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Role of anticoagulants in therapy and prevention of recurrent venous thromboembolism in patients with cancer: a meta-analysis of randomized trials with apixaban

Background Venous thromboembolic complications (VTEC) are a major non-oncological cause of death of patients with malignant neoplasm (MNP). This determines the high significance of antithrombotic therapy for the treatment and secondary prevention of VTEC in this population. During recent years, low-molecular weight heparins (LMWH) have been a «gold standard» for the treatment of cancer-associated venous thrombosis (CAVT). In the recent decade, direct oral anticoagulants (DOACs) have become extensively used for the treatment and prevention of VTEC relapse in non-oncological patients and also for primary prevention of VTEC following orthopedic surgery. Taking into account the oral route of administration, the predictable and convenient pharmacokinetic profile, and the absence of need for coagulation monitoring, it seems possible to use DOACs for the treatment and secondary prevention of VTEC in oncological patients. A meta-analysis of 4 randomized clinical trials (RCTs) showed a higher efficacy of DOACs compared to LMWHs, however, with a greater risk of bleedings in CAVT. In two of four studies using apixaban (more than 40% of weight in meta-analysis), no increase in bleedings was noted.

Aim The aim of this study was to perform a systematic search for comparative clinical studies with apixaban and to perform a meta-analysis to answer the question on clinical efficacy and safety of apixaban in the treatment and secondary prevention of recurrent VTEC in patients with CAVT.

Material and methods The systematic search was performed in three reference databases, Medline (PubMed), Cochrane Library (CENTRAL), and eLibrary. The search was aimed at publications containing results of RCTs using apixaban for the treatment and prevention of VTEC in patients with MNP. A totality of 678 titles was found; 15 articles were selected for detailed studying, and 4 RCTs were included into the final analysis. The meta-analysis was performed according to the criteria of PRISMA guidelines. Relative risk (RR) was used as a measure of the effect. The meta-analysis was performed by the Mantel-Haenszel method using the R software. Statistical heterogeneity was evaluated with the Cochran criterion (I^2); heterogeneity was considered significant at $I^2 \geq 50\%$, which was a reason for performing a random-effects meta-analysis. For this meta-analysis, the primary outcome measure was new VTECs (symptomatic or detected proximal deep vein thrombosis and/or symptomatic, detected or fatal pulmonary thromboembolism plus symptomatic upper extremity thromboses, celiac veinous thromboses, and cerebral veinous thromboses if they were included into the efficacy endpoint of the primary studies). The primary safety measure was major bleeding according to ISTH criteria. Other variables included major and clinically significant minor bleedings as well as overall death rate.

Results During the systematic search, 4 RCTs were selected. The meta-analysis of the treatment and secondary prevention of VTEC in patients with MNP showed that apixaban was more effective than the active control (88% of LMWHs) in prevention of VTEC relapse. The RR was 0.59; 95% confidence interval (CI): 0.40–0.86 in the absence of statistically significant differences from the control in the risk of major bleedings (statistically non-significant decrease by 21%), the sum of major and clinically significant minor bleedings, and overall death rate.

Conclusion According to the results of the meta-analysis, the DOAC apixaban may be a drug of choice for the treatment and prevention of VTEC relapse in patients with MNO.

Keywords Apixaban; venous thromboembolic complications; malignant neoplasm; meta-analysis; systematic review; efficacy; safety; VTEC relapse; major bleeding

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Cancer-associated thrombosis (CAT)

After the malignancy itself, the second most common cause of death in cancer patients consists of venous thromboembolism (VTE) adverse events (AEs) [1]. Signs of malignancy described by the French physician Armand Trousseau from 1861–1865 include episodes of vascular inflammation due to blood clots, recurring or appearing in different locations over time (migratory thrombophlebitis); this was later given the designation Trousseau's syndrome [2]. A detailed analysis (1977) expanded the concept of Trousseau's syndrome to include chronic disseminated intravascular coagulopathy associated with microangiopathy, verrucous endocarditis, and arterial embolism in cancer patients, most frequently occurring in patients with mucin-positive carcinomas [3].

The main current ideas on the mechanisms of cancer-associated clotting are summarized in Figure 1 [4–7]. The classical Virchow's triad observed in cancer-associated thrombosis (CAT) comprises:

1) vascular wall lesions with a particularly important role played by endothelial dysfunction, which can contribute to increased clot formation;
2) blood stasis;
3) blood clotting disorders.

Naturally, the development of coagulopathy in cancer and the mechanisms of increased clotting are of key interest. There are three key factors:

1) excessive mucin production by tumor cells activates greater platelet aggregation [4];
2) activation of tissue factor formation also increases platelet aggregation and inhibits thrombin destruction, which promotes fibrin production [5];
3) significant activation of heparinase synthesis, an enzyme produced by tumor cells and macrophages, responsible for heparin inactivation [6], which results in the degradation of endogenous heparin and significantly increased activity of thrombin and production of fibrin fibers that stabilize the clot [7].

