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Short review

Venous thromboembolism and cancer: Current and future role of direct-acting oral anticoagulants☆,☆☆

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ABSTRACT

Approximately one-fifth of all cases of venous thromboembolism (VTE) are related to cancer and anticoagulant treatment in these patients has remained a challenge. Cancer patients with VTE are at increased risk of developing recurrent VTE compared to patients without cancer, but also have a higher risk of major bleeding. In these patients, low molecular weight heparins (LMWHs) have been shown to be more effective and as safe as vitamin K-antagonists (VKAs) for the treatment of VTE. Therefore, the majority of current clinical guidelines recommend LMWHs as the treatment of choice for cancer-associated VTE. However, several issues should be considered regarding the use of LMWHs as daily subcutaneous injections, the costs or risk of heparin-induced thrombocytopenia. In recent years, direct-acting oral anticoagulants (DOACs) have shown similar efficacy and better safety profile compared to VKAs and have become the standard of care for the treatment of VTE in the general population. Because DOACs offer a simple oral treatment regimen without the need for anticoagulation control, they could be an attractive alternative to LMWH.

Before DOACs become an accepted treatment option for cancer associated VTE, they have to be evaluated in a head-to-head comparison with LMWH. Data from two randomized trials comparing DOACs vs. LMWH have recently been published. In the present review, we will provide three clinically relevant questions on the use of DOACs in patients with cancer and VTE and provide an overview on recent evidence on this topic: 1) are DOACs a treatment option for the prevention of VTE in cancer patients?; 2) what is the place for DOACs in patients with cancer-associated VTE?; 3) should I use DOACs for the extended treatment of cancer-related VTE?.

1. Introduction

Cancer and venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), are linked by a two-way association [1]. On one hand, VTE occurs in up to 15% of cancer patients during the course of the disease and, on the other hand, cancer accounts for an estimated 18% of the total number of VTE cases [2,3]. Furthermore, the incidence of VTE is six-fold higher in patients with cancer than in patients without cancer and it is associated with significant morbidity and mortality [4]. The prevention and treatment of VTE in cancer patients is challenging, as several factors expose these patients to thrombotic complications: from the prothrombotic state related to the malignancy itself, to cancer treatments (chemo or radiation therapy or surgery) [5]. It is also recognised that while on anticoagulant treatment, patients with cancer have an increased risk of bleeding complications compared to patients without cancer [6]. In these patients, low molecular weight heparins (LMWHs) have been shown to be more effective than, and as safe as, vitamin K-antagonists (VKAs) for the treatment of VTE [7–12]. Therefore, the majority of current clinical guidelines recommend LMWHs as the treatment of choice for cancer-associated VTE [13–18]. However, several issues should be considered with regard to the long-term use of LMWHs as daily subcutaneous injections and their associated costs. In recent years, direct-acting oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban and edoxaban), have shown a similar efficacy and a better safety profile compared to VKAs and have become the standard of care for the treatment of VTE in the general population [19–22]. Their fixed-dose regimens with predictable effect, oral administration, lack of need

Abbreviations: CI, Confidence interval; DOACs, direct-acting oral anticoagulants; DVT, deep vein thrombosis; HR, hazard ratio; LMWHs, low molecular weight heparins; PE, pulmonary embolism; RR, relative risk; VKAs, vitamin K-antagonists; VTE, venous thromboembolism

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for monitoring and limited drug-food interactions, make DOACs an attractive choice for thromboprophylaxis and treatment of cancer-associated VTE. However, studies assessing the efficacy and safety of DOACs specifically focusing on VTE cancer patients have only recently become available [23,24].

In the present review, we will answer three clinically relevant questions and provide an overview on recent evidence of DOACs in patients with cancer and VTE.

2. Clinical question 1: are DOACs a treatment option for the prevention of VTE in cancer patients?

The risk of cancer-associated VTE is strongly correlated with the stage and type of cancer. Pancreatic and gastric cancers are the two gastrointestinal malignancies most commonly associated with the development of VTE with a relative rate of 23 (95% CI 19–28) and of 9.7 (95% CI 8.1–12) respectively, compared to the control population [25]. High risk malignancies with overall higher rates of VTE relative to the general population include lung cancer, gynaecological malignancies, lymphoma, and renal cell carcinoma [26]. Furthermore, the risk of VTE is increased in the presence of metastatic disease. Beyond the tumour itself, other factors are associated with the risk of VTE: many anticancer treatments for e.g. chemotherapy, radiation and surgery [5].

Routine thromboprophylaxis is not recommended in patients with cancer, however it should be considered in high risk outpatients undergoing chemotherapy, in patients with acute medical illness and in those undergoing major surgery [15].

2.1. Outpatient setting

In the outpatient setting, several risk assessment tools have been developed for calculating the risk of thrombosis in cancer patients [27–30]. The Khorana score is the most studied risk assessment model in these patients. It combines the cancer type, complete blood count and body mass index and has been designed and validated to risk-stratify ambulatory patients at high risk of VTE [27].

To improve the discriminatory performance of the Khorana score, others have proposed modifications by adding biomarker measurements [28] or type of chemotherapy [29] or performance status [30]. Moreover, a simple model including only one clinical factor (tumour-site category) and one biomarker (D-dimer) has recently been developed and validated for predicting VTE in ambulatory patients with solid cancers [31]. However, the relevance of these items for VTE risk prediction in cancer patients is still debated, as the predictive performance of the scores is limited. In a prospective cohort study aimed to compare the performance for predicting VTE in cancer patients of the Khorana, Vienna, PROTECHT, and CONKO scores, only the Vienna CATS and PROTECHT scores appear to allow better discrimination between low and high risk patients [32]. More recently, in a meta-analysis including 34,555 ambulatory cancer patients, the estimated risk of VTE in the first 6 months was 5.1% in patients with a low-risk Khorana score (0 points), 6.6% in those with an intermediate-risk Khorana score (1 or 2 points), and 11.0% in those with a high-risk Khorana score (3 points or higher) [33]. However, 23.4% of the VTE events occurred in patients with a high-risk Khorana score. The use of parenteral pharmacological prophylaxis in ambulatory cancer patients remains controversial due to concerns over the risk-to-benefit ratio, the cost and the inconvenience of parenteral therapy. In a Cochrane review including 12,352 ambulatory cancer patients receiving treatment with chemotherapy, LMWH was associated with a significant reduction of recurrent VTE [relative risk (RR) 0.54, 95% CI 0.38 to 0.75] but with an increased risk of major bleeding (RR 1.44, 95% CI 0.98 to 2.11) compared to placebo [34]. No difference in mortality at 1 year was observed between the 2 groups (RR 1.02, 95% CI 0.96 to 1.08). Therefore, current clinical practice guidelines do not recommend routine thromboprophylaxis for ambulatory cancer patients, except in selected high-risk patients, such as patients with multiple myeloma receiving anti-angiogenesis agents with chemotherapy and/or dexamethasone, where prophylaxis with LMWH or low-dose aspirin is recommended [13–15].

The use of DOACs as thromboprophylactic agents in ambulatory cancer patients receiving chemotherapy may offer important advantages regarding route of administrations and costs. However, whether DOACs represent a suitable alternative for the prevention of VTE in these patients still remains unknown. In a phase II, randomized, dose finding study, apixaban at a dose of 5 mg, 10 mg or 20 mg was associated with similar rate of major bleeding (3.4% vs. 2.1%) and with low rate of symptomatic VTE (1.1% vs. 13.8%) compared to placebo in cancer patients receiving chemotherapy [35]. Recently, findings from two randomized trials aiming to assess the efficacy and safety of DOACs in ambulatory cancer patients at high risk for VTE have been presented. The CASSINI study was a double-blind randomized trial, aiming at assessing the efficacy and safety of 10 mg rivaroxaban (once daily) vs. placebo in 841 ambulatory patients with various cancers at high risk of VTE (Khorana score ≥ 2) initiating a new systemic regimen [36]. During the study period of 180 days, the primary efficacy outcome (the composite of objectively confirmed symptomatic or asymptomatic lower-extremity proximal DVT, symptomatic upper- or lower-extremity distal DVT, symptomatic or incidental pulmonary embolism and VTE-related death) occurred in 5.9% and in 8.8% of patients in the rivaroxaban and placebo groups, respectively (HR 0.66; 95% CI, 0.40 to 1.09; p = 0.101). Over one-third of events occurred post discontinuation of study drug. Major bleeding occurred in 1.98% and in 0.99% of patients in the rivaroxaban and placebo groups, respectively (HR 1.96; 95% CI, 0.59 to 6.49; p = 0.265). Clinically relevant non-major bleeding occurred in 2.72% and 1.98% in the two groups, respectively (HR 1.34; 95% CI, 0.54 to 3.32; p = 0.53). Similarly, results from the AVERT study, a randomized trial comparing 2.5 mg apixaban (twice daily) or placebo in patients with various cancer at high risk for VTE (Khorana score ≥ 2) and initiating chemotherapy have recently been published [37]. The incidence of major VTE – defined as any symptomatic or incidentally detected proximal DVT of the lower or upper extremities, any nonfatal symptomatic or incidental pulmonary embolism, and pulmonary embolism-related death, occurred in 4.2% of the 288 apixaban-treated patients and 10.2% of the 275 given placebo, and equated to a significant 59% reduction in the risk for major VTE with the DOAC (HR 0.41; 95% CI 0.26–0.65; P < 0.001). Rates of major bleeding were 3.5% in the apixaban group and 1.8% in the placebo group over the 180-day follow-up period (HR 2.00; 95% CI 1.01–3.95; P = 0.046). However, despite brain cancer patients not being excluded from the study, no cases of fatal bleeding or bleeding into critical organs occurred in either groups.

