Vascular Pharmacology 120 (2019) 106567

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Extended treatment with non-vitamin K antagonist oral anticoagulants versus low-molecular-weight heparins in cancer patients following venous thromboembolism. A pilot study

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ARTICLE INFO

Keywords:
Cancer
Venous thromboembolism
Bleeding
Low-molecular-weight heparin
Non-vitamin K antagonist oral anticoagulants

ABSTRACT

Background: Low-molecular-weight heparins (LMWH) are the drug of choice for treatment of cancer-associated thrombosis (CAT), however non-vitamin K antagonist oral anticoagulants (NOAC) seem to be a reasonable alternative. We investigated the safety and efficacy of NOAC versus LMWH in patients with a history of CAT.
Methods: In a prospective cohort study 128 consecutive patients with active cancer who experienced CAT were enrolled following LMWH treatment for ≥3 months. Symptomatic recurrent venous thromboembolism (VTE), bleeding and death were recorded during follow-up.
Results: 65 (50.8%) patients were switched to NOAC and 63 (49.2%) continued with LMWH. During a median follow-up of 17 (interquartile range, 15–21) months, recurrent VTE was observed in 6 (9.2%) patients on NOAC and in 12 (19.0%) on LMWH (hazard ratio [HR] 0.44, 95% confidence interval [CI] 0.16–1.16). The rate of major bleeding was 9.2% and 4.8%, respectively (HR 2.00, 95% CI 0.50–8.00). The median time to bleeding was shorter in patients on NOAC (3 [2.25–5.5] months) versus on LMWH (9 [6.5–13.0] months). The mortality rates were similar in both groups (15.4% versus 15.9%, respectively, HR 0.76, 95% CI 0.32–1.84).
Conclusions: In patients following CAT, extended treatment with NOAC, compared with LMWH, appears to be associated with similar effectiveness and safety.

1. Introduction

Patients with cancer are at a 7 fold higher risk of venous thromboembolism (VTE) compared with non-oncological patients [1,2]. Venous thromboembolic complications may affect up to 20% of hospitalized cancer patients [3]. The increased risk of VTE is associated with some types of cancer (mostly involving the pancreas, brain, stomach, kidney, lung or lymphoma, multiple myeloma), initial period after cancer diagnosis, the presence of distant metastases, chemotherapy, hormonal therapy, the use of anti-angiogenic agents, patients' age and comorbidities [2,4,5]. After cancer progression, VTE is the second leading cause of death in cancer patients [6,7].

Low-molecular-weight heparins (LMWH) remain the treatment and prophylaxis of choice in cancer-associated thrombosis (CAT) [8–13]. This strong recommendation results from randomized studies in which LMWH have been shown more effective than coumarin derivatives in reducing the risk of recurrent VTE without increasing the risk of bleeding [14,15]. In a seminal study, patients with cancer and symptomatic VTE randomly assigned to 6 months therapy with dalteparin had twice lower risk of recurrent VTE (hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.3–0.77, P = 0.002) and similar rate of major bleeding (6% versus 4%, P = 0.27) as compared with warfarin with target INR of 2.5 [14]. However, during the 6-month study period the use of LMWH did not influence overall mortality. Most experts suggest that LMWH should be considered for first 3–6 months. However, current guidelines do not determine precisely the time and the type of

Abbreviations: CAT, cancer-associated thrombosis; CI, confidence interval; DVT, deep-vein thrombosis; HR, hazard ratio; IQR, interquartile range; ISTH, International Society on Thrombosis and Hemostasis; LMWH, low-molecular-weight heparins; NOAC, non-vitamin K antagonist oral anticoagulants; PE, pulmonary embolism; VTE, venous thromboembolism

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https://doi.org/10.1016/j.vph.2019.106567
Received 4 December 2018; Received in revised form 5 April 2019; Accepted 30 May 2019
Available online 31 May 2019

long-term anticoagulation in patients after CAT. Decision as to whether discontinue anticoagulation, maintain LMWH, switch LMWH to warfarin or implant the vena cava filter depends on patient and cancer status, benefit-to-risk ratio, tolerability, drug availability, patient preferences and always should be discussed on an individual basis [8–13].