The designation of increased risk of thrombosis in cancer as «cross-linking between cancer and thrombosis» emphasizes the inextricable link between the two conditions [8].

Frequency and characteristics of CAT

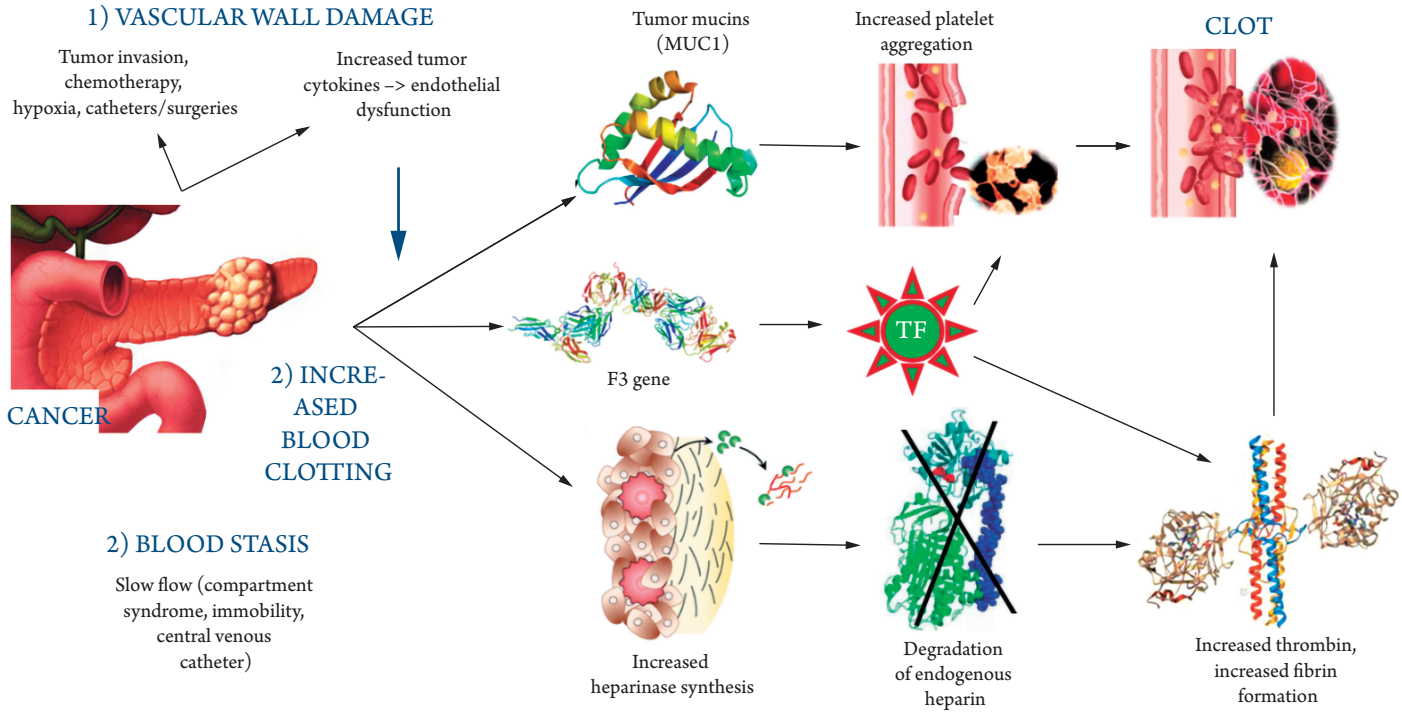
The incidence of VTE AEs, including deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is 4–7 times higher in cancer patients than in patients without a known malignancy. While fatal thrombosis can result from a tumor and its effect on the body, antitumor therapies also involve vascular toxicity, such as local foci of endothelial inflammation and increased clotting [9, 10].

The incidence of VTE AEs was significantly higher (4.1-fold) in cancer patients than in patients without cancer ($p<0.001$); here, the risk increased up to 6.5-fold during chemotherapy ($p<0.001$) [11]. In the large cohort study MEGA, the risk of VTE AEs was found to be 6.7-fold higher in cancer patients than in non-cancer patients; the first three months following cancer diagnosis are the most critical (53.5-fold increase in the risk of VTE AEs). In patients with cancer and distant metastases, the risk of VTE AEs increased 19.8-fold as compared to cancer patients without metastases [12]. In the largest and most detailed analysis, which included over 17,000 cancer patients, the risk of VTE AEs was 12.6% versus 1.4% ($p<0.001$) in non-cancer patients [13]. Patients with pancreatic cancer (odds ratio (OR) 5.39), stomach cancer (OR 4.00), and lung cancer (OR 3.15) had the highest risk of VTE AEs. The increased risk was also observed in ovarian cancer, colorectal cancer, and bladder tumors in descending order. Aggravating factors included various comorbidities such as obesity, as well as antitumor therapies including erythropoietin, endothelium-specific antibodies, and cytostatics.