According to these results, a reduced risk of VTE in patients with various cancers initiating chemotherapy has been observed with DOACs. Although the studies were not powered to detect bleeding differences, a two-fold increased risk of major bleeding was observed for DOACs: a not significant increase in the CASSINI and a significant increase in the AVERT modified intention-to-treat analysis (the difference was lost when the analysis was limited to the treatment period [(HR 1.89, 95% CI, 0.39–9.24)]. No difference in mortality was observed between the two groups. However, it may be difficult to imagine how an antithrombotic can protect the negative evolution of an advanced cancer. Few limitations should also be taken into account such as the non-generalizability of the results in the overall cancer patient population. Indeed, cancer patients on chemotherapy with a Khorana score < 2, with kidney failure or severe thrombocytopenia or receiving drugs potentially interfering with DOAC were excluded from the study.

Similarly, the preliminary results of the CASSINI study are promising and corroborate with those from the AVERT trial. Indeed, in our opinion, the prophylactic use of rivaroxaban and apixaban in cancer patients undergoing chemotherapy who are at risk for VTE events (Khorana score ≥ 2) should be encouraged.

Moreover, apixaban (2.5 mg twice daily for 6 months) is also being

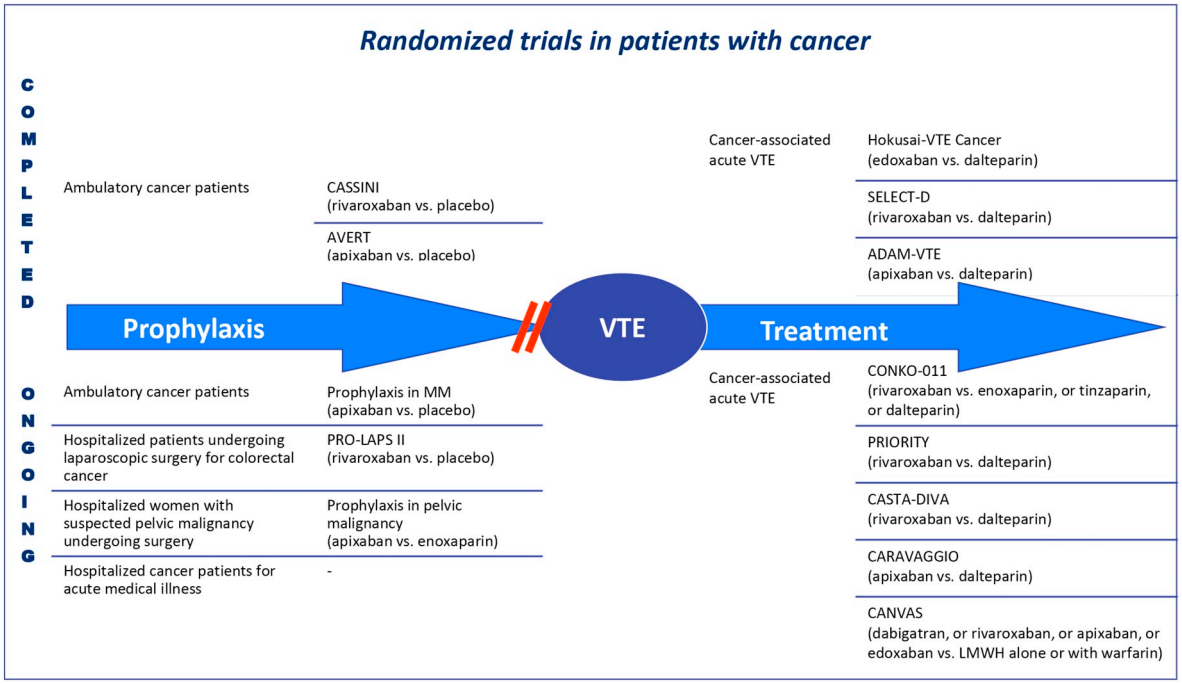

Fig. 1. Summary of randomized trials on DOACs in patients with cancer.
VTE = venous thromboembolism.

compared to placebo for primary prevention of VTE in patients with multiple myeloma receiving immunomodulatory therapy without a history of prior VTE (NCT02958969) [38]. Positive data in this setting have recently become available [39]. Data from the 3-months interim analysis of a pilot phase IV study on 50 patients with multiple myeloma receiving immunomodulatory and apixaban 2.5 mg twice daily as thromboprophylaxis showed that no patients experienced VTE, major hemorrhage, stroke, or myocardial infarction [39]. A summary of ongoing randomized trials on DOACs in patients with cancer is shown in Fig. 1.

However, how long thromboprophylaxis should be extended or whether thromboprophylaxis may impact on the prognosis of cancer patients is still debated. Indeed, an individual patient data meta-analysis including 13 RCTs to evaluate the impact of thromboprophylaxis in oncological patients showed a reduced risk of VTE with LMWHs (RR 0.58, 95% CI, 0.48 to 0.71) and no increase of bleedings. However, no improvement in survival was observed [40].

2.2. Surgical setting

Among hospitalized patients affected by cancer, the risk of VTE is particularly high in the first 6 weeks after cancer surgery or during hospitalization, due to an acute medical illness [41].

Multiple randomized controlled trials have explored the role and optimal duration of thromboprophylaxis in cancer patients undergoing surgery. In a meta-analysis including studies comparing perioperative pharmacological thromboprophylaxis in cancer patients undergoing surgery with no pharmacological prophylaxis (including mechanical prophylaxis or no prophylaxis), a 50% reduction in the rate of DVT with pharmacological prophylaxis was observed [42]. Patients in the pharmacological prophylaxis arm had an acceptable increase in the risk of bleeding, without a difference in mortality and PE. In addition, a meta-analysis based on 7 randomized studies (4807 patients) showed that extended thromboprophylaxis (2–6 weeks) following abdominopelvic cancer surgery significantly reduced the risk of all VTE (RR 0.44, 95% CI 0.28–0.70) and proximal DVT (RR 0.46, 95% CI 0.23–0.91) by approximately 50% when compared to conventional duration of thromboprophylaxis (< 2 weeks) [43]. No difference was found in the incidence of symptomatic PE, major bleeding events, and 3-month all-cause mortality. International guidelines recommend the use of thromboprophylaxis with LMWH before and 7–10 days after surgery and to extend thromboprophylaxis with LMWH or fondaparinux for 4 weeks after extensive abdominal or pelvic surgery for cancer [44].

Data on the efficacy and safety of DOACs in these settings are not yet available. In the PRO-LAPS study, we have previously compared the efficacy and safety of antithrombotic prophylaxis with LMWHs for 1 week (short) or 4 weeks (extended) in patients undergoing laparoscopic surgery for colorectal cancer [45]. In the same population and setting (after one week from laparoscopic surgery), the randomized double-blind controlled PRO-LAPS II study, is recruiting patients to assess the efficacy and safety of extended prophylaxis with 10 mg rivaroxaban (once daily) vs. placebo (NCT03055026) [46].

In another ongoing trial, women with suspected pelvic malignancy are receiving prophylactic doses of apixaban (2.5 mg twice daily) compared to enoxaparin (40 mg once daily) for 28 days post-surgery (NCT02366871) [47].

2.3. Inpatient medical setting

Albeit it is reasonable that hospitalized cancer patients for medical illness need thromboprophylaxis, no specific trials on this setting are currently available. Data from cancer subgroups from 3 RCTs showed a pooled RR of venous thromboembolic events of 0.91 (95% CI, 0.21–4.0) among hospitalized patients with cancer who were receiving thromboprophylaxis compared with placebo [48]. The use of anticoagulant thromboprophylaxis for all hospitalized patients with cancer for acute medical illness is considered standard practice, but recommendations are extrapolated from trials on non-cancer medically ill patients. In these patients, in-hospital thromboprophylaxis should be considered in cases of acute medical illness. This conclusion is supported by findings from a subgroup analysis showing that antithrombotic prophylaxis administered to cancer patients during admission for medical illness reduced the risk of symptomatic VTE complications by approximately 70%, with a bleeding risk lower than 1.5% [49].

In conclusion, thromboprophylaxis is required in cancer patients during hospital stay, undergoing surgical procedures and in those receiving chemotherapy at high risk of VTE. To date, LMWHs are the first-choice agents but DOACs could be an attractive alternative. However, further data on the efficacy and safety of DOACs in these settings are needed.

3. Clinical question 2: what is the place for DOACs in patients with cancer-associated VTE?

The proportion of cancer patients included in phase III trials comparing DOACs with VKAs (EINSTEIN PE and DVT, AMPLIFY, RECOVER I & II and Hokusai-VTE) ranged between 3 and 9% [50–53]. Although some limitations should be taken into account (cancer patients included probably had a low risk profile, VKAs was used as comparator), the sub-group analyses evaluating the efficacy and safety of DOACs in cancer patients from these studies showed encouraging results. When the data on cancer patients from the 6 randomized controlled trials were pooled in a meta-analysis DOACs were associated with a non-significant reduction of recurrent VTEs [odds ratio (OR) 0.63, 95% CI 0.37 to 1.10] and of major bleeding (OR 0.77, 95% CI 0.41 to 1.44) compared to conventional therapy (heparin/VKAs) [54].

3.1. Completed studies

Only recently, two randomized trials comparing DOACs vs. LMWH (the currently recommended treatment in cancer patients) have been reported [23,24]. The first trial, the Hokusai-VTE Cancer was an-open label, randomizing 1050 patients with cancer and acute symptomatic or incidental VTE of whom 1046 were finally included. These patients were randomized to LMWH for at least 5 days followed by 60 mg edoxaban (once daily) or to dalteparin (200 IU/Kg daily the first month followed by 150 IU/Kg) [23]. In cases of patients with 1) a creatinine clearance of 30 to 50 ml/min or 2) a body weight ≤ 60 kg or 3) in those receiving concomitant treatment with potent P-glycoprotein inhibitors, edoxaban dose was given at the half dose of 30 mg once daily. The primary composite outcome (recurrent VTE or major bleeding), occurred in 12.8% of patients in the edoxaban arm and 13.5% patients in the dalteparin arm [hazard ratio (HR) 0.97, 95% CI 0.7 to 1.36]. In the analyses of the components of the primary outcome, recurrent VTE occurred in 7.9% of patients in the edoxaban group and in 11.3% in the dalteparin group (HR 0.71, 95% CI 0.48 to 1.06) while major bleeding occurred in 6.9% and in 4.0% in the two groups, respectively (HR 1.77, 95% CI 1.03 to 3.04). The excess of bleeding in the edoxaban-treated group was mainly accounted for by gastrointestinal bleeding in patients with gastrointestinal cancer. However, when major bleedings were divided according to their severity (categories 1 to 4), severe major bleeding at presentation (category 3 or 4) in patients with gastrointestinal cancer similar rates occurred in patients in the edoxaban and in the dalteparin groups (3.0% vs. 2.1% of patients). It should be stated that the study was underpowered to assess a difference in major bleedings between the treatment groups by cancer site [55].

The second trial, the SELECT-D, was a pilot study aimed at assessing whether rivaroxaban would offer an alternative treatment for VTE in patients with cancer. Overall, 406 cancer patients with acute VTE (instead of the 530 estimated) were randomized to rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) or dalteparin (200 IU/Kg daily the first month followed by 150 IU/Kg) [24]. At 6-months, recurrent VTEs were significantly reduced in patients in the rivaroxaban arm compared to those in the dalteparin arm (4% vs. 11%, HR 0.43, 95% CI 0.19 to 0.99). Both major and clinically relevant non-major bleeding occurred more frequently in patients receiving rivaroxaban compared to those receiving dalteparin (HR 1.83, 95% CI 0.68 to 4.96, for major bleeding and HR 3.76, 95% CI 1.63 to 8.69, for clinically relevant non-major bleeding). Similar to the Hokusai-VTE Cancer trial, most of the bleeding events also occurred at the gastrointestinal site.

Data from these two studies were pooled together with randomized clinical trials comparing different anticoagulant strategies in patients with cancer-associated VTE in a network meta-analysis [56]. Many limitations should be underlined for this approach, mainly because the results of cancer-specific studies and of the subgroups from the phase 3 DOAC trials were pooled together. Moreover, the definition of active cancer was heterogeneous throughout the studies. Overall, 4720 patients from 12 studies revealed no significant differences in terms of recurrent VTE for LMWHs compared to DOACs (RR 1.3, 95% CI 0.91 to 2.0), but a significant reduction for both LMWHs and DOACs compared to VKAs was observed. No significant differences among groups were observed for major bleeding: 4.9%, 4.3% and 4.1% for DOACs, LMWHs and VKAs, respectively.

Results from these trials have been discussed in a recent consensus document from ISTH SSC [57]. Indeed, authors suggested using: i) DOACs as first option for cancer patients with acute VTE, provided they had a low risk of bleeding and no drug-drug interactions with concomitant systemic therapy; ii) LMWH for cancer patients with acute VTE and high risk of bleeding (e.g. patients with luminal gastrointestinal or with genitourinary cancer) [57]. However, it should be stated that no formal systematic review of the literature was performed in making these ISTH guidance recommendations, as in other guidelines [18,57,58]. The use of DOACs also entered as an alternative treatment in the recent NCCN guidelines [18]. Panel members categorized as level 1 (high-level evidence, uniform NCCN consensus that the intervention is appropriate) the use of dalteparin and LMWH followed by edoxaban. The use of other DOACs has been categorized as 2A (lower-level evidence, uniform NCCN consensus that the intervention is appropriate). NCCN Guidelines list urinary or GI tract lesions, pathology, or instrumentation as relative contraindications to DOACs in patients with cancer.

According to the treatment algorithm of the Canadian expert opinion consensus, LMWHs should still be considered in patients at high risk of bleeding (active gastrointestinal or urothelial cancer) or those taking concomitant medications with potentially serious drug–drug interactions with DOACs, in those with body weight > 120 kg (or BMI > 40 kg/m2), extensive VTE, moderate renal impairment, significant gastrointestinal surgery or absorption disorders [58]. Further positive data on DOACs have just been released. In the ADAM-VTE study (NCT02585713), lower rates of major bleedings (0 vs. 2.1%, p = 0.996) and of VTE recurrences (3.4 vs. 14.1%, p = 0.018) were observed in the apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) compared to the dalteparin group [59].

The various aforementioned consensus documents provide advice on the use of DOACs in patients with gastrointestinal or genitourinary lesions. The mechanism responsible for these organ-specific bleeding in patients with DOACs is unclear. A likely explanation may be the concentration of active drug that accumulates in the gastrointestinal tract, which has the potential to induce local bleeding [60]. Other mechanisms include mucositis and toxicity provoked by chemotherapy. Increased bleeding has also been observed at genitourinary sites for which the risk related to the local lesion has been advocated. Among patients with genitourinary cancer from the Hokusai-VTE Cancer, major bleeding occurred in 4.6% of patients receiving edoxaban and in 1.4% of those receiving dalteparin [55]. Similarly, clinically relevant non-major bleedings at genitourinary site occurred in 5.4% of patients receiving rivaroxaban and 1% receiving dalteparin [24]. Considering these observations, we agree on the cautious use of DOACs in these settings until results from ongoing studies become available.