The widespread availability of non-vitamin K antagonist oral anticoagulants (NOAC) has resulted in a number of reports regarding their effectiveness and safety also in cancer patients. The strongest evidence for the usefulness of NOAC in CAT patients comes from the randomized controlled Hokusai VTE Cancer trial with edoxaban [16]. In 1050 cancer patients with symptomatic or incidental VTE, treatment with oral edoxaban as compared to subcutaneous dalteparin for at least 6 months and up to 12 months was associated with similar rates of recurrent VTE or major bleeding during 12-month observation (HR 0.97, 95% CI 0.70–1.36, P = 0.006 for non-inferiority) [16]. In turn, a pilot randomized SELECT-D trial has demonstrated that in 203 cancer patients with CAT, a 6- month treatment with rivaroxaban was associated with lower VTE recurrence (HR 0.43, 95% CI 0.19–0.99) but a higher rate of clinically relevant non-major bleedings (HR 3.76, 95% CI 1.63–8.69) as compared with dalteparin [17]. Meta-analysis of both Hokusai VTE and SELECT-D randomized studies [18] indicates that NOACs are associated with a tendency to lower 6-month rates of recurrent VTE when compared to LMWH (risk ratio 0.65, 95% CI 0.42–1.01, P = 0.06). The results of a recent observational study have suggested that cancer patients with VTE treated with rivaroxaban for a median time of 3 months had a significantly lower risk of recurrent VTE after 12 months as compared with LMWH (HR 0.72, 95% CI 0.52–0.95, P = 0.024) or warfarin (HR 0.74, 95% CI 0.56–0.96, P = 0.028) and similar risk of major bleeding compared to both LMWH as well as warfarin [19].

Little is known about long-term use of NOAC in patients with CAT given the fact that such patients should receive anticoagulation until the disease is cured [10–12]. The aim of this study was to evaluate the effectiveness and safety of NOAC in an extended treatment of patients with CAT following the initial LMWH therapy.

2. Material and methods

In this prospective, cohort study, with protocol prepared before the inclusion of the first patient, we enrolled 128 consecutive ambulatory patients with cancer who experienced symptomatic VTE and were referred to our center for further clinical and laboratory work-up. Patients with active cancer were eligible if they had history of symptomatic deep-vein thrombosis (DVT) and/or acute symptomatic pulmonary embolism (PE) that were confirmed by means of imaging. Active cancer was defined as cancer receiving active antimitotic treatment, or diagnosed within the past 6 months, or recurrent, or metastatic, or inoperable, with exclusion of squamous skin cancer and basal cell carcinoma [20]. We excluded patients with severe (stage 4 or 5) chronic kidney disease, with postoperative VTE, high-risk thrombophilia including antiphospholipid syndrome, antithrombin deficiency, homozygosity for factor V Leiden, or prothrombin 20210A mutations or combined variants, pregnancy, acute coronary syndrome or ischemic stroke within the previous 6 months or acute infection or exacerbated chronic inflammatory disease e.g. inflammatory bowel disease.

Following documented VTE episodes all patients were treated with LMWH (enoxaparin at therapeutic doses) at least three months. The decision as to whether LMWH would be continued or stopped with the subsequent initiation of rivaroxaban, dabigatran or apixaban adjusted to the renal function was left at the discretion of the treating physician based on the patient preferences (Fig. 1). Renal failure was diagnosed when creatinine clearance calculated using the Cockcroft-Gault formula was lower than 50 ml/min. Heart failure referred to a symptomatic condition with relevant structural heart disease with diastolic dysfunction or reduced left ventricular ejection fraction of < 40%.