According to the analysis of the US insurance claim database, the outcome following initial hospital treatment largely depended on the combination of cancer and VTE AEs [14]. In patients with VTE AEs (n=124,106), the risk of rehospitalization was 6.5%, while the risk of death was 29%; this compares with risks of 13.5% and 42%, respectively, in cancer patients (n=1,211,944). However, the risks of rehospitalization and death increased to 21.7% and 94%, respectively, in the combination of cancer and VTE (n=7,238), ($p<0.001$, as compared with VTE AEs alone or cancer alone).

However, in most cancers, alongside with a significant increase in the risk of VTE AEs, there is also an increased risk of bleeding (17.7% versus 7.2%; $p<0.001$), including major bleeding (0.9% versus 0.1%; $p<0.001$) and clinically significant minor bleeding also known as nuisance bleeding [13]. Predictors of bleeding

Figure 1. Main mechanisms of increased clotting in cancer



TF – tissue factor.

risk differed from predictors of the risk of VTE AEs: in descending order of effect on the risk of bleeding, these were bladder cancer (OR 4.09), stomach cancer (OR 2.16), atrial fibrillation (OR 1.46), erythropoietin therapy and chemotherapy.

Other trials and analyses showed also a simultaneous 3.2-fold increase in the risk of VTE AEs and a 2.2-fold increase in the risk of bleeding in cancer and CAT [15]. In the large RIETE registry, the risk of fatal PE was 2.6% in cancer patients with VTE as compared to 1.4% in patients with VTE and without cancer. At the same time, the risk of bleeding increased from 0.3% to 1.0% in patients with VTE when cancer developed [16].

The COMPASS RCT showed that the relationship between bleeding during combination therapy with aspirin and low-dose rivaroxaban and the risk of detecting cancer of the corresponding location [17]. Gastrointestinal (GI) bleeding was accompanied by a 20 fold increase in detecting of de novo GI cancer and a 1.7-fold increase in detecting new cancer location. In case of urogenital bleeding, new cases of genitourinary and bladder cancer were detected 32 and 98 times more often, respectively. Bleeding during anticoagulant therapy can thus be considered as a predictor of de novo cancer.

Thus, anticoagulant therapy is one of the most important components in the management of cancer patients for treating and preventing recurrent VTE AEs, including fatalities. Since, as well involving an increased risk of thrombosis, the progression of malignancy is associated with a high risk of bleeding, an effective anticoagulant agent having a favorable safety profile should be used in CAT.

Anticoagulant therapy in patients with CAT

Low-molecular-weight heparin (LMWH) has long been the gold standard of anticoagulant therapy in cancer patients [18, 19]. As well as reducing the risk of death by 12.3% (p=0.015), there is no statistically significant increased risk of major bleeding associated with LMWH use. Nevertheless, the cumulative risk of major and clinically significant minor bleeding was found to increase 2.03-fold (p=0.008) [20]. A systematic meta-analysis of the Cochrane library did not show a decrease in the risk of death in cancer patients with VTE AEs. At the same time, while anticoagulant therapy significantly reduced the risk of VTE AEs and PE by 44% and 39%, respectively, this came with a relatively increased risk of bleeding and statistically insignificantly increased risk of major bleeding (+30%; p=0.11) along with a significantly increased risk of clinically significant minor bleeding (+70%; p=0.01) [21]. Despite the high efficacy and relatively favorable safety profile of anticoagulant drugs, the injection route causes some inconveniences for the long-term administration, which may affect treatment compliance and consequent efficacy.

Attempts to use vitamin K antagonists (VKA), especially warfarin, have been less successful. In the

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comparative RCT of LMWH (CLOT), the number of VTE AEs was 9% and 17% in the dalteparin and warfarin groups, respectively (HR 0.48; p=0.002), without involving any significant difference in the risk of bleeding [22]. A meta-analysis of comparative trials of warfarin did not reveal a statistically significant reduction in the risk of death in cancer patients with VTE AEs; conversely, VKAs significantly increased the risk of major bleeding (2.37-fold; p<0.001) and the cumulative risk of major/clinically significant minor bleeding (2.98-fold; p<0.001).

Direct oral anticoagulants (DOACs) combine predictable pharmacokinetics, few drug and food interactions and a stable anticoagulant effect; moreover, their use does not require laboratory monitoring of coagulation. Successful experiences in using DOACs for the treatment and secondary prevention of VTE AEs in the general patient population introduced new possibilities in the treatment of cancer patients with VTE AEs instead of LMWH. However, given the high risk of VTE AEs, bleeding, and potential drug interactions in cancer patients, a strong evidence base was necessary for confident use of DOACs in this population.

