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Review

Anticoagulant treatment of cancer-associated thromboembolism

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ABSTRACT

Venous thromboembolism (VTE) is a frequent and potentially fatal complication in patients with cancer. During the initial period after the thromboembolic event, a patient receiving anticoagulant treatment is exposed both to a risk of VTE recurrence and also to an elevated bleeding risk conferred by the treatment. For this reason, the choice of anticoagulant is critical. The choice should take into account patient-related factors (such as functional status, age, body mass index, platelet count and renal function), VTE-related factors (such as severity or site), cancer-related factors (such as activity and progression) