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Review Article

Extended treatment of cancer-associated thrombosis

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ABSTRACT

Venous thromboembolism (VTE) is a growing concern in patients with cancer. Current guidelines recommend that cancer patients with VTE should receive anticoagulation for at least 3–6 months. However, the question as to whether anticoagulants should be continued after 3 to 6 months of treatment remains open. In presence of an active malignancy, physicians should weigh the benefits and burdens of ongoing anticoagulation taking into account the clinical status, patient expectations, and the risk of bleeding. As the length of time from the index event increases, the available evidence is not conclusive. The most critical unresolved issues include the decision to continue or discontinue anticoagulation and the selection of the most appropriate anticoagulant agent. On this background, our article provides an overview of the available studies focusing on extended (*i.e.*, > 6 months) anticoagulation treatment in cancer-associated thrombosis, with the ultimate goal of refining real-world clinical decision-making in this patient population.

1. Introduction

Patients with cancer have an increased risk of venous thromboembolism (VTE) – a complication that generally portends worse outcomes in terms of morbidity (*e.g.*, bleeding, recurrent VTE events), mortality, and costs [1]. Numerous factors may contribute to the development of cancer-associated thrombosis (CAT), including chemotherapy, radiotherapy, surgery, and patient-related characteristics (*e.g.*, immobilization and advanced age). To rationalize the management of CAT, evidence-based clinical guidelines have been issued by several scientific societies in different countries. Given that the available evidence is the same, irrespective of the issuing body, one would expect these guidelines to include broadly similar recommendations regarding anticoagulation.

Guidelines released by the British Society for Haematology (2015) recommend that patients with CAT should be treated for 6 months with low molecular weight heparin (LMWH), if tolerated (grade 1A) [2]. Extended treatment after the initial 6 months is recommended in presence of an active malignancy taking into account the clinical status, patient expectations, and the risk of bleeding. As far as specific anticoagulant agents are concerned, these guidelines maintain that there is a rationale – albeit with scarce direct evidence – favouring LMWH maintenance (grade 2B). In their review of the literature (2015), Khalil et al. [3] concluded that early treatment (from day 10 to month 3) and long-term maintenance (*i.e.*, after 3 months of the index event) with LMWH is clinically useful to prevent VTE recurrences in patients with CAT, without increasing the risk of bleeding. The 2016 American College of Chest Physicians (ACCP) Guidelines indicate that LMWH should be preferred over vitamin K antagonists (VKA), dabigatran, rivaroxaban, edoxaban, or apixaban (grade 2C) for long-term therapy (first 3 months after the index event) of CAT [4]. Treatment after 3 months from the index event is recommended for both patients without (grade 2B) and with (grade 2C) a high risk of bleeding. The 2016 International Clinical Practice Guidelines based on the International Initiative on Thrombosis and Cancer (ITAC-CME) consensus issued the following recommendations: 1) LMWH should be used for the initial treatment of established CAT (grade 1B); 2) LMWH should be preferred over VKAs (grade 1A); and 3) anticoagulation should be continued for at least 3 months (grade 1A) [5]. These guidelines maintain that the strength of evidence for continuing treatment up to 6 months is low. Consequently, the decision to continue or discontinue anticoagulation after 3 months should be tailored at the individual level by taking into account the benefits and burdens of extended treatment, drug availability and tolerability, the patient's preferences, and cancer activity. The 2016 National Comprehensive Cancer Network (NCNN) Clinical Practice Guidelines recommend the use of LMWH for both acute and chronic treatment of CAT (Grade 1), with a minimum duration of 3 months [6]. When VTE is not catheter-related, extended anticoagulation is recommended for patients with active cancer, during oncological treatment, or in presence of risk factors for recurrent VTE. The 2017

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Table 1
Summary of the principal recommendations issued by different guidelines for patients with CAT.

Guidelines	Initial treatment	Long-term treatment
BSH (2015) [REF 2]	LMWH	LMWH for at least 6 months. In presence of active malignancy, anticoagulation should be continued. Warfarin and other oral anticoagulants are acceptable alternatives if LMWH is impractical and there is an indication for anticoagulation.
WJSO (2015) [REF 3]	LMWH	LMWH between 3 and 6 months. Long-term treatment for 6 months with 75% to 80% of the initial dose of LMWH.
ACCP (2016) [REF 4]	LMWH	LMWH for at least 3 months. Over 3 months in patients without high bleeding risk (grade 2B) and with high bleeding risk (grade 2C)
ITAC-CME (2016) [REF 5]	LMWH	LMWH for at least 3 months. After 3–6 months, continuation of anticoagulation (LMWH, VKA, or DOAC) should be based on the individual assessment of the benefit-to-risk ratio, tolerability, drug availability, patient preference, and cancer activity.
NCNN (2016) [REF 6]	LMWH	LMWH for 6 months. Indefinite anticoagulation in presence of active malignancy, anticancer treatment, or persistence of risk factors for recurrences.
ESC (2017) [REF 7]	LMWH	LMWH between 3 and 6 months. After 6 months, termination or continuation of anticoagulation should be tailored at the individual level.
Cochrane (2018) [REF 24]	LMWH	Decisions to start long-term LMWHs *versus* DOACs should take into account the benefits and burdens of each drug and the patient's preferences.
ISTH (2018) [REF 8]	DOACs LMWH	Individualized treatment regimens DOACs for patients with cancer and acute VTE, low risk of bleeding, and no drug-drug interactions with current systemic therapy. LMWHs for patients with cancer and acute VTE at high risk of bleeding.
NCNN (2018) [REF 9]	LMWH Edoxaban Rivaroxaban	LMWH Edoxaban Rivaroxaban Transition to a VKA based on clinical judgment

consensus document from the European Society of Cardiology [7] recommends LMWH for the initial treatment of CAT (for at least 3 months and up to 6 months) – suggesting a similar efficacy and a higher safety as compared with unfractioned heparin. LMWH is also preferred over VKAs because of its higher efficacy for the prevention of VTE recurrences and a similar safety profile.