Four main RCTs were conducted to compare DOACs and LMWHs in the treatment of cancer patients and the prevention of VTE AEs:

- HOKUSAI VTE Cancer; n=1046; LMWH for 5 days followed by edoxaban 60 mg/day versus dalteparin 200 IU/kg for one month followed by dose reduction to 150 IU/kg [23];
- SELECT-D; n=406; rivaroxaban 15 mg bid for 21 days followed by dose elevation to 20 mg/day versus dalteparin 200 IU/kg for one month followed by dose reduction to 150 IU/kg [24];
- ADAM-VTE; n=287; apixaban 10 mg bid in the first week with dose reduction to 5 mg bid. versus dalteparin 200 IU/kg for one month followed by dose reduction to 150 IU/kg [25];
- CARAVAGGIO; n=1155; apixaban 10 mg bid in the first week with dose reduction to 5 mg bid versus dalteparin 200 IU/kg for one month followed by dose reduction to 150 IU/kg [26];

Several published meta-analyses of these trials have shown a statistically significant increase in the risk of VTE AEs during the use of LMWHs compared to DOACs (1.55-fold; p=0.001; with moderate heterogeneity I^2 =24%). Increased risk of PE (1.38-fold) did not achieve statistical significance and had no effect on mortality (–5%) [25]. The risk of major bleeding during dalteparin therapy was 24% lower (p=0.11), while the risk of GI bleeding was significantly lower by 47% and clinically significant minor bleeding was lower by 32% when LMWHs were used [27]. Similar findings were received when DOACs were compared with LMWHs or placebo in preventing VTE AEs in cancer patients: a statistically significant 42% reduction in the risk of VTE AEs and simultaneous increase in the risk of major bleeding and the cumulative risk of major/clinically significant minor bleeding [28].

The analysis of outcomes of 4,720 patients with CAT (12 RCTs) demonstrated a minimal risk of VTE AEs during the DOAC therapy (4.9%) compared to LMWHs (8.4%) or VKAs (9.6%). However, the risk of major bleeding was 4.9%, 4.3%, and 4.1% in the DOAC, LMWH, and warfarin groups, respectively [29]. VKA therapy was significantly less effective than LMWHs (1.5-fold) and DOACs (2.0-fold) without any significant differences in the safety profile. No statistically significant differences in efficacy or safety were identified between the DOAC and LMWH groups. Nevertheless, the clinical benefit (VTE AEs and major bleeding) was maximal for the DOAC therapy (9.8%) compared to LMWHs and VKAs (12.7% and 13.7%, respectively). In patients with CAT, DOACs prevent one event (adverse VTE event or major bleeding) per 35 patients compared to LMWH and 26 patients compared to warfarin [29].

The risk of GI bleeding in patients with CAT increased 3.6-fold in the metastatic disease and 4.8-fold with reduced hemoglobin levels (<10 g/dL) during anticoagulant therapy but increased statistically insignificantly during chemotherapy [30]. The risk of bleeding reduced insignificantly after tumor resection. In another study, reduced hemoglobin was the predictor of the risk of major bleeding (HR 1.67 per 1 mg/dL, p=0.008) and clinically significant minor bleeding (HR 1.31 per 1 mg/dL) during the DOAC therapy in cancer patients with VTE AEs [31]. Thus, despite their high efficacy and safety, the use of DOACs in CAT requires careful consideration of the possible bleeding factors.

Using apixaban for patients with CAT

The DOAC apixaban inhibits the coagulation factor Xa. The efficacy and safety of the drug in treating and preventing recurrent VTE AEs was well shown in the AMPLIFY [32] and AMPLIFY-EXT [33] trials. The efficacy and safety of the drug were also demonstrated for the primary prevention of VTE AEs in patients with a history of hip and knee replacement in the ADVANCE research program [34, 35].

In order to study the efficacy and safety of apixaban compared with LMWH and warfarin in the treatment of cancer patients having a risk of VTE AEs in real-world clinical practice, a retrospective analysis of

the health insurance databases was conducted. This analysis demonstrated a statistically significant 39% reduced risk of VTE AEs when using apixaban as compared with LMWH (maximum in patients without metastases), along with a reduced risk of major bleeding by 37% (irrespective of the severity of malignancy) [36]. Similarly, when compared to VKAs, apixaban statistically significantly reduced the risk of VTE AEs by 32% and the risk of major bleeding by 27% in cancer patients of any severity with VTE AEs. There were no statistically significant differences in the efficacy and safety between warfarin and LMWH.

In the previously mentioned meta-analysis of using DOACs in patients with CAT, two (ADAM and Cravaggio) of four included RCTs studied the comparative efficacy of apixaban and the LMWH dalteparin [25, 26]. In the former (ADAM–VTE), apixaban statistically significantly reduced the risk of VTE AEs by 90.1% as compared to LMWH (hazard ratio (HR) 0.099; p=0.028) with the same risk of bleeding. In the larger CARAVAGGIO study, apixaban was associated with a 37% decrease in the risk of VTE AEs compared to dalteparin (p=0.09); again, no significant difference for bleeding was identified. The chances of survival without VTE AEs and major bleeding were statistically significantly higher in the DOAC group compared with LMWH (HR 1.36; 95% CI: 1.05; 1.76).

Thus, given that the evidence base for apixaban in the treatment and prevention of recurrent VTE AEs in cancer patients is based on several trials conducted by different expert groups, it becomes relevant to summarize the findings in a meta-analysis in order to create more convincing evidence for using the drug in this patient group.

Thus, the objective of this work was a systematic search for the comparative RCTs of the clinical efficacy and safety of apixaban in cancer patients with acute VTE AEs who require treatment and prevention of recurrent events.

New meta-analysis on using apixaban in CAT

The study was conducted following the protocol and the PRISMA guideline [37]. A systematic literature search was carried out in the database of abstracts Medline (PubMed), Cochrane Library (CENTRAL database), and eLibrary. The temporal search range was unlimited. The following keywords were queried: «apixaban AND cancer», «apixaban AND malignancy», «apixaban AND tumor» in Medline and the Cochrane Library; «apixaban and cancer», «apixaban and malignancy» in the eLibrary. The systematic search was carried out from December 1 to December 10, 2020.

Given the objective of this study to assess the efficacy and safety of apixaban for the treatment and secondary prevention of VTE AEs in cancer, the following criteria were formulated for the selection of papers: RCTs of using apixaban in adult patients with VTE AEs developed during active cancer (CAT), who have absolute indications for anticoagulant therapy, as compared to LMWHs and/or VKAs; RCTs presenting information on at least one parameter of clinical efficacy and safety used in this systematic review.

In this systematic review and meta-analysis, new VTE AEs (symptomatic or documented proximal DVT and/or symptomatic, documented, or fatal PE with symptomatic upper limb thrombosis, as well as celiac and cerebral venous thrombosis, if not included in the efficacy endpoint in the initial trials) were used as the primary endpoint of clinical efficacy. Major bleeding, in accordance with ISTH criteria, was the primary safety endpoint. Other endpoints were major/clinically significant minor bleeding and all-cause mortality. The follow-up period was 6 months.

The systematic search and selection of papers was conducted by three independent investigators. In case of divergence of opinions, the decision was made in favor of the opinion held by two of the three investigators. Language or type of papers were not inclusion criteria in this meta-analysis. Two independent investigators extracted information from the selected trials.

Hazard ratio (HR) was used as a measure of effect. Meta-analysis was performed using the Mantel-Haenszel method and R software. Statistical heterogeneity assessed using the Cochrane test (I^2) and considered significant with $I^2 \geq 50\%$ formed the basis for meta-analysis applied using a random effects model. Heterogeneity was also estimated using the chi squared test (χ^2) with a statistical significance threshold of $p<0.1$.

The selected value of I^2 is that commonly used in systematic reviews performed according to Cochrane guidelines [38] by Cochrane researchers [39–42]. When statistical heterogeneity did not achieve 50%, a fixed-effect model was used for the meta-analysis.

The methodological quality of the included RCTs was assessed using a Cochrane tool [41]. Since only a few trials were included in the meta-analysis, the risk of publication bias was not assessed.

The complete scheme of selection is shown in Figure 2. The systematic search identified 678 records, of which 663 records were excluded following analysis of headings and abstracts. In the second stage, the complete versions of the papers selected the previous stage were evaluated. Of the fifteen previous trials selected at the first stage,

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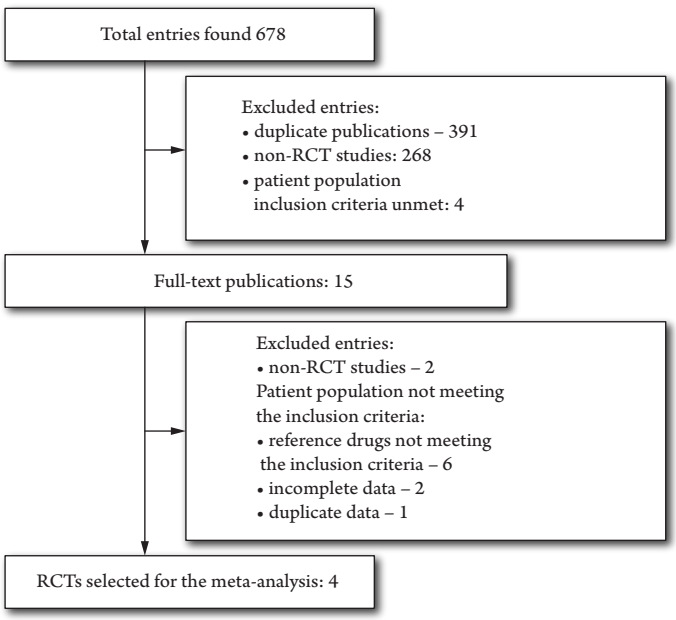
four papers presenting the results of four RCTs were selected for the meta-analysis.