3.2. Ongoing studies

The scenario in the near future will be enriched by other ongoing studies comparing DOACs to LMWH for cancer-related VTE. Both the CASTA-DIVA (NCT02746185) and CONKO-011 (NCT02583191) trials

randomized patients with cancer-associated VTE to receive rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) or LMWH (being dalteparin in the CASTA-DIVA and enoxaparin, or tinzaparin, or dalteparin given at standard doses in the CONKO-011) for 3 months [61,62]. The PRIORITY trial (NCT03139487) is comparing rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) to dalteparin (200 IU/Kg daily for 30 days followed by 150 IU/kg daily thereafter) for a treatment duration of 6 months [63].

One ongoing study (CARAVAGGIO) is comparing apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) to dalteparin (200 IU/Kg daily for 30 days followed by 150 IU/kg daily thereafter) for 6 months (NCT03045406) [64]. Furthermore, the CANVAS study randomizes patients with cancer-associated VTE to receive one of the DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) or LMWH alone or with warfarin for 6 months (NCT02744092) [65].

3.3. Cohort studies

Since their approval, the use of DOACs for the treatment of acute VTE in clinical practice has rapidly increased. Thus, multiple observational cohort studies have recently been published, describing initial experiences even in the cancer population. A systematic review and meta-analysis of real-world studies evaluating rivaroxaban for cancer-associated VTE showed an incidence of recurrent VTE of 4.2% (95% CI 2.6 to 6.6%; $I^2 = 31\%$), major bleeding of 2.9% (95% CI 1.6 to 5.0%; $I^2 = 59\%$), and all-cause mortality of 16.1% (95% CI 6.0 to 36.6%; $I^2 = 96\%$) [66]. Recently, a large observational study including 2428 patients with newly diagnosed cancer who initiated anticoagulation (707 patients on rivaroxaban; 660 patients on LMWH; 1061 patients on warfarin) from the Humana database has been published [67]. The 6-month rate of VTE recurrence in rivaroxaban users was (non-significantly) lower than that observed in LMWH users (13.2% vs. 17.1%; $P = 0.06$), while rates of major bleeding were similar between the two groups (8.3% vs. 8.2%, respectively; $P = 0.917$). The majority of bleeding events were gastro-intestinal in each group. In this real-world cohort, event rates were higher than those reported in phase III clinical trials. However, no bleeding concerns were observed for rivaroxaban in these real-world studies.

3.4. Specific situations

Further important issues should be considered in cancer patients on anticoagulation for an acute VTE episode. Studies and registries report suboptimal adherence to guideline-recommended anticoagulant therapy even during the acute treatment period [68]. Data from the RIETE study database showed that one in every two patients received lower daily doses of LMWH than those used in the randomized trials [69]. Among LMWHs, a 25% dose reduction after the first month of treatment has only been validated in RCTs for dalteparin. This regimen, already tested in the CLOT study, could be supported by data from a study showing that although initially similar, the case-fatality rates of recurrent VTE progressively decreased during anticoagulation, while those of major bleeding barely varied over time. The case-fatality rates of major bleeding exceeded those of recurrent VTE after the first month of therapy [70].

Another issue is the fluctuations of hematological parameters due to anticancer treatment and blood cancer. In particular, thrombocytopenia challenges clinicians in the management of antithrombotic therapy, often resulting in treatment discontinuation and increasing the risk of bleeding. Several studies reported on the administration of reduced doses of LMWH according to platelet count in cancer patients with VTE and thrombocytopenia [71–73] but no randomized trials are yet available. Therefore, the empirical cut off of 50,000/mm^3 for full dose of LMWH administration was based on the consensus of having a low risk of spontaneous bleeding above this level [74]. When platelet count falls ranging from 49,000 to 30,000/mm^3, the dose of LMWH should be halved [74]. Below 30,000/mm^3 platelets, LMWHs at prophylactic dose or inferior cava filters or platelet transfusion should be considered. When using DOACs in patients with acute VTE and thrombocytopenia some aspects should be considered. In the phase 3 studies on DOACs vs. LMWH, different cut-off values of platelets have been used among inclusion criteria. The minimum platelet value for study inclusion was 50,000/mm^3 in the Hokusai VTE Cancer (6.1% of patients in the edoxaban group had platelet values between 50,000 and 100,000/mm^3) in the ADAM-VTE and in the ongoing CANVAS and CASTA-DIVA, 75,000/mm^3 for the ongoing Caravaggio and PRIORITY trials, and 100,000/mm^3 for the SELECT-D and the ongoing CONKO-011. These considerations should be taken into account when choosing anticoagulant treatment.