In 2018, a subcommittee of the International Society of the Thrombosis and Haemostasis (ISTH) released recommendations on the role of direct oral anticoagulants (DOAC) in CAT [8]. It is recommended to adopt individualized treatment regimens after shared decision-making with the patient. In addition, it is suggested to use specific DOACs for patients with cancer and a diagnosis of acute VTE, a low risk of bleeding, and no drug-drug interactions with the current systemic therapy. LMWHs are also recommended for patients with a diagnosis of acute VTE and a high risk of bleeding. A 2018 update of the NCNN guidelines has recommended the use of LMWH, edoxaban, and rivaroxaban in relation to specific scenarios (*e.g.*, clinical setting and bleeding risk assessment) [9]. After 6 months, continuation or discontinuation of anticoagulation should be tailored at the individual level. Table 1 summarizes the main recommendations issued by major guidelines for the clinical management of CAT. As the length of time from the index event increases, however, the available evidence becomes inconclusive. On this background, this article provides an overview of the available studies focusing on extended (*i.e.*, > 6 months) anticoagulation treatment in CAT, with the ultimate goal of refining real-world clinical decision-making in this patient population.

2. Methods

We conducted a PubMed search for original articles, reviews, and guidelines using the following MESH terms: "Venous Thromboembolism"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Embolism and Thrombosis"[Mesh] OR "Venous Thrombosis"[Mesh] AND "Neoplasms"[Mesh]. Original article were eligible for inclusion if they focused on CAT occurring in adult patients. Abstracts, animal studies, and papers written in languages other than English were excluded. The references of each article included in this review were screened to eventually identify other studies of interest. Ongoing clinical trials in the field of CAT were identified using clinicaltrials.gov.

3. Results

3.1. Post-hoc analyses of trials in patients with CAT

With regard to post-hoc analyses of trials performed in patients with CAT, we identified five eligible studies. The **EINSTEIN-DVT and EINSTEIN-PE STUDIES** compared 12-month rivaroxaban *versus* VKAs in a subgroup of patients with CAT [10]. The **Hokusai-VTE study** compared edoxaban *versus* warfarin in 771 patients with current or past cancer history [11]. The **RECOVER I and II** [12] compared dabigatran *versus* warfarin in 355 patients with cancer. Finally, the **AMPLIFY** study [13] compared apixaban *versus* warfarin in 159 patients. Post-hoc analyses of the RECOVER I and II and AMPLIFY studies are not detailed because their duration was limited to 6 months.

The **EINSTEIN-DVT** (n = 3449) and **EINSTEIN-PE** (n = 4832) studies were randomized, open-label, phase 3 trials that compared rivaroxaban *versus* VKAs for the treatment of symptomatic DVT (EINSTEIN-DVT) or symptomatic PE (EINSTEIN-PE) [10]. A *post-hoc* analysis of these studies specifically focused on patients with either active cancer or a history of malignancy, using symptomatic recurrent VTE as the primary endpoint. The planned treatment duration was 12 months for approximately one third of the study participants, both the exact number of patients who underwent extended treatment (*i.e.*, continuing after 6 months from the index event) and the complication rates in this subgroup have not been reported. The **Hokusai-VTE** study was a randomized, double-blind, double-dummy, multicenter trial that compared edoxaban *versus* warfarin in 8292 patients with VTE. A *post-hoc* analysis specifically focused on the subgroup of patients with active cancer or a history of malignancies (n = 771) [11]. Of them, 378 were treated with edoxaban and 393 with warfarin. Recurrent VTE occurred in 4% and 7% of cases in the edoxaban and warfarin arms, respectively (HR = 0.53, 95% CI = 0.28–1.00; P = 0.0007). Notably, the upper limit of the 95% CI did not exceed the non-inferiority margin of 1.5 that was pre-specified for the trial. The rates of CRB were 12% and 19% in the edoxaban and warfarin groups, respectively (HR = 0.64, 95% CI = 0.45–0.92; P = 0.017). An identical rate of major bleeding (3%) was observed in the two treatment arms (HR = 0.80, 95% CI = 0.35–1.83). A limitation inherent in the study was the unknown number of patients with active cancer. The results of *post-hoc* analyses are summarized in Supplemental Table 1.

In summary, rivaroxaban (EINSTEIN DVT and EINSTEIN PE) and edoxaban (HOKUSAI) were not inferior to warfarin in terms of efficacy. While rivaroxaban did not require an initial parenteral anticoagulant, edoxaban was preceded by an initial 5-day LMWH administration. With regard to safety, edoxaban was associated with a significant reduction in clinically relevant bleeding (*i.e.*, a combination of major and non-major clinically relevant bleeding) but not of major bleeding alone in the Hokusai-VTE trial [11]. In contrast, the use of rivaroxaban reduced the number of major bleeding episodes in the subgroup of patients with pulmonary embolism [10].

Systematic reviews and meta-analysis: too much analysis of too few studies.

