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Commentary to the guidelines: "Guidelines on the prevention and treatment of venous thromboembolism in cancer patients treated surgically, including patients under 18 years of age"

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Patients with malignant tumors are at high risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis and/or pulmonary embolism. Thrombotic events are the second most common cause of death of oncological patients after death due to cancer itself [1]. Therefore, appropriate treatment, i.e. appropriate medication administered for an appropriate period is crucial for the survival of patients with VTE and cancer.

We are witnessing a major shift in the VTE treatment regimens disease as compared to the guidelines published in 2012 and 2016 [2] dictating the use of rivaroxaban and other direct oral anticoagulants (DOACs) in the treatment of deep limb thrombosis and pulmonary embolism in patients without cancer while recommending low molecular weight heparin (LMWH) as the medication of choice in patients with cancer-associated thrombosis (CAT). Cancer-associated venous thromboembolism is thromboembolism occurring in a patient with active malignancy or as the result of oncological treatment. The treatment of VTE in cancer patients is one of the most difficult clinical challenges as delivered simultaneously to the cancer treatment. Oncological therapies often require invasive surgeries, increase the risk of infections, and may lead to thrombocytopenia, consequently increasing the risk of bleeding. In many cancer patients, it is impossible to predict the length of the period in which the risk of VTE will be significantly increased in a particular patient.

In patients requiring long-term anticoagulation treatment, periodic assessment of the risk of bleeding complications as well as the risk of VTE recurrence (treatment benefit vs. risk of bleeding) is required.

The current guidance as discussed in this commentary highlights the fact that the choice of drugs to be used in VTE treatment no longer depends on whether or not the patient's thrombosis is associated with cancer DOACs, albeit only xabans are now considered to be the first-line drugs in all cancer patients with thromboembolic complications. In short, all cancer patients excluding pregnant women and other contraindications specific to the selected direct factor Xa inhibitor may be treated with rivaroxaban, apixaban, or edoxaban just as non-cancer patients. The shift can be seen in the documents published by the American Society of Clinical Oncology (ASCO 2019), National Comprehensive Cancer Network (NCCN 2018), International Society on Thrombosis and Hemostasis (ISTH 2018 and 2019), European Cardiology Society/European Respiratory Society (2019), as well as the most recent, document published in 2021 by the American Society of Hematology [3–8].

Most recommendations regarding anticoagulation therapy assume that the treatment is in line with patient's preference regarding the objective of care and life expectancy. Venous thromboembolism often develops in the natural history of cancer. Cancer management, particularly interventional treatment, may also increase the risk of this complication. Surgical procedures affect the risk of thrombosis in a multifactorial fashion; factors of importance include intraprocedural damage to the tissues, periprocedural immobilization, blood and plasma replacement, positive pressure ven-

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tilation, presence of potential infectious foci, or central venous catheters. Therefore, when treating VTE in patients with malignant tumors one must take into account the higher rates of thrombotic recurrence as well as the high risk of bleeding complications in this group of patients.

In the light of current knowledge, it is also important to take into account the presence of other risk factors, particularly those related to concomitant diseases and clinical conditions contributing to the increased risk of VTE (obesity, prolonged immobilization, varicose veins, hormonal therapy, history of stroke with paresis, history of VTE episodes etc.). Notably, conditions which have been until recently considered to be within the domain of non-interventional disciplines, such as exacerbations of chronic circulatory failure and inflammatory bowel diseases, are now considered the factors for VTE. Other potential risk factors, such as postoperative infection – intraabdominal abscess or other surgical site infection following a colorectal procedure – as well as any other acute infection, should also be taken into account. All of the above-mentioned conditions are very important in the context of the choice of a particular anticoagulant for VTE therapy, with limitations associated with renal and hepatic function and drug-drug interactions being considered.

Rivaroxaban is one of the most commonly used non-vitamin K agonist oral anticoagulants and the first xaban to feature an indication for use in oncological patients in its summary of product characteristics. Thanks to numerous large-scale clinical trials conducted in diverse patient groups, DOACs have become the first-line treatment, particularly in patients in whom anticoagulant therapy is being initiated for the first time [9–11].

Therefore, our commentary to guidelines on the prevention and treatment of venous thromboembolism in cancer patients undergoing surgical treatment, will be based on EBM-based data not included or included only to a small extent in the above document. The importance of these data consists in that they confirm the role of this medication in CAT treatment.

In our opinion, the first of the documents of importance is the meta-analysis by Yang et al. [12]. The objective of this meta-analysis was to compare direct Xa inhibitors with LMWH in the treatment of VTE in patients with cancer based on data from all available randomized and retrospective cohort studies encompassing a population of > 4000 patients. Direct Xa inhibitors were shown to be associated with a 33% reduction of VTE recurrence in cancer patients as compared to LMWH. No significant difference was observed between the two treatments as regards the occurrence of major bleeding. Subgroup analyses revealed that only rivaroxaban was associated with a reduction in the rate of VTE recurrence. The previous guidelines recommended direct Xa inhibitors being used to prevent VTE recurrence on the basis of evidence obtained from patients without malignant tumors, and that is what has changed since that time. Bleeding is the main adverse effect of direct Xa inhibitors. In their meta-analysis, Yang et al. [12] demonstrated no significant difference in the incidence of major bleeding between the use of direct Xa inhibitors and LMWH. The meta-analysis suggests that direct Xa inhibitors outperform LMWH in terms of reducing VET recurrence rates in cancer patients without putting these patients at high risk of major bleeding. Another valuable paper regarding the use of rivaroxaban in a group of CAT patients was published by Streiff et al. [13].

