH, the dose can be increased. If the LMWH dose was reduced previously (ex: with 25% after 1 month of treatment), it is indicated to resume to the initial dose. If the patients were on a full LMWH dose, this can be increased with approximately 25%. If the patient was treated with once-daily LMWH, it can be switched to a twice-daily scheme (14).
Expertise for choosing one NOAC over another exists for non-cancer patients. In cancer patients, there is insufficient data to justify the choice of a specific NOAC, or the choice of a NOAC over AKA, because of the following:

- There are no direct comparisons of different NOACs
- NOAC were not compared to AKA in large series of patients with VTE and cancer
- Indirect comparisons didn't give convincing results for the selection of a certain class of anticoagulants.

Conclusions

1. In our study, the PE complications were recorded in 19.81%, with bleeding representing 12.26%, and recurrences 7.55%.
2. The prevalence of complications increased with the higher cancer stage, from 0% in stage 1 to 21.74% in stage 4.
3. We didn't record any bleeding or recurrence in patients in stage 1. Bleeding was recorded mostly in patients in stage 4 (13.04%).
4. Recurrences were registered only in stages 3 and 4
5. Similar prevalence of complications was recorded in patients with initial PE (18.42%), in post-chemotherapy PE (14.29%), postchemotherapy + post-surgery PE (11.11%), and post-surgery PE (15%).
6. The risk for bleeding in cancer patients on classic treatment is 2.3 higher than in patients on NOAC.
7. In our study, embolic recurrences were recorded only in patients with post-surgery PE and initial PE.
8. There were no recurrences in patients with PE in segmental arteries, and the percentage of recurrences was similar in PE in lobar arteries and PE in main arteries.
9. Embolic recurrences were slightly more frequent in patient on classic anticoagulant treatment.
10. We didn't record any recurrence in patients treated with apixaban.
11. In comparison with LMWH treatment, the risk for recurrence was 1.3 times higher for rivaroxaban, and 2.3 times higher for dabigatran.
12. The recurrence risk is similar for patients treated with rivaroxaban and for thos treated with LMWH + AKA, while the risk of recurrence in patients treated with dabigatran is 1.9 times higher than those on LMWH + AKA.
13. In our group, 60 patients died (56.60%), with a higher percentage of late deaths.
14. Regarding the site of PE, there were similar percentages of mortality in all groups, with a slighly higher percentage in patients with main arteries PE.
15. Mortality was significantly higher in patients on classic anticoagulant treatment as compared to patients treated with NOAC.
16. Overall mortality (early and late) was significantly higher in patients treated with classic anticoagulant therapy as copared to NOAC.

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Informed Consent Statement

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Data Availability Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Dalen JE. Pulmonary embolism: what have we learned since Virchow? Natural history, pathophysiology, and diagnosis. Chest 2002; 122:1440-56.
2. Keron C. Natural history of venous thromboembolism. Circulation 2003;107:122-30.
3. Konstantinides SV, Torbicki A, Agnelli G et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Endorsed by the European Respiratory Society (ERS). Eur Heart J 2014; 35, 3033 -3080.
4. Goldhaber SZ. Pulmonary Embolism. In: Bonow RO, Mann DL, Zipes DP, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Philadelphia , 9th Ed. 2012;1679-1695.
5. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cance-associated venous thrombosis. Blood 2013; 122(10):1712-1723.
6. Ginghină C. Mic Tratat de Cardiologie, Ediția a II-a; Editura Academiei Române, București 2017.
7. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008; 111(10): 4902-4907.
8. Eduard A. Cardiologie Clinică , Editura: Medicala Callistro 2015; p 721-737.
9. Zamrano JL, Lancellotti P, Munoz DR et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. Eur Heart J 2016; 37, 2768-2801.
10. Louzada ML, Carrier M, Lazo-Langner A, et al. Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. Circulation 2012, 126(4):448-454.
11. Petriș A., Țînț D., Tatu-Chițoiu G., Petrescu L., Tromboembolismul pulmonar în situații speciale. Editura pim Iași 2017 ; p 197-207.
12. Akl EA, Vasireddi SR, Gunukula S, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev 2011, (6): CD006649.
13. Carrier M, Le Gal G, Cho R, et al. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. J Thromb Haemost 2009, 7(5):760-765.
14. Kearon C, Akl EA, OrnelasJ, et al. antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149(2):315-352
15. Mantha S, Ansell J. Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatmentof acute venous thromboembolism. J Thromb Thrombolysis 2015;39(2):155-156.
16. Carrier M, Cameron C, Delluc A, Castellucci L, Khorana AA, Lee AY. Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis. Thromb Res. 2014;134(6):1214-1219.
17. Bochenek T, Nizankowski R. The treatment of venous thromboembolism with low-molecular-weight heparins. A meta-analysis. Thromb Haemost. 2012;107(4):699-716.
18. Castellucci L.A, Cameron C, Le Gal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. JAMA.2014;312(11):1122-1135.
19. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR.Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood. 2014;124(12):1968-1975.
20. Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. Blood.2014;124(15):2450-2458.
21. Bloom BJ, Filion KB, Atallah R, Eisenberg MJ. Meta-analysis of randomized controlled trials on the risk of bleeding with dabigatran. Am I Cardiol. 2014;113(6):1066-1074.
22. Touma L, Filion KB, Atallah R, Eberg M, Eisenberg MJ. A meta-analysis of randomized controlled trials of the risk of bleeding with apixaban versus vitamin K antagonists. Am J Cardiol. 2015;115(4):533-541.

23. Boutitie F, Pinede L, Schulman S, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. BMJ. 2011;342:3036
24. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica. 2007;92(2):199-205.
25. Prandoni P, Lensing AWA, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med.1996;125(1):1-7.
26. Palareti G, Legnani C, Lee A, et al. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignancy. Thromb Haemost. 2000;84(5):805- 810.
27. Carrier M, Righini M, Le Gal G. Symptomatic subsegmental pulmonary embolism: what is the next step? J Thromb Haemost.2012;10(8):1486-1490
28. Stein PD, Goodman LR, Hull RD, Dalen JE, Matta F. Diagnosis and management of isolated subsegmental pulmonary embolism: review and assessment of the options. Clin Appl Thromb Hemost. 2012;18(1):20-26.
29. Le Gal G, Righini M, Parent F, van Strijen M, Couturaud F. Diagnosis and management of subsegmental pulmonary embolism.J Thromb Haemost. 2006;4(4):724-731.
30. den Exter PL, van Es J, Klok FA, et al. Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism. Blood. 2013;122(7):1144-1149; quiz 1329.
31. Farge D, Debourdeau P, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. J Thromb Haemost.2013:11(1):56-70.