Data from meta-analysis in the field of CAT should be taken with caution because of their dependence on the quality of original studies and the potential presence of residual confounding. In 2015, Posch et al. [14] conducted a network meta-analyses aiming at providing indirect estimates of the comparative efficacy (in terms of recurrent VTE) and safety (in terms of major bleeding) of direct-acting oral anticoagulants (DOACs), LMWH, and VKAs for the treatment of CAT. The authors concluded that the efficacy and safety of LMWH and DOACs was comparable. In their 2017 meta-analysis of randomized controlled trials, Di Minno et al. [15] maintained that the incidence of VTE recurrence in CAT was similar for DOACs and VKAs, although the risk of major bleeding was significantly lower with the use of DOACs compared with VKAs. However, the authors cautioned against drawing definite conclusions on safety owing to the lack of comparative data between DOACs and LMWH. Another systematic review and network meta-analysis of randomized trials published in 2018 indicated that DOACs appeared superior to LMWH and VKAs in reducing recurrent VTE in patients with CAT, despite an increased risk of major bleeding as compared with LMWH [16].

Two meta-analyses including the only two randomized trials comparing DOACs with LMWH were recently published. Vedovati and coworkers [17] concluded that DOACs were characterized by good efficacy and safety (compared with other anticoagulants) in CAT, potentially serving as an alternative to LMWH. However, Li et al. [18] analyzed the same studies and concluded that DOACs were more effective than LMWH in the prevention of recurrent VTE – albeit being associated with a significantly higher risk of major bleeding, as well as a trend toward more CRNMB. Table 2 summarizes the results of recent systematic reviews and meta-analyses in CAT. A systematic review published in 2018 in the Cochrane library – including randomized controlled trials evaluating the benefits and harms of long-term treatment with LMWH, DOACs or VKAs in patients with cancer and symptomatic VTE – concluded that LMWH – as compared with VKAs – are likely to significantly reduce VTE recurrences in the long-term. Compared with LMWH, DOACs seem to lower the risk of recurrent VTE but portend an increased likelihood of major bleeding. The authors maintained that the decision to use LMWH *versus* DOACs in the long-term should take into account not only potential risks and benefits but also patient preferences [19].

3.2. Randomized clinical trials prematurely terminated

Certain prematurely stopped trials addressed clinically relevant research questions but were unfortunately stopped because of futility and unexpected issues. For this reasons, these studies are briefly mentioned in our review. When evidence from clinical trials is unavailable, data from registries, prospective or retrospectives studies may be helpful to elucidate the most suitable approach. The goal of the **ALICAT** trial (ISRCTN37913976) was to investigate the feasibility of conducting a randomized, open-label, controlled trial comparing 6-month treatment with LMWH *versus* indefinite anticoagulation with the same drug in CAT patients with locally advanced or metastatic cancer [20]. Unfortunately, the trial was prematurely terminated because early data indicated that the conduct of the study was unfeasible. The **Longheva** study (NCT01164046) was a multicenter, multinational, randomized, open-label trial involving patients with CAT who received 6–12 months of anticoagulation for VTE and having a clinical indication for extended treatment. The study patients were going to be randomized to a weight-adjusted scheme of LMWH (65–75% of the full therapeutic dose) *versus* VKAs for 6 additional months. Unfortunately, this trial was terminated because of an excessively slow recruitment.

3.3. Ongoing randomized trials

CAT represents a critical unmet medical need and it is not surprising that several clinical trials in this field are currently being performed. Curiously, most of them are not focused on extended treatment (*i.e.*, > 6 months from the index VTE events), being either limited to 3 (two trials) or 6 (four trials) months. The **CASTA-DIVA** (NCT02746185) trial is comparing 3-month treatment with rivaroxaban *versus* dalteparin. Karata et al. designed a trial to compare rivaroxaban *versus* LMWH given for 3 months (NCT02583191). The **ADAM-VTE** (NCT02585713) study is a randomized, open-label trial that will compare apixaban *versus* dalteparin for 6 months. The **CARAVAGGIO** (NCT03045406), **PRIORITY** (NCT03139487) and **CANVAS** (NCT02744092) trials are going to compare apixaban *versus* dalteparin, rivaroxaban *versus* dalteparin, and DOACs *versus* LMWH for six months, respectively. Although these studies share a number of similarities, significant methodological differences also exist – mainly in terms of the endpoints of interest. The outcome of the **CASTA-DIVA** study is the occurrence of symptomatic DVT or PE at 3 months, whereas the study by Karata et al. will focus on patient's satisfaction (convenience). Major bleeding was the main outcome measure for the ADAM-VTE study – whose results were presented at the ASH 2018 meeting [21]. With regard to the primary outcome, no significant differences in terms of major bleeding were observed between apixaban (0%) and dalteparin (2.1%; $p = 0.99$). The bleeding rates in this study were lower than expected, possibly because only 4% of the patients had upper gastrointestinal malignancies. Other limitations of the study included the open-label design, the relatively small sample size, and the reliance on self-reported questionnaires to evaluate secondary outcomes. The

Table 2
Recent systematic reviews and meta-analyses in the field of cancer-associated thromboembolism.

	Year of publication	Number of included studies	Comparisons
Posch et al. [REF 14]	2015	10	LMWH *versus* VKA ($n = 6$) DOAC *versus* VKA ($n = 4$)
Di Minno et al. [REF 25]	2017	4	DOAC *versus* VKA (n = 4)
Sobieraj et al. [REF 16]	2018	13	LMWH *versus* VKA ($n = 7$) DOAC *versus* VKA (n = 4) DOAC *versus* LMWH ($n = 2$)
Vedovati et al. [REF 17]	2018	12	LMWH *versus* VKA (n = 6) DOAC *versus* VKA (n = 4) DOAC *versus* LMWH (n = 2)
Li et al. [REF 18]	2018	2	DOAC *versus* LMWH (n = 2)

Table 3
Comparison of the clinical characteristics of patients included in retrospective studies and registries focused on cancer-associated thrombosis beyond 6 months.

	Bott-Kitslaar 2015 [Ref. 22]	Xavier 2017 [Ref. 23]	Pignataro 2017 [Ref. 24]	Chai-Adisaksopha 2018 [Ref. 25]	
	Rivaroxaban (n = 118)	Rivaroxaban (n = 41)	Rivaroxaban (*n* = 400)	LMWH (*n* = 482)	VKA (n = 482)
Age, years, mean	66 ± 10	62.5	60.1	66 ± 13	66 ± 14
Female, %	51%	48.8%	55.8%	47%	47%
Caucasian ethnicity	–	80.5%	–	–	–
VTE location					
DVT, %	62%	38.6%	70.9%	44%	40%
PE, %	24%	41.4%	29.1%	38%	41%
DVT plus PE, %	14%	14.6%	–	18%	19%
ECOG					
0	–	–	32.4%	–	–
1	–	–	41.4%	–	–
2	–	–	17.8%	–	–
CrCl < 50 mL-min^{-1}, %	5%	0%	–	–	–
Platelets < 50.000, %	–	–	–	–	–
Cancer location					
Lung, %	13.5%	2.4%	14.9%	8.9%	9.5%
Colorectal, %	29.1%	39%	25.4%	23%	21%
Gastrointestinal (upper), %		26.8%		4.5%	4.7%
Breast, %	9.3%	9.7%	15.5%	13%	13%
Ovary, %	–	–	–	5.6%	4.4%
Hematological, %	10.1%	9.7%	9.5%	3.7%	4.8%
Gynecologic, %	–	–	9.9%	4.1%	4.1%
Genitourinary, %	23.6%	–	–	7.7%	7%
Prostate, %	–	–	–	5.6%	6%
Brain, %	1.6%	–	–	9.7%	9.5%
Metastases or stage IV, %	–	87.8%	61%	–	–
Oncological treatment, %	76%	–	–	43%	37%
Outcomes					
VTE recurrences	3.3%	12.2%	3.3%	> 6 m: 0.17 per 100 Pat-Year	> 6 m: 0.14 per 100 Pat-Year
DVT, %	2.5%	–	2%	3 per 100 Pat-Year	1.7 per 100 Pat-Year
PE, %	0.8%	–	1.3%	1.9 per 100 Pat-Year	2 per 100 Pat-Year
Total bleedings	–	–	–	5.9 per 100 Pat-Year	4.7 per 100 Pat-Year
Major bleeding	2.5%	0%	5.5%	3 per 100 Pat-Year	2.7 per 100 Pat-Year
NMCRB	3.4%	12.2%	15.2%	–	–
Minor bleeding, %	2.5%			–	–
All causes mortality, %	31%	–	–	13.1 per 100 Pat-Year	6.7 per 100 Pat-Year
Cancer progression, %	–	–	–	–	–
Fatal PE, %	–	–	0.3%	–	–
Fatal bleeding, %	–	–	–	–	–

endpoints of the **CARAVAGGIO**, **PRIORITY**, and **CANVAS** studies are objectively confirmed recurrent VTE occurring during the study period, rate of clinical relevant bleeding, and cumulative VTE recurrence, respectively. The COBRRA trial (NCT02559856) will compare the risk of bleeding between rivaroxaban and apixaban, although patients with active cancer are not included.

With regard to the use of extended treatment beyond 6 months, two ongoing clinical trials are comparing long-term DOAC at low doses *versus* DOAC at full doses in patients with CAT. Low doses are expected to be associated with a reduced risk of bleeding, hopefully with a similar efficacy. The API-CAT study (NCT03692065) is a phase 3 multicenter, international, prospective, randomized, parallel-group, double-blind non-inferiority trial with blinded adjudication. Eligible participants are patients with active cancer who have already completed 6 months of anticoagulant therapy after a VTE episode. The main study goal is to demonstrate the non-inferiority of 12-month apixaban at low doses (2.5 mg twice per day) compared with full doses (5 mg twice) for the prevention of recurrent VTE. The main strengths of the study include stratification of patients according to the type of cancer and the initial thrombotic event. The RENOVE study (NCT 03285438) is a multicenter, prospective randomized open-blinded endpoint (PROBE), parallel arm, controlled trial. Patients are randomized to receive either a reduced dose of DOAC (apixaban 2.5 mg twice daily or rivaroxaban 10 mg once daily) or a full dose of DOAC (apixaban 5 mg twice daily or rivaroxaban 20 mg once daily) during a mean follow-up period of 24 months (12 to 48 months). Treatment effects will be evaluated in predefined patient strata, with a special focus on cardiovascular events. Because this study is expected to enrol patients classified at "high risk of recurrence" – *i.e.*, not only those with cancer – their results might not be applicable to patients with CAT. A summary of the on-going trials is provided in Supplemental Table 2.

3.4. Retrospective studies with data beyond 6 months

Bott-Kitslaar et al. [22] retrospectively analyzed a patient registry (either with or without cancer) treated with DOACs. The primary efficacy outcome was symptomatic venous or arterial thromboembolism, whereas the primary safety endpoint was major bleeding. Of the 404 study patients, 296 were treated with rivaroxaban and 118 had a diagnosis of cancer. After a mean follow-up of 1.36 ± 0.5 years, the rates of VTE recurrence and major bleeding were 3.3% and 2.5%, respectively. In 2017, Xavier and coworkers [23] conducted a retrospective analysis of patients with cancer and VTE who were treated with rivaroxaban (*n* = 41). The aim of the study was to compare the efficacy, safety, and cost of rivaroxaban and LMWH alone followed by VKAs. During a median follow-up of 5.5 months, non-major bleeding and recurrent VTE occurred in 12.2% and 12.2% of the participants, respectively. Under a quality assessment initiative, In 2017, Pignataro et al. [24] published a single-center experience with the use of rivaroxaban in 400 patients with CAT. The authors retrospectively analyzed both safety and efficacy. During follow-up (up to 12 months) VTE recurrences and major bleeding occurred in 3.25% and 5.5% of patients during anticoagulant treatment (median = 118 days, mean = 163.9 days, standard deviation = 159.9 days). Chai-

Table 4
Comparison of the clinical characteristics of patients included in prospective studies/trials focused on cancer-associated thrombosis treated for up to 12 months.

	Hull 2006 (LITE Trial) [Ref. 28]		Prins 2014 (*post-hoc* EINSTEIN) [Ref. 10]		Raskob 2016 (*post-hoc* Hokusai) [Ref. 11]		TiCAT [Ref. 30] (Prospective study)	DALTECAN [Ref. 29] (Prospective study)
	Tinzaparin	VKA	Rivaroxaban	VKA	Edoxaban	Warfarin	Tinzaparin	Dalteparin
N	100	100	258	204	85	77	247	334
Age, years, mean	< 60; n: 38 > 60; n: 62	< 60; n: 24 > 60; n: 76	–	–	67 (63–74)	66 (60–73)	62.4 ± 13.4	63.8
Female, %	48%	50%	41%	47%	44%	35%	45.3%	51.2%
Caucasian ethnicity, %	–	–	–	–	–	–	–	–
ECOG, %								
0	–	–	–	–	–	–	23.6%	29.6%
1	–	–	–	–	–	–	61.6%	48.8%
2	–	–	–	–	–	–	11.6%	20.7%
CrCl < 50 mL-min^{-1}, %			13%	17%	–	–	6.5%	6.0%
Platelets 50 × 10^9/L, %	–	–	–	–	–	–	–	–
VTE location, %								
DVT, %	3 m: 92%	3 m: 94%	–	–	59%	61%	51.8%	49.1%
PE, %	3 m: 21%	3 m: 21%	–	–	41%	39%	30.4%	38.9%
DVT plus PE, %	–	–	–	–	–	–	17.8%	12%
Incidental VTE, %	–	–	0%	0%	0%	0%	32.8%	–
Cancer location, %								
Lung	–	–	8.1%	6.4%	7%	5%	16.6%	16.8%
Genitourinary	–	–	28.7%	33.8%	Renal 3% Bladder 3%	Renal 5% Bladder 5%	Kidney 10.1% Gallbladder 5.7%	–
Prostate	–	–	–	–	14%	10%	4%	–
Gastrointestinal (upper)	–	–	6.6%	2.5%	Pancreas and gastric 2%	Pancreas and gastric 14%	Pancreas 2.8%	–
Colorectal	–	–	–	–	10%		10.9%	12%
Gynecologic	–	–	–	–	Uterine 7%	Uterine 9%	–	–
Breast	–	–	10.5%	12.7%	18%	15%	14.2%	9.3%
Ovarian	–	–	–	–	3%	1%	4.9%	–
Hematological	10%	13%	16.3%	12.3%	Lymphoma 3% Leukaemia 3% Myeloma 2%	Lymphoma 5% Leukaemia 2% Myeloma < 1%	8.1%	8.4%
Brain	–	–	1.6%	1.5%	1%	2%	2.4%	–
Metastases or stage IV, %	47%	36%	19%	25%	28%	29%	66%	62.6%
Oncological treatment, %	–	–	29%	30%	39%	36%	62%	–
Outcomes								
Total bleedings	27%	24%	16%	21%			8.5%	36.5%
Major bleeding	7%	7%	2%	5%	5%	3%	4.9%	10.2%
NMCRB	20%	17%	14%	16%	14%	23%	2.4%	–
VTE recurrences, %	7%	16%	5%	7%	4%* Active cancer: 2%	7%* Active cancer: 9%	5.3%	11%
Symptomatic DVT, %	6%	8%	–	–	–	–	–	–
Symptomatic non-fatal PE, %	1%	8%	–	–	–	–	–	–
All-cause mortality, %	47%	47%	16%	18%	11% Active cancer: 31%	10% Active cancer: 31%	15.8%	16.8%
Cancer progression, %	–	–	–	–	–	–	90%	31.4%
Fatal PE, %	0%	3%	–	–	1.3%*	1.3%*	0.4%	2.6%
Fatal bleeding, %	2%	3%	–	–	0%	0.5%*	0.8%	1.3%

*: In the global population included in the study.
Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; NMCRB, non-major clinically relevant bleeding; CRB, clinical relevant bleeding; CAT, cancer-associated thromboembolism; Chemo, chemotherapy; Radio, radiotherapy.

Adisaksopha et al. [25] conducted a sub-analysis of the RIETE registry aimed at investigating the rates of VTE recurrences and major bleeding occurring after the first 6 months of anticoagulation in patients with CAT. Specifically, a propensity score-matched cohort study consisting of 482 patients treated with LMWH and 482 who received VKAs was performed. In total, 57 patients presented VTE recurrences and 28 had major bleeding. Compared with the VKAs arm, those in the LMWH arm had similar rates of DVT recurrences (RR = 1.41; 95% CI = 0.68–2.93), PE recurrences (RR = 0.73; 95% CI = 0.34–1.58), and major bleeding (RR = 0.96; 95% CI = 0.51–1.79). A potential caveat inherent in this study is that information on extended anticoagulation was available for 1464 patients only (out of 4460 patients with CAT included in the registry) – of which 964 were involved in the propensity score analysis (482 in each group). Another limitation is that propensity matching does not exclude the presence of residual confounding. In this regard, it should be kept in mind that clinicians tend to maintain LMWH in more complex patients, potentially resulting into a bias that can be solved only through a randomized clinical trial. In addition, the number of censored patients should have been taken into account to compare the characteristics of patients who were followed-up for more *versus* < 6 months (Table 3).

Two retrospectives studies have recently focused on findings from the *Humana* database [26] and from commercially insured patients [27]. Although real-life data comparing LMWH, warfarin, and rivaroxaban have been obtained in a large number of patients, some relevant limitations merit comment. In the study by Streiff et al. [26], the

median treatment duration was short, especially in the LMWH group (only one month). In the study of Khorana et al. [27], the mean length of anticoagulation was 3.6, 4.0, and 2.0 months for patients initiated on rivaroxaban, warfarin, and LMWH, respectively. We believe that firm conclusions cannot be drawn from these data, especially with respect to outcomes beyond 6 months.

3.5. Trials or prospective studies beyond 6 months

The **LITE** trial analyzed and published results obtained up to 12 months obtained in patients with CAT [28]. This was a multi-center, randomized, open-label trial aimed at comparing long-term treatment with tinzaparin administered subcutaneously once per day ($n = 100$) with VKAs (n = 100). Outcomes were assessed at 3 and 12 months. The results at 12 months revealed that recurrent VTE occurred more frequently in patients treated with VKAs than in those who received tinzaparin (16% *versus* 7%, respectively; RR = 0.44; absolute difference = −9.0; 95% CI = −21.7 to −0.7; $P = 0.044$). However, there were no intergroup differences in terms of bleedings (27% in the tinzaparin arm *versus* 24% in the VKA arm, respectively; absolute difference = −3.0; 95% CI = −9.1 to 15.1).

The extended use of dalteparin after 6 months of the index VTE episode was investigated in a prospective, international, multicenter, open-label, single-arm trial (**DALTECAN study**) [29]. The rate of VTE recurrences at 7–12 months was 4.1%, being – in relative terms – > 50% lower than that observed during the first 6 months (8.7%). Similarly, major bleeding events were less frequent after 6 months of treatment. Taken together, these data provide prospective evidence on the efficacy and safety of extended (*i.e.*, > 6 months) dalteparin treatment. In 2017, Jara-Palomares et al. [30] published the **TiCAT study** – a prospective, multicenter, open-label, single-arm study of tinzaparin in CAT. The main goal was to assess drug safety (using major bleeding, CRB, and NMCRB as endpoints) beyond 6 months. When months 1–6 were compared to months 7–12, the authors did not observe statistically significant differences in terms of CRB (5.4% *versus* 3.7%, respectively). Similarly, recurrences occurred at similar rates during months 7–12 (1.1%, 95% CI = 0.1–3.9%) and months 1–6 (4.5%, 95% CI = 2.2–7.8%; $P = 0.08$). The DALTECAN and TiCAT studies provided clinically relevant information on the safety of extended treatment (*i.e.*, > 6 months) with LMWHs in CAT, albeit with the limitation of not being randomized clinical trials. Hopefully, future *post-hoc* analyses of the Select-D and the Hokusai VTE cancer studies will provide data on extended treatment with dalteparin, rivaroxaban, and edoxaban. Table 4 summarizes both prospective studies and trials of extended treatment (*i.e.*, > 6 months).

3.6. Pharmacological interactions of DOACs (drug-drug interactions)

Recently published clinical trials (Hokusai and SELECT-D) have shown the non-inferiority of DOACs compared with LMWH in the treatment of patients with CAT. Nonetheless, pharmacological interactions with DOACs need to be considered. In this regard, it should be noted that numerous anticancer drugs can either inhibit or stimulate different metabolic pathways – especially cytochrome P450 (CYP3A4). Moreover, DOACs may interact with transporter proteins – including p-glycoprotein (P-gp) or BCRP (breast cancer resistance protein) – may affect the absorption, distribution, metabolism, and excretion of DOACs [31].

Because DOACs are substrates of CYP3A4 and P-glycoprotein, anticancer therapies that induce these enzymes can significantly increase DOACs metabolism – ultimately lowering their plasma concentrations and increasing the risk of recurrences. In turn, inhibitors of DOACs metabolism may portend a higher bleeding risk [32].

3.6.1. DOACs–CYP3A4 interactions

Hepatic metabolism is involved in the clearance of all DOACs, albeit at a different extent [31]. Dabigatran is chiefly (80%) excreted by the kidney, whereas the remaining 20% is metabolized in the liver in a CYP3A4-independent fashion. Edoxaban is characterized by 50% renal and 50% hepatic excretion, the latter being minimally CYP3A4-dependent. Apixaban is the DOAC with the highest CYP3A4-dependent hepatic excretion (75% of the drug). Rivaroxaban is also mainly metabolized in the liver (66% of the drug) by both CYP3A4 and CYP2J2 [31].

3.6.2. DOACs–P-glycoprotein interactions

Edoxaban, apixaban, and rivaroxaban are all glycoprotein-p substrates and their metabolism may be significantly influenced by anticancer drugs. In the case of dabigatran, its prodrug (dabigatran-etexilate) acts as the enzyme substrate – ultimately making its metabolism less influenced by chemotherapeutic agents [31]. Phase I pharmacokinetic studies have shown that concomitant administration of apixaban or rivaroxaban with inhibitors of both glycoprotein-p and CYP3A4 (*e.g.*, azoles or certain antiretroviral drugs) may produce a marked increase in DOAC plasma concentrations – an effect that should be clinically avoided. However, apixaban or rivaroxaban are not contraindicated when drugs that separately inhibit P-gp or CYP3A4 are concomitantly given (Bristol-Myers Squibb, Pfizer, 2018, Bayer, 2018). In contrast, drugs like phenytoin, carbamazepine, and rifampicin are able to simultaneously induce both p-gp and CYP4A3 [33]. Table 5 summarizes the most frequent pharmacological interactions of DOACs with anticancer therapies and other drugs.

3.7. Practical approach to extended treatment in cancer-associated thrombosis

The question as to whether anticoagulants should be continued after 6 months of treatment remains open and with a lack of evidences. In presence of an active malignancy, physicians should weigh the benefits and burdens of ongoing anticoagulation taking into account the clinical status, patient expectations, and the risk of bleeding. Another point that needs to be carefully considered when deciding to prolong or discontinue anticoagulant treatment is the occurrence of drug-drug interactions between anticoagulants and anticancer therapies or other concomitant drugs. As the length of time from the index event increases, the available evidence becomes inconclusive. The most critical unresolved issues include the decision to continue or discontinue anticoagulation and the selection of the most appropriate anticoagulant agent (especially in patients with malignancies not commonly included in clinical trials and registries).

The current literature – albeit limited – indicates that complications (in terms of VTE recurrences and bleeding) seem to occur less frequently following 6 months, ultimately decreasing over time. Notably, there are two interesting works (DACUS study and Hispalis study) that investigated the suspension of anticoagulation in CAT. The **DACUS** study was conducted in patients with malignancies and proximal DVT or PE who received LMWH for 6 months [35]. The presence of residual DVT was analyzed by ultrasound at the end of the treatment period. Patients who showed residual DVT were randomized either to terminate treatment or to receive LMWH for 6 additional months, with a total follow-up of 12 months. Treatment with LMWH for six additional months reduced the rate of VTE recurrence, although the difference between the group that terminated treatment and the group that continued LMWH was not statistically significant (22%; 95% CI = 15–30% *versus* 15%; 95% CI = 9.2–22.9%, respectively; $P = 0.18$). Moreover, the results revealed that termination of treatment after 6 months in patients without residual DVT was associated with a low risk of VTE recurrences within 12 months (2.8%, 95% CI = 0.6–8.1%). Additional data are required to shed more light on the role of residual venous thrombosis in cancer-associated VTE. Published in 2018, the **Hispalis** study was a multicenter, prospective investigation that focused on the role of D-dimer and C-reactive protein as predictive biomarkers of

Table 5
Most frequent pharmacological interactions of DOACs with anticancer therapies and other drugs.

	Edoxaban	Apixaban	Rivaroxaban	Apixaban	Rivaroxaban
	P-glycoprotein*			Cytochrome P450 (CYP 3A4)	
Oncologic therapies					
Corticosteroids	↑	↑	↑	↓	↑
Anthracyclines	↑	↑	↑	↓	↓
Tyrosine kinase inhibitors	↓[1]	↓[1]	↓[1]	↓[2]	↓[2]
Immunomodulating agents	↓	↓	↓	↓	↓
Hormonal therapy	↓	↓	↓	↓[3]	↓[3]
Topoisomerase inhibitors	↑	↑	↑	↓	↓
Alkylating agents				↓	↓
Antimycotic agents	↑	↑	↑	↓[4]	↓[4]
Other therapies					
Azoles-antimycotics	↓	↓↓	↓↓	↓↓	↓↓
HIV protease inhibitors	↓	↓↓	↓↓	↓↓	↓↓
Erythromycin	–	–	–	–	↓**
Rifampicin	↑	↑↑	↑↑	↑↑	↑↑
Carbamazepine	↑	↑↑	↑↑	↑↑	↑↑
Phenytoin	↑	↑↑	↑↑	↑↑	↑↑
Atorvastatin	0	↓↓	↓↓	↓↓	0
Verapamil	↓	↓↓	↓↓	↓↓	↓↓↓
Diltiazem	–	↓↓	↓↓	↓↓	↓↓↓
Digoxin	0	↓	↓	–	0
Amiodarone	↓	↓	↓↓↓	–	–

Adapted from Riess et al. [32] and Kraaijpoel et al. [34].
*Dabigatran has moderate interactions with the P-glycoprotein pathway; [1]Except lenvatinib (↓); [2]Except lenvatinib and vemurafenib (↑); [3]Except enzalutamide and mitotane (↑); [4]Except paclitaxel (↑). **Erythromycin increases levels of rivaroxaban in moderate renal insufficiency [40]; 0 = no effect.