Thus, the meta-analysis of data on using apixaban in CAT included four trials: ADAM VTE [25], data for cancer subgroup in AMPLIFY [32], CARAVAGGIO [26], and Mokadem M.E. et al., 2020 [43]. The characteristics of the trials are also provided in Table 1.

The evaluation of the methodological quality of the selected studies is provided in Table 2. Among the RCTs evaluating the efficacy of apixaban in treating VTE AEs, two trials (ADAM VTE and CARAVAGGIO) had high methodological quality, AMPLIFY had moderate methodological quality, while the trial by Mokadem M. E. et al., 2020 had low methodological quality.

Figure 2. Selection of publications to be included in the meta-analysis



The selected high doses of apixaban (20 mg/day in the first week following by 10 mg/day) were based on the results of a preliminary study carried out in patients with metastatic cancer [44]. These doses are now standard to treat patients with any VTE AEs [32, 33]. The results of the meta-analysis showed that apixaban is statistically significantly more effective than active control in reducing the risk of recurrent VTE AEs in cancer patients: HR 0.59, 95% CI: 0.40–0.86; p=0.006 (Table 3). The heterogeneity of the trials was low (χ^2=3.58; p=0.32; I^2=14%). There were no statistically significant differences between apixaban and active control in terms of the effect on the risk of major bleeding (HR 0.79, 95% CI: 0.48–1.30; p=0.35 (Table 3); however, there were less statistically significant differences between the DOAC therapy as compared to LMWHs or VKAs. The heterogeneity of the trials was low (χ^2=1.96; p=0.58; I^2=0). Additional analysis did not identify intergroup differences in the secondary endpoints: the cumulative risk of major/clinically significant minor bleeding (HR 0.94, 95% CI: 0.56–1.57) (Table 3) and the risk of all-cause death (HR 0.96, 95% CI: 0.80–1.16, including PE and cancer (Table 3).

Three RCTs compared apixaban with LMWHs, the gold standard for treating CAT. In the AMPLIFY study, LMWH was used in the control group for 5–7 days, followed by a transfer to VKA. Therefore, we carried out an additional sensitivity analysis to exclude the latter study, leaving only the comparison of the DOAC apixaban and LMWH.

Table 1. Characteristics of RCTs included in the meta-analysis

RCT	Apixaban	Control	Age, years	Type of thrombosis	Type of cancer	Duration
ADAM VTE [25]	N = 150, -10 mg bidfor 7 days followed by 5 mg bid	N = 150, dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily	Apixaban 64.4 ± 11.3; control 64.0 ± 10.8	API: PE 55.1%; DVT 48.3%; control: PE 50.7%; DVT 47.3%	Lung cancer, pancreatic cancer, colorectal cancer, breast cancer, etc.	6 months
AMPLIFY [32]	N = 88, 10 mg bidfor 7 days followed by 5 mg bid	N = 81, enoxaparin 1 mg/kg bid for 5–7 days followed by warfarin (INR 2–3)	Apixaban ≈ 65.5; control ≈ 65.1	API: PE 83.3%; DVT 79.3%; control: PE 77.3%; DVT 82.4%	Prostate cancer, breast cancer, rectal cancer, etc.	6 months
CARAVAGGIO [26]	N = 576, 10 mg bidfor 7 days followed by 5 mg bid	N = 579, dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily	Apixaban – 67.2 ± 11.3; control – 67.2 ± 10.9	API: PE – 52.8%; DVT – 47.2%; control: PE 57.7%; DVT 42.3%	Colorectal cancer, lung cancer, breast cancer, urogenital cancer, etc.	6 months
Mokadem M. E. et al., 2020 [43]	N = 59, 10 mg bidfor 7 days followed by 5 mg bid	N = 50, enoxaparin 1 mg/kg bid	Apixaban 61.3 ± 11.2; control – 59.9 ± 9.7	API: DVT 100.0%; control: DVT 100.0%	Rectal cancer, prostate cancer, breast cancer, ovarian cancer, etc.	6 months

API – apixaban; PE – pulmonary embolism; DVT – deep vein thrombosis.

Table 2. Assessment of the methodological quality of analyzed RCTs

RCT	Offset resulting from the randomization process	Offset due to deviations from the scheduled interventions	Offset due to lacking data on results	Bias in measuring the result	Bias in selecting the reported result
ADAM VTE trial [25]	?	+	+	+	+
AMPLIFY [32]	+	+	+	+	?
CARAVAGGIO [26]	?	+	+	+	+
Mokadem M. E. et al. 2020 [43]	?	?	–	–	?

Table created by RoB 2 [41]. Designation: green color and a plus sign – low risk of offset (bias); yellow color and a question mark – unclear risk of offset; red color and a minus sign – high risk of offset.

In general, the results for efficacy or safety were unchanged. The reduction of the risk of VTE AEs during the apixaban therapy compared to LMWH was 40% (HR=0.60; 95% CI 0.41–0.89; p=0.01) with low heterogeneity (χ^2=3.11; p=0.21; I^2=36%). The risks of major bleeding were not statistically significantly different between the apixaban and LMWH groups (HR=0.83; 95% CI 0.49–1.41; p=0.50) with acceptable heterogeneity (χ^2=1.48; p=0.48; I^2=0). There were no statistically significant differences between the cumulative risk of major/clinically significant minor bleeding (HR=1.22; 95% CI 0.89–1.61; p=0.21) with acceptable heterogeneity (χ^2=0.26; p=0.61; I^2=0). The differences in all-cause mortality were calculated in only three trials where the DOAC apixaban was compared to LMWH.

Discussion

A meta-analysis of trials estimating the clinical efficacy and safety of apixaban in treating and preventing recurrent VTE AEs demonstrated its statistically significantly superiority to the active control, including the accepted gold standard of CAT therapy, in terms of its efficacy (reducing the risk of VTE AEs) in cancer patients. There were no statistically significant differences between apixaban and the active control in either the incidence of major bleeding or the incidence of major/clinically significant minor bleeding, and all-cause mortality, although the risk of major bleeding was 21% lower than when using DOACs (17% lower than in case of using LMWHs in the additional sensitivity analysis). Thus, apixaban was shown in this trial to be more effective in preventing recurrent VTE AEs in cancer patients than in the control without an increased risk of bleeding complications and with comparable all-cause mortality. At the same time, a convenient dosing regimen makes this drug a first choice when treating CAT.

These results do not generally contradict the previously published findings on apixaban in the treatment and prevention of VTE AEs in various groups of patients. Apixaban administered in non-cancer patients with acute DVT or PE was shown in the AMPLIFY study to be effective in preventing recurrent VTE AEs comparable to the conventional regimen with LMWH followed by VKA, with a lower risk of major bleeding and major/clinically significant minor bleeding [32]. A retrospective sub-analysis in the AMPLIFY patients with cancer showed a 61% reduction in the risk of VTE AEs with a 54% reduction in the risk of major bleeding and a 44% reduction in major/clinically significant minor bleeding compared to the control [42].

When interpreting the findings, it is important to take into consideration some limitations due to the peculiarities of the evidence base. First, the range of cancers (tumor localization and extent) was different, and there were differences in the percentages of subjects with DVT and PE. Nevertheless, the groups were well balanced in each included RCT. Therefore, differences in the structure of VTE AEs and the range of malignancies can be assumed have the least influence on the interpretability of the results given the common pathophysiological mechanisms of VTE AEs in cancer.

Second, the included RCTs differed in the individual elements of the design. In the RCTs on apixaban used to treat CAT, different drugs were used in the comparison groups: enoxaparin (Mokadem et al. [43]), dalteparin (ADAM VTE [25], CARAVAGGIO [26]), and enoxaparin followed by warfarin (AMPLIFY [42]);

It should be noted regarding the heterogeneity of the included trials that the weight of trials of using apixaban to treat VTE AEs compared to LMWH, the gold standard for treating VTE AEs in cancer patients, was more than 85% in terms of the effect on the risk of VTE AEs, major bleeding and all-cause mortality, and more than 70% in terms of the risk of major/clinically

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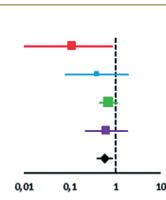
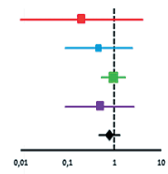
Table 3. Meta-analysis of the trials of using apixaban to treat VTE AEs in cancer patients

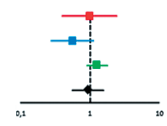
A. Adverse events of venous thromboembolism

Trial	Apixaban		Control		Trial weight	HR, MH, fixed, 95% CI	HR, MH, fixed, 95% CI
	Event	n	Event	n			
ADAM VTE	1	145	9	142	13.4%	0.11 (0.01; 0.85)	
AMPLIFY	2	81	5	78	7.5%	0.39 (0.08; 1.93)	
CARAVAGGIO	32	576	46	579	67.4%	0.70 (0.45; 1.08)	
Mokadem M. E. et al, 2020	5	69	8	69	11.8%	0.63 (0.22; 1.82)	
Result (95% CI)	40	871	68	868	100%	0.59 (0.40; 0.86)	
Assessment of heterogeneity p = 0.32, I^2 = 14%							

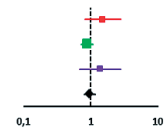
B. Major bleeding

Trial	Apixaban		Control		Trial weight	HR, MH, fixed, 95% CI	HR, MH, fixed, 95% CI
	Event	n	Event	n			
ADAM VTE	0	145	2	142	7.5%	0.20 (0.01; 4.04)	
AMPLIFY	2	87	4	80	12.4%	0.46 (0.09; 2.44)	
CARAVAGGIO	22	576	23	579	68.2%	0.96 (0.54; 1.71)	
Mokadem M. E. et al, 2020	2	69	4	69	11.9%	0.50 (0.09; 2.64)	
Result (95% CI)	26	877	33	870	100%	0.79 (0.48; 1.30)	
Assessment of heterogeneity p = 0.58, I^2 = 0%							

B. Major/clinically significant minor bleeding

Trial	Apixaban		Control		Trial weight	HR, MH, random, 95% CI	HR, MH, random, 95% CI
	Event	n	Event	n			
ADAM VTE	9	145	9	142	21.6%	0.98 (0.40; 2.40)	
AMPLIFY	11	87	18	80	29.5%	0.56 (0.28; 1.12)	
CARAVAGGIO	70	576	56	579	48.9%	1.26 (0.90; 1.75)	
Result (95% CI)	90	808	83	801	100%	0.94 (0.56; 1.57)	
Assessment of heterogeneity p = 0.12, I^2 = 54%							

D. All-cause mortality

Trial	Apixaban		Control		Trial weight	HR, MH, fixed, 95% CI	HR, MH, fixed, 95% CI
	Event	n	Event	n			
ADAM VTE	23	145	15	142	8.5%	1.50 (0.82; 2.76)	
CARAVAGGIO	135	576	153	585	85.4%	0.88 (0.72; 1.08)	
Mokadem M. E. et al, 2020	15	69	11	69	6.1%	1.36 (0.68; 2.75)	
Result (95% CI)	173	799	179	796	100%	0.96 (0.80; 1.16)	
Assessment of heterogeneity p = 0.12, I^2 = 54%							

A – adverse events of venous thromboembolism; B – major bleeding;
C – major/clinically significant minor bleeding; D – all-cause mortality.

significant minor bleeding. An additional sensitivity analysis confirmed the superiority of apixaban to LMWH in treating CAT.

Third, the appraisal of methodological quality in studies of VTE AE treatment and prevention in cancer patients identified trials with high-to-moderate and low methodological quality. However, it seems unlikely that low-quality trials could have introduced significant bias. In the case of the RCTs evaluating the treatment of VTE AEs, the weight of the RCT by Mokadem M. E. et al.,

2020 [43], which had a relatively low quality, did not exceed 12%. Thus, its influence on the result was low.

It should also be noted that the meta-analysis showed a relatively low heterogeneity in the primary efficacy and safety endpoints, e.g., I^2 was 14% for the influence on the risk of VTE AEs in cancer patients with venous thrombosis and 0% in the analysis of the influence on the risk of major bleeding.

In a previous meta-analysis comparing DOACs to LMWHs in CAT, which also included rivaroxaban and edoxaban, the weight of two RCTs on apixaban was more than 40%, and only one of them (ADAM–VTE) showed a significant superiority of DOACs to LMWHs [25]. Moreover, apixaban was effective and safe in preventing VTE AEs in cancer patients [36]. Our meta-analysis allowed the combination of data on the clinical efficacy and safety of the DOAC apixaban in the treatment and prevention of recurrent VTE AEs in cancer patients. Thus, the relevance of our work is determined by the fact that the individual RCTs included in the analysis did not provide comprehensive information on the efficacy and safety profile of apixaban in this patient population. Three of the four RCTs on apixaban used in VTE AEs in cancer patients showed only a statistically insignificant trend to greater efficacy of apixaban compared to control, which was apparently because of an insufficient power of the individual trials [26, 32, 43]. Combining the results of the four RCTs allowed making the conclusion that apixaban was superior to active control in reducing the risk of recurrent VTE AEs in cancer patients. All studies showed no differences with the comparison group in the safety of apixaban in treating VTE AEs. The synthesis of data from the four studies confirmed that there were no statistically significant differences in safety between apixaban and the active control.

Thus, the DOAC apixaban may be a first choice for the treatment and prevention of recurrent VTE AEs in cancer patients given its significant superiority in terms of efficacy, safety, and ease of administration as compared to LMWHs, formerly the gold standard of CAT therapy.

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Conflict of interest

The article was prepared with organizational support of the company Pfizer. The authors' opinion stated in the article may differ from the opinion of the company Pfizer.

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