In the LMWH group all patients (n = 63) received subcutaneously enoxaparin at a dose 1 mg per kilogram of body weight once daily if anticoagulant therapy was longer than 12 months with 75% of therapeutic dose prescribed in the first year since the index CAT. In the NOAC group (n = 65) full dose or reduced dose of rivaroxaban, dabigatran or apixaban were administered in 43 (66.2%) and 22 (33.8%) patients, respectively. The latter regimen was used if bleeding risk was assessed as high.

The study protocol complied with the Declaration of Helsinki was approved by the Ethics Committee of the Jagiellonian University. All included patients gave informed consent.

2.1. Follow-up

The follow-up started at the time of decision about anticoagulation treatment. During follow-up all patients were assessed in the outpatient clinic or by phone. They were instructed to report symptoms that suggested recurrent VTE or bleeding requiring appropriate confirmatory diagnostic and/or laboratory tests. The primary efficacy endpoint in this study was symptomatic recurrent VTE [21], whereas the primary safety endpoint was major bleeding diagnosed in accordance to the International Society on Thrombosis and Hemostasis (ISTH) definition [22]. The net clinical outcome was a composite of recurrent VTE or major bleeding. The secondary endpoints included death, composite of major or minor bleeding and survival free of death, recurrent VTE or major bleeding. The diagnosis of recurrent symptomatic DVT was established based on positive findings of color duplex ultrasonography. In cases of suspected DVT recurrence in the same leg, non-compressibility of a previously compressible venous segment or an increase of at least 4 mm in the residual diameters was applied to confirm the diagnosis. PE was each time confirmed by computed tomography angiography. Persistence on and compliance to treatment in our patients was assessed only on the basis of the patients' declaration. The follow-up was censored at the time of death of the study participant.

2.2. Statistical analysis

In this pilot study there was no formal sample size calculation. Statistical analyses were performed with Statistica 12.5 software (StatSoft, Tulsa, OK). Continuous variables are expressed as mean ± standard deviation or median and IQR, whereas categorical variables as number (percentage). Continuous variables were checked for normal distribution by the Shapiro-Wilk test. For baseline characteristics, differences between means of continuous variables or between proportions of categorical variables were expressed as 95% confidence intervals (CI). The Kaplan-Meier curves of the survival free of VTE and major bleeding were created and then the Cox proportional hazard regressions were done to estimate treatment effects and to determine independent predictors of overall survival and survival free of VTE and bleeding. The results were presented as hazard ratios (HR) with 95% CI.

3. Results

3.1. Baseline characteristics

A total of 128 patients with CAT were enrolled. Subjects treated with NOAC and those on LMWH were similar in terms of demographics, VTE risk factors, most of the co-morbidities, cancer type, and initial VTE diagnosis (Table 1).

Patients on NOAC were more often diagnosed with heart failure (38.5% vs 19.1%) and less often with hyperlipidemia (56.9% vs 79.4%) as compared with those on LMWH. Among patients treated with NOAC, 38 (58.5%) patients were treated with rivaroxaban, 14 (21.5%) with dabigatran and 13 (20.0%) with apixaban. Of them, a reduced dose regimen of NOAC was used in 11 (16.9%) patients treated with rivaroxaban (15 mg/d), in 4 (6.1%) patients with dabigatran (110 mg bid)

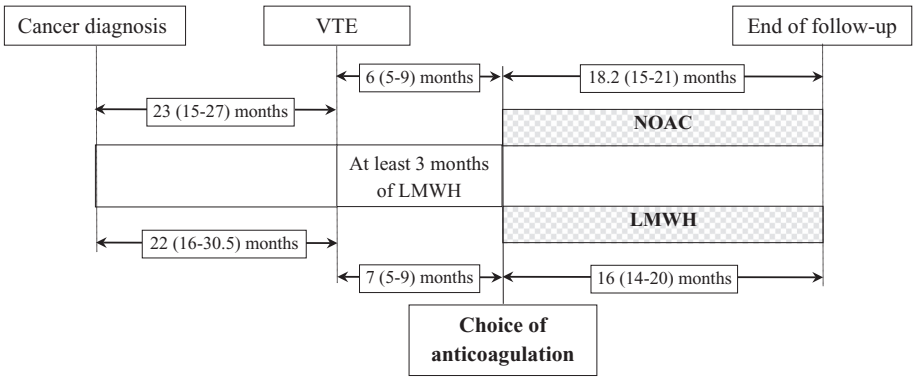


Fig. 1. Study flow chart.
The time intervals are expressed as median (interquartile range).
Abbreviations: LMWH: low-molecular-weight heparin, NOAC: non-vitamin K antagonist oral anticoagulants, VTE: venous thromboembolism

Table 1
Baseline characteristics of the studied groups.

	NOAC N = 65	LMWH N = 63	95% CI of difference
Age, years	66.5 ± 7.0	67.9 ± 6.6	−3.8 to 1.0
Male gender	22 (33.9)	22 (34.9)	−0.2 to 0.2
Body mass index, kg/m^2	28.2 ± 5.8	28.3 ± 3.7	−1.8 to 1.6
Active smoking	21 (32.3)	15 (23.8)	−0.1 to 0.2
Hyperlipidemia	37 (56.9)	50 (79.4)	0.1 to 0.4
Hypertension	47 (72.3)	45 (71.4)	−0.1 to 0.3
Diabetes mellitus	4 (6.2)	4 (6.4)	−0.1 to 0.01[a]
Renal failure	15 (23.1)	13 (20.6)	−0.1 to 0.2
Heart failure	26 (38.5)	12 (19.1)	0.1 to 0.4
Prior stroke	12 (18.5)	13 (20.6)	−0.1 to 0.2
Prior myocardial infarction	8 (12.3)	7 (11.1)	−0.1 to 0.1
Prior gastrointestinal bleeding	4 (6.2)	1 (1.6)	−0.04 to 0.1[a]
Time since cancer diagnosis to the index VTE, months	22.4 ± 8.2	24.3 ± 10.1	−5.1 to 1.3
Time since the VTE incident to choice of NOAC/LMWH, months	7.6 ± 3.7	7.5 ± 3.3	−1.1 to 1.3
Initial VTE diagnosis:			−0.1 to 0.3
DVT alone	36 (55.4)	40 (63.5)	
PE with or without DVT	29 (44.6)	23 (36.5)	
Type of cancer:			NA
Genitourinary	16 (24.6)	14 (22.2)	
Breast	17 (26.2)	19 (30.2)	
Gastrointestinal	11 (16.9)	11 (17.5)	
Lung	11 (16.9)	8 (12.7)	
Other	10 (15.4)	11 (17.5)	
Metastatic disease	30 (46.2)	23 (36.5)	−0.1 to 0.3
Laboratory investigations at enrolment:			
Haemoglobin, g/dL	12.5 ± 1.8	12.6 ± 1.6	−0.7 to 0.5
Platelet count, ×10^3/μL	173 ± 74	190 ± 79	−43 to 10
Creatinine, μmol/L	98.6 ± 25.3	93.0 ± 23.4	−2.8 to 14.1
Alanine aminotransferase, IU/L	34.7 ± 22.5	32.5 ± 17.3	−4.8 to 9.2

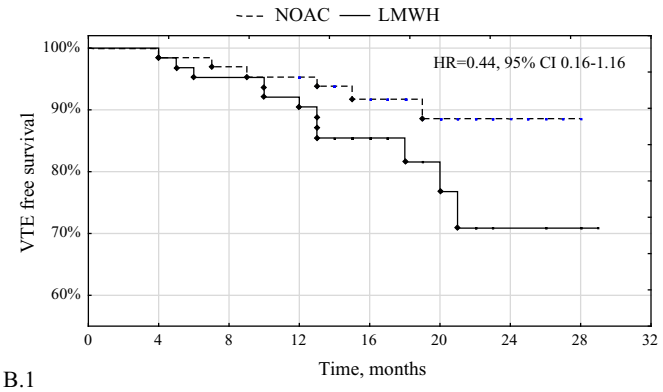
Abbreviations: Data are shown as mean ± standard deviation or number (percentage). CI: confidence interval for difference between means of continuous variables and between proportions of categorical variables, DVT: deep-vein thrombosis, LMWH: low-molecular-weight heparins, NOAC: non-vitamin K antagonist oral anticoagulants, PE: pulmonary embolism, VTE: venous thromboembolism, NA: not applicable.
[a] Calculation of CI with continuity correction.

and in 7 (10.8%) patients with apixaban (2.5 mg bid)

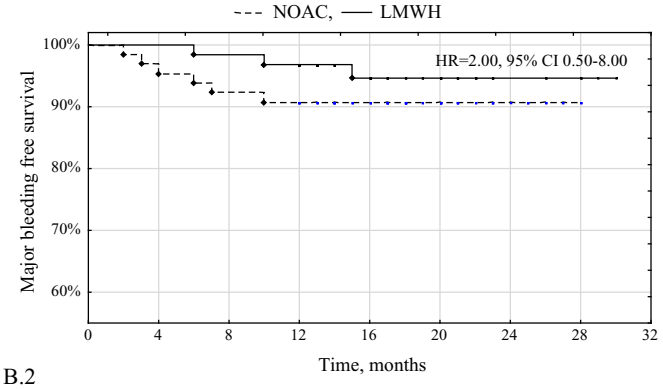
3.2. Follow-up

The median follow-up for patients treated with NOAC was 18.2 (15.0–21.0) months and for patients on LMWH was 16.0 (14.0–20.0) months (95% CI -0.5 to 2.7). Recurrent VTE occurred in 6 (9.2%) patients in the NOAC group and in 12 (19%) patients in the LMWH group (Fig. 2). Recurrent VTE was observed after 8.0 (4.75–12.0) months in patients on NOAC, with similar time intervals in those on LMWH (5.5 [1.75–13.0] months).

Major bleeding occurred in 6 (9.2%) patients receiving NOAC and in 3 (4.8%) patients treated with LMWH (Fig. 2). This event occurred after



B.1



B.2

Fig. 2. Probability of survival free of recurrent venous thromboembolism (VTE) (B.1), and major bleeding (B.2) in patients treated with non-vitamin K antagonist oral anticoagulants (NOAC) or low-molecular-weight heparins (LMWH).

Table 2
Clinical outcomes in both treatment groups.

	NOAC N = 65	LMWH N = 63	95% CI
Recurrent VTE	6 (6.2)	12 (13.9)	0.16 to 1.16
Major bleeding	6 (6.3)	3 (3.3)	0.50 to 8.00
Recurrent VTE or major bleeding	11 (12.0)*	15 (17.8)	0.31 to 1.50
Death from any cause	10 (9.9)	10 (10.8)	0.32 to 1.84
Major or minor bleeding	10 (11.1)	6 (6.8)	0.62 to 4.69
Death, recurrent VTE or major bleeding	18 (19.6)**	22 (26.1)***	0.37 to 1.31

Abbreviations: Data are shown as number of patients with index event (percentage of patients with index event/year). CI: confidence interval for hazard ratios calculated in the Cox proportional hazard regressions, LMWH: low-molecular-weight heparins, NOAC: non-vitamin K antagonist oral anticoagulants, VTE: venous thromboembolism. Two outcomes occurred in 1 (*), 4 (**) and 3 (***) patients.

on average 5.0 (3.25–6.75) months in patients on NOAC versus 10.0 (8.0–12.5) months for those on LMWH (95% CI -10.8 to 0.8). The rate of major or minor bleedings was similar in both groups (Table 2), however the median time to their occurrence was shorter in patients on NOAC (3.0 [2.25–5.5] months) as compared with those on LMWH (9.0 [6.5–13.0] months) (95% CI -9.3 to −1.0).

There was no difference in the mortality rate depending on the anticoagulant used (15.4% for NOAC versus 15.9% for LMWH). Death largely due to cancer progression occurred after 16.5 (14.25–17.75) months in the NOAC group versus 17.0 (15.25–21.0) months in the LMWH group.

The chosen anticoagulant therapy did not influence significantly VTE occurrence (HR = 0.44 for NOAC vs LMWH, 95% CI 0.16–1.16), major bleeding (HR = 2.00 for NOAC vs LMWH, 95% CI 0.50–8.00), net clinical outcomes of recurrent VTE or major bleeding (HR = 0.68 for NOAC vs LMWH, 95% CI 0.31–1.50) or death (HR = 0.76 for NOAC vs LMWH, 95% CI 0.32–1.84).

Major bleeding occurred in 3 (13.6%) patients with reduced dose of NOAC and in 3 (7.0%) patients with full dose of NOAC. The rate of recurrent VTE was similar in patients with reduced and full dose of NOAC (9.1% and 9.3%, respectively). Mortality rate was also similar in patients treated with reduced and full dose regimens of NOAC (18.2% and 14.0%, respectively) and in patients treated with LMWH (15.9%).

3.3. Multivariable analysis

Only the time elapsed since cancer diagnosis to the index VTE was independently associated with the recurrence of VTE (HR 1.05 per month, 95% CI 1.01–1.11). After adjustment for the anticoagulant used, lung cancer as compared with other cancers was found to be an independent predictor of death (HR 3.77, 95% CI 1.54–9.26). Data for different cancer types were shown in Supplementary Table 1.

4. Discussion

In the current cohort study we found that in CAT patients with a relatively good prognosis, who preferred continuation of anticoagulant therapy after a few months of the LMWH use, extended treatment with NOAC as compared with LMWH is associated with similar incidence of VTE recurrence and bleeding complications during almost 2 years of follow-up. On the other hand, half-therapeutic daily doses of enoxaparin appeared acceptable option for CAT patients who chose LMWH. In this clinical setting metastatic disease or any specific cancer type as well as demographic or clinical factors determined the clinical outcomes of prolonged anticoagulation. This study provides additional arguments for the benefits from broader use of NOAC in CAT patients including those with gastrointestinal cancer.

Growing evidence supports use of NOAC in cancer patients who experienced VTE. The ISTH experts indicate that NOAC can be considered for VTE treatment of patients with stable cancer not receiving systemic anticancer therapy, and in cases where vitamin K antagonist is an acceptable, but not an available, treatment choice [12]. Several arguments make NOAC attractive alternatives to either LMWH or vitamin K antagonists. NOAC do not require laboratory monitoring, have fixed-dose regimens with predictable anticoagulant effects, have fewer drug and food interactions than vitamin K antagonists and the oral route of administration is an important advantage as compared to subcutaneously injected LMWH [13,23]. It has been shown that only approximately 50% of patients adhere to long-term treatment with parenteral LMWH [24]. Moreover, LMWH administration might also result in heparin induced thrombocytopenia, a rare but life-threatening thrombotic complication [25]. On the other hand, NOAC absorption might be compromised by vomiting, which is a common side-effect of anticancer agents [26]. The present study confirms that despite limitations of oral anticoagulation, cancer patients after a few months of LMWH injection often choose NOAC. According to the US registers, nearly one-fifth of patients diagnosed with CAT have been already treated with rivaroxaban [24]. The available registry data did not differentiate between patients in acute VTE and those using NOAC in a long-term basis, and most of high-quality data are restricted to 12-month use of NOAC initiated at the time of CAT diagnosis. Our findings may support the view that in real-life population of CAT patients with life expectancy of > 12 months, long-term treatment with NOAC is as effective and safe as LMWH therapy.

The effectiveness and safety of NOAC in our cohort were comparable to those reported previously. In CAT patients treated with rivaroxaban for 4–6 months the incidence of recurrent VTE ranged from 3.3% to 8.9% [27–30]. In turn, the incidence of recurrent VTE in 266 CAT patients treated with either rivaroxaban or enoxaparin was 1% versus 4.2%, respectively (P = 0.15) and did not differ at 12 months [31]. The subanalysis of AMPLIFY study [32] showed that among patients with active cancer recurrent VTE was not less frequent in the apixaban group as compared with enoxaparin/warfarin groups (risk ratio 0.56, 95% CI 0.13–2.37). Finally, the results of the randomized trials consistently indicate that NOAC compared to LMWH are as effective or even more effective in preventing subsequent thromboembolic complications within a 6–12 month follow-up [16,17]. Our study has shown acceptable clinical outcomes of treatment of CAT patients in much longer follow-up than those from the published observational and randomized studies.

We did not observe increased risk of major bleeding in cancer patients on NOAC. However, we found that median time to any major or minor bleeding was shorter in NOAC as compared with LMWH. In the Hokusai VTE trial [16] major bleeding within 12-month observation was more frequent with edoxaban as compared to dalteparin (HR 1.77, 95% CI 1.03–3.04, P = 0.04). In turn, in the SELECT-D trial [17] the rate of major bleeding was similar in both compared groups, however the frequency of clinically relevant non-major bleedings was significantly higher in the rivaroxaban group as compared with dalteparin. The present population was recruited a few months since the VTE event in contrast to the two trials focused on acute VTE patients [16,17]. Similar signals came from recent small observational studies. In CAT patients treated with rivaroxaban for 4–6 months, the incidence of major bleeding ranged from 2.2% to 5.5% [27,28,30]. Moreover, the

incidence of major bleeding in 266 CAT patients treated with either rivaroxaban or enoxaparin was 5.1% versus 3.6%, respectively (P = 0.55) and did not differ at 12 months [31]. In turn, in the subanalysis of the AMPLIFY study [32], apixaban was associated with not significantly lower rate of major bleeding as compared with enoxaparin/warfarin (risk ratio 0.45, 95% CI 0.08–2.46). Importantly, in our study the dose of NOAC was adjusted to the renal function. One third of patients based on creatinine clearance received reduced dose of NOAC and such approach in our cohort was associated with similar rate of major bleedings regardless of the NOAC dose comparable with LMWH without increasing the rate of thromboembolic complications.

An interesting finding is the observation that the longer time between cancer diagnosis and the index VTE, the greater risk of developing the recurrence of VTE among cancer patients on NOAC or LMWH. It might be speculated that such patients have a persistent prothrombotic tendency in part unrelated to cancer, and they did not experience VTE within the first months since establishing the diagnosis which represent the highest risk time in this clinical setting [2]. This hypothesis requires further investigations.

Our study has several limitations. First, our pilot, observational study has all inherent shortcomings including lack of sample size calculation. As a consequence, the study was likely underpowered to show differences between the study groups as well as among individual NOAC agents or different types of cancer. Therefore, our findings should be interpreted with extreme caution. Second, patients with poor prognosis were underrepresented and these observations refer to patients who survived 1–2 years since cancer diagnosis and then a few months of LMWH therapy. Third, noncompliance as a factor affecting VTE recurrence cannot be excluded given the study design.

5. Conclusions

Our findings suggest that in the active cancer patients with a history of symptomatic VTE, extended treatment with NOAC as compared with LMWH is associated with similar incidence of VTE recurrence and bleeding complications. It might be concluded that after initial treatment with LMWH for at least 3 months, cancer patients could receive NOAC therapy. Oral administration of NOAC as compared with subcutaneous LMWH and no need for treatment monitoring supported by results of recent trials make NOAC attractive anticoagulants for extended therapy in CAT patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vph.2019.106567.

Acknowledgements

None.

Funding

This work was supported by a grant from the Jagiellonian University Medical College (K/ZDS/007717 to A.U.).

Conflict of interests

A.U. received lecture honoraria from Bayer, Boehringer Ingelheim, Pfizer and Sanofi-Aventis. The remaining authors have nothing to disclose in relation to this study.

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