Beyond the evaluation of cancer patient's comorbidities (i.e. renal or liver failure) and hematological parameters, a careful assessment of concomitant medication is mandatory. This includes considering the bleeding risk increase of the antithrombotic effect if acetylsalicylic acid or nonsteroidal anti-inflammatory drugs are used concomitantly with anticoagulants and the potential pharmacokinetic interaction of DOACs with anticancer treatments. Being substrates of P-glycoprotein (all DOACs) and of cytochrome P450 (rivaroxaban and apixaban), the anticipated effects of common anticancer drugs on DOAC plasma levels should be considered [58,75]. Main drug-drug interactions include vinblastine, doxorubicin, anti-mycotic agents, some hormonal agents (e.g. abiraterone, enzalutamide), some tyrosine kinase inhibitors (eg. vandetanib, sunitinib, imatinib, crizotinib), immune-modulating agents (e.g. cyclosporine, tacrolimus, dexamethasone) and protease inhibitors. However, if these pharmacokinetic interactions translate into clinically significant interactions is unknown. Furthermore, vomiting and gastrointestinal toxicity of some anticancer therapies (provoking stomatitis, diarrhea, etc.) should also be taken into account when choosing anticoagulant strategy, as it may compromise the absorption of DOACs from gastrointestinal tract [58]. Other issues such as upper extremity and catheter-related deep vein thrombosis lack of specific trials comparing DOACs to LMWHs.

In conclusion, several issues should be considered when choosing anticoagulation: comorbidities, interactions and even the risk of a possible reduced adherence to injectable LMWHs. From recent data, DOACs are a valid option for the treatment of VTE in cancer patients. However, the management of cancer patients at high risk of bleeding, as those with gastrointestinal and genitourinary disease, should require particular attention and LMWH may be a preferred option.

4. Clinical question 3: should I use DOACs for the extended treatment of cancer-related VTE?

The risk of recurrence of VTE is known to be high after anticoagulant discontinuation and it is estimated to be 40% within 10 years in patients with unprovoked VTE [76]. Moreover, > 10% of these recurrent VTE are fatal events [77]. Therefore, the decision to go on or to discontinue anticoagulation after a first episode of VTE should be individually tailored and balanced against the haemorrhagic risk. This is particularly true in cancer patients, as active cancer is a major risk factor for both recurrence of VTE and for major bleeding while on anticoagulant treatment (10 and 5%, respectively) [78]. As mortality after cancer-associated VTE is approximately 35% at 6 months [79] is important to know the case fatality rates of recurrent VTE and major bleeding for weighing the relative risks and benefits of anticoagulation in patients with cancer-associated VTE. In this context, in a recent systematic review, the case fatality from recurrent thrombosis was higher than the case fatality from major bleeding in RCTs (17.3% vs. 10.8%) [80]. However, there is no consensus with regard to the duration of anticoagulation following the diagnosis of VTE in cancer patients. To date, due to the high risk for VTE recurrence, patients with cancer should receive anticoagulation after a first episode of VTE for at least 3 to 6 months, as long as there is clinical evidence of active

Table 1
Venous thromboembolism and cancer: from clinical questions to clinical practice.

Current recommendations	Near future
Clinical question 1: are DOACs a viable treatment option for the prevention of VTE in cancer patients?	
Routine thromboprophylaxis for ambulatory cancer patients is not recommended, except in selected high-risk patients (e.g. multiple myeloma receiving anti-angiogenesis agents with chemotherapy and/or dexamethasone) using LMWHs [13–15].	CASSINI: DB, 10 mg rivaroxaban o.d. vs. placebo in ambulatory cancer patients (Khorana score ≥ 2) receiving chemotherapy. TD: 6 months (preliminary data available) Prophylaxis in patients with multiple myeloma: DB, 2.5 mg apixaban b.i.d. vs. placebo in patients with multiple myeloma receiving immunomodulatory therapy. TD: 6 months
Guidelines recommend the use of thromboprophylaxis with LMWH before and 7–10 days after surgery and to extend thromboprophylaxis with LMWH or fondaparinux for 4 weeks after extensive abdominal or pelvic surgery for cancer [13–15].	PRO-LAPS II: DB, 10 mg rivaroxaban o.d. vs. placebo in colorectal cancer patients undergoing laparoscopic surgery. TD: 3 weeks Prophylaxis in woman with suspected pelvic malignancy: Open, apixaban 2.5 mg b.i.d vs. enoxaparin 40 mg o.d. TD: 28 days
Thromboprophylaxis with LMWHs should be considered in hospitalized cancer patients affected by an acute medical illness [13–15].	–
Clinical question 2: what is the place for DOACs in patients with cancer-associated VTE?	
ACCP recommendations: for VTE and cancer, LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban [16]. SSC ISTH consensus: i) DOACs can be used, provided patients had a low risk of bleeding and no drug-drug interactions with concomitant systemic therapy; ii) LMWHs should be preferred in patients with high risk of bleeding (e.g. patients with luminal GI or with genitourinary cancer) [57]. NCCN guidelines: DOACs are among recommend agents for VTE and cancer unless contraindications exist (stage IV chronic kidney disease, active/clinically significant liver disease, strong dual inhibitors/inducers of CYP3A4 and P-gp for rivaroxaban and apixaban,inducers/inhibitors of P-gp for dabigatran and edoxaban) [18]. Canadian consensus: consider LMWHs in patients with high bleeding risk; taking drugs with strong drug-drug interaction; body weight > 120 kg (or BMI > 40 kg/m^2); extensive VTE; moderate renal impairment; significant GI surgery; absorption disorders [58].	CASTA-DIVA: Open, rivaroxaban (15 mg b.i.d. for 3 weeks then 20 mg o.d.) vs. dalteparin 200 IU/Kg o.d. the first month then 150 IU/Kg. TD: 3 months CONKO-011: Open, rivaroxaban (15 mg b.i.d. for 3 weeks then 20 mg o.d.) vs. enoxaparin, or tinzaparin, or dalteparin given at standard doses*. TD: 3 months PRIORITY: Open, rivaroxaban (15 mg b.i.d. for 3 weeks then 20 mg o.d.) vs. dalteparin 200 IU/Kg o.d. the first month then 150 IU/Kg. TD: 6 months ADAM-VTE: Open, apixaban (10 mg b.i.d. for 7 days then 5 mg b.i.d.) vs. dalteparin (200 IU/Kg o.d. for 30 days then 150 IU/kg o.d.). TD: 3 months (preliminary data available) CARAVAGGIO: Open, apixaban (10 mg b.i.d. for 7 days then 5 mg b.i.d.) vs. dalteparin (200 IU/Kg o.d. for 30 days then 150 IU/kg o.d.). TD: 6 months CANVAS: Open, dabigatran or rivaroxaban or apixaban or edoxaban (given at standard doses) vs. LMWH° alone or with warfarin. TD: 6 months
Clinical question 3: should I use DOACs for the extended treatment of cancer-related VTE?	
In patients with cancer-associated VTE anticoagulation is recommended for at least 3 to 6 months and as long as there is clinical evidence of active malignant disease or until the end of specific cancer treatment [16].	API-CAT: DB, 2.5 mg b.i.d. apixaban vs. 5 mg b.i.d. apixaban in patients with active cancer after completing at least 6 months of anticoagulant treatment for VTE. TD: 12 months