In 2013–2015, the team analyzed the cases of newly diagnosed cancer patients in whom the treatment with rivaroxaban, LMWH, or warfarin was initiated. A total of 2428 patients (rivaroxaban: 707; LMWH: 660; warfarin: 1061) were included in the analysis. A trend toward lower VTE recurrence rates was observed in rivaroxaban users compared to LMWH users after 6 months (13.2% vs. 17.1%; $p = 0.060$); the difference was even greater after 12 months (16.5% vs. 22.2%; $p = 0030$) (HR [hazard ratio]: 0.72; 95% CI [confidence interval]: 0.52–0.95; $p = 0.024$). The VTE recurrence rates in rivaroxaban users were also lower when compared to those in warfarin users after 6 monts (13.2% vs. 17.5%; $p = 0.014$) and 12 months (15.7% vs. 19.9%; $p = 0.017$; HR: 0.74; 95% CI: 0.56–0.96; $p = 0.028$). The incidence of severe bleeding was similar in all groups. The results of the analysis by Streiff et al. [13] suggest that cancer patients with VTE receiving rivaroxaban are at a significantly lower risk of recurrence and a similar risk of bleeding than patients treated with LMWH or warfarin.

Real-world data are very important as they may sometimes contradict the results from randomized design studies; such data were published by an expert in CAT and author of numerous guidelines — Khorana et al. [14]. In this publication, Medicare patients' data were compared in terms of the efficacy and risk of severe bleeding associated with the use of anticoagulation (rivaroxaban, warfarin, LMWH) in the group of patients with primary CAT. VTE relapses were defined as hospitalizations due to the primary diagnosis of VTE ≥ 7 days after the first incident of VTE. A total of 12,457 patients (LMWH = 4313; warfarin = 4774; rivaroxaban = 3,370) were included in the study. The baseline demographic and clinical characteristics of the enrolled patients were well balanced. The average age of patients ranged from 61.3 to 63.6 years. The median follow-up time for the LMWH treatment group was

shorter than that for rivaroxaban (6.8 vs. 8.3 months; $p < 0.001$) and warfarin (7.4 vs. 9.8 months; $p < 0.001$). Notably, the treatment time was significantly shorter for heparins which may also speak in favor of DOACs. The VTE recurrence rates in rivaroxaban users was significantly lower than in warfarin users after 6 months (8.7% vs. 11.7%; $p = 0.003$) and 12 months (11.9% vs. 14.7%; $p = 0.006$); HR: 0.83; $p = 0.010$. The incidence of severe bleeding was similar in rivaroxaban and LMWH users after 3 months (3.2% vs. 3.5%; $p = 0.592$) and 6 months (4.4% vs. 4.9%; $p = 0.438$); HR: 0.91; $p = 0.455$). The VTE recurrence rates in patients receiving rivaroxaban and warfarin was similar after 6 months (8.2% vs. 8.8%; $p = 0.530$) and 12 months (11.3% vs. 11.6%; $p = 0.675$; HR: 0.95; $p = 0.456$). The incidence of severe bleeding among patients using rivaroxaban and warfarin was similar after 3 months (3.2% vs. 2.8%; $p = 0.199$) and 6 months (4.2% vs. 3.8%; $p = 0.362$); (HR: 1,08; $p = 0.500$). A surprising fact consisted is the significantly lower VTE recurrence rates in patients receiving warfarin as compared to patients on LMWH after 6 months (10.2% vs. 12.4%; $p = 0.006$) and 12 months (13.3% vs. 15.3%; $p = 0.011$), although the overall recurrence rates did not differ significantly between the two groups in the entire follow-up period (HR: 0.91; $p = 0.103$). The conclusions from the aforementioned study are very practical; importantly, they were derived from regular clinical practice. In this large group of cancer patients treated for VTE, the treatment times were shorter in patients treated with LMWH than in those receiving oral medications. Rivaroxaban was associated with significantly lower VTE recurrence rates and major bleeding rates were similar for all study groups. Although in previous clinical trials carried out in CAT patients LMWH was shown to be associated with lower VTE recurrence rates as compared to warfarin, the much shorter duration of LMWH treatment (and thus its much lower efficacy in recurrence prevention) in real world settings may explain the lack of comparable efficacies shown in the analysis.

Concluding our commentary to the 2021 Polish guidelines on CAT treatment, we dare say that the era of warfarin and LMWH use has been superseded by the DOAC era. For oncological patients, only xabans can be taken into consideration; among these, rivaroxaban stands out in terms of large study populations and recommendations from recognized bodies.

Conflict of interest

Zbigniew Krasinski: Yes. Educational lectures: Bayer, Boehringer Ingelheim, Sanofi, Aspen, Pfizer, Alpha Sigma, COOK, GORE, Pierre Fabre, ADAMED.

Beata Begier-Krasińska: No.

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