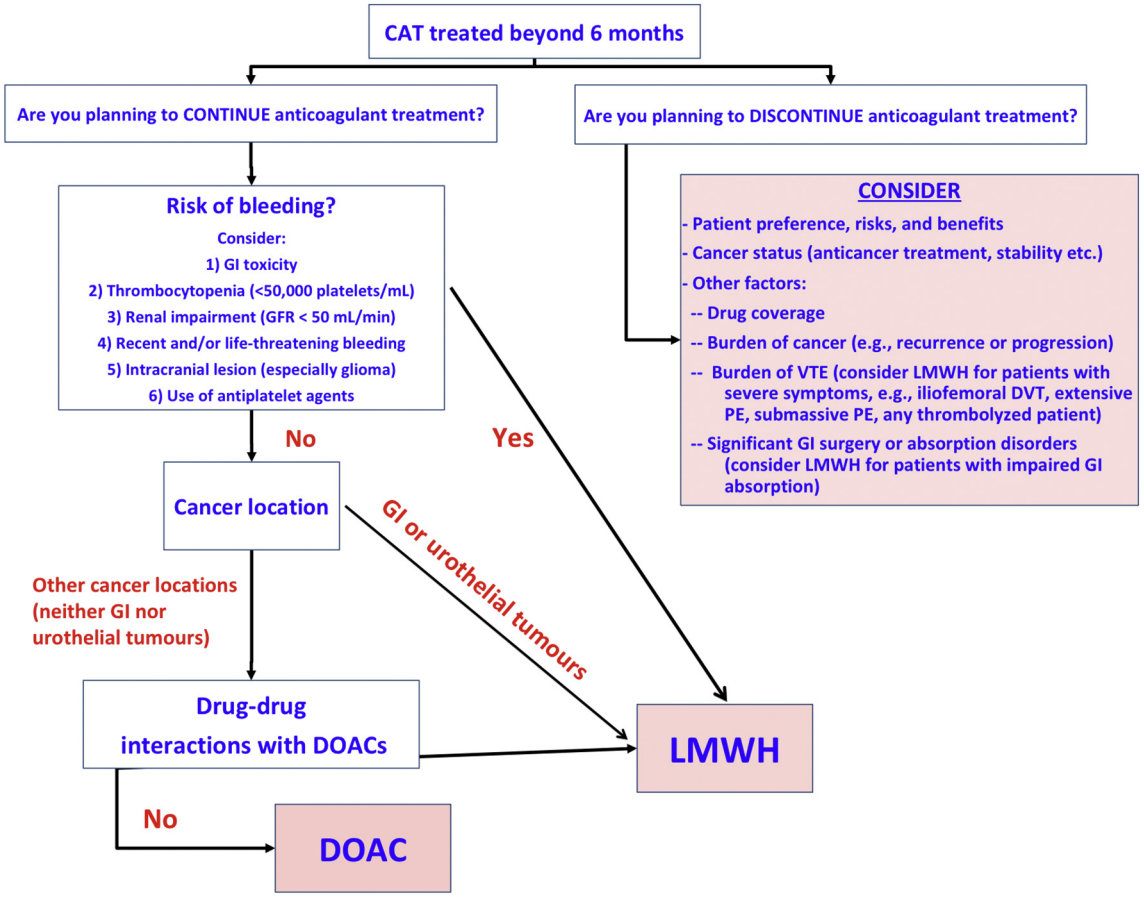

Fig. 1. Risk stratification algorithm for the extended (*i.e.*, > 6 months) treatment of cancer-associated thromboembolism. Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; GI, gastrointestinal; GFR, glomerular filtration rate; DOAC, direct-acting oral anticoagulant; LMWH, low molecular weight heparin; VTE, venous thromboembolism (modified from Carrier et al., REF 37).

recurrent VTE. The study sample consisted of 114 patients with CAT in whom anticoagulation was discontinued [36]. In the six months that followed discontinuation of anticoagulation, there were 10 VTE recurrences (8.8%; 95% CI = 4.3–11.5%).

The results identified a statistically significant association between D-dimer and C-reactive protein levels measured at day 21 and recurrent VTE with a subdistribution hazard ratio of 9.82 (95% CI: 19–52) and 5.81 (95% CI: 1.1–31.7) for C-reactive protein and D-dimer, respectively. If independently validated, these results can potentially lead to the identification of a specific subgroup of patients with cancer-associated VTE in whom anticoagulation can be safely discontinued.

From a practical point of view, we should decide to prolong or discontinue anticoagulant treatment beyond 6 months. Treatment interruption should take into account patient preferences, cancer status, and other variables (*e.g.*, burden of cancer). In case of continuation, we should first perform a careful assessment of the bleeding risk. In the absence of significant risk, tumor location should be subsequently considered. Subgroup analyses of bleeding in the Select-D [38] and Hokusai VTE cancer [39] studies have shown that – besides gastrointestinal malignancies – urothelial cancer is associated with a high bleeding risk. Finally, drug-drug interactions between DOACs and other drugs currently in use should be considered. If all of these three points have negative replies, DOACs may be considered. In all other cases, LMWH should be considered. A management proposal for CAT patients beyond 6 months is summarized in Fig. 1.

4. Conclusions

We have currently plenty of data on the optimal treatment of CAT within the first 6 months. However, as the length of time from the index event increases, the available evidence becomes inconclusive. The most critical unresolved issues include the decision to continue or discontinue anticoagulation and the selection of the most appropriate anticoagulant agent. A potential research agenda for the future will need to specifically examine patients with different solid malignancies, because it is likely that the optimal treatment duration and/or strategy may vary according to the underlying form of cancer.

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Author agreement/declaration

This work is not currently under consideration elsewhere and has not previously been published. All authors have contributed significantly and have read and approved the manuscript.

Declaration of Competing Interest

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Authors' contribution

Study concept and design: LJP; acquisition, analysis, and interpretation of data: all authors; drafting of the manuscript: all authors; critical revision of the manuscript for important intellectual content: all authors; study supervision: LJP.

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