GI = gastrointestinal; TD = treatment duration; VTE = venous thromboembolism.
Three FDA-approved LMWH drugs may be used for this study: Dalteparin, Enoxaparin, or Fondaparinux used at approved doses.
* Enoxaparin 1 mg/kg b.i.d., Tinzaparin 175 I.E./kg o.d., Dalteparin 200 I.E./kg o.d.

malignant disease or until the end of specific cancer treatment, moreover a periodical re-assessment of the benefit-to-risk ratio is needed [16].

In this setting, risk predicting scores can be helpful. The Ottawa score assessing the risk of VTE includes the following items: breast cancer (minus 1 point), tumour node metastasis Stage I or II (minus 1 point), female sex, lung cancer, and previous VTE (plus 1 point each) [81,82]. In the derivation and validation cohort of 819 patients, the recurrence rate in patients with a score of ≤0 was ≤4.5% (low-risk group) while in patients with a score of > 1 was ≥19% (high-risk group). However, to date, validation studies involving the Ottawa prognostic score reported conflicting results [83]. Therefore, it is still debatable whether the application of this score could help in the decision on whether to extend anticoagulant treatment or not.

Data on extended treatment for VTE in cancer patients are limited and do not go beyond the 12-month period. The two single-arm cohort studies DALTECAN and TiCAT followed cancer patients receiving dalteparin and tinzaparin, respectively, for VTE treatment up to 12 months [84,85]. Both studies showed that the risk of recurrent VTE or major bleeding was higher during the first 3–6 months and that the risk of recurrent VTE persist beyond 6 months. These data were confirmed in the recent Hokusai-VTE Cancer study where patients could remain in the study up to 12 months [86].

The Select-D study was initially designed with a second phase after the initial 6 months of anticoagulation [24]: patients presenting with PE or with residual DVT should have been randomized to rivaroxaban or placebo for a further 6 months. However, this phase of the study was prematurely terminated because of slow recruitment. No data on the few cancer patients included in the extended treatment phase studies on DOACs are available since sub-group analysis were not performed.

Recently, the EINSTEIN-CHOICE study compared once-daily rivaroxaban (at doses of 20 mg or 10 mg) to 100 mg of aspirin in 3396 patients with VTE who had completed 6 to 12 months [87]. Among patients included, only a minority had active cancer (2.3% on 20 mg rivaroxaban; 2.4% on 10 mg rivaroxaban, 3.3% on aspirin) and no subgroup analysis was performed in cancer patients either.

The ongoing API-CAT trial (NCT03692065) is comparing the prophylactic dose (2.5 mg twice daily) with the full dose of apixaban (5 mg twice daily) in patients with active cancer (colon, breast and prostate) after completing at least 6 months of anticoagulant treatment from the index VTE event [88].

In conclusion, DOACs represent an alternative strategy for the long-term treatment of VTE but further evidence is still needed.

5. Conclusion

The prevention and treatment of VTE in cancer patients is challenging. Current guidelines (Table 1) recommend LMWH as the first-choice agent for prophylaxis and for acute and long-term treatment of VTE in cancer patients. However, DOACs have become the standard of care for VTE treatment in the general population and have been proposed to overcome some drawbacks of LMWHs such as daily subcutaneous injection. Results from recent randomized trials on VTE treatment suggest that DOACs could be used in cancer patients at low risk of bleeding and without luminal gastrointestinal or genitourinary disease. Further data are still needed to confirm the risk-benefit profile of DOACs in various clinical scenarios of neoplastic disease.

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The authors of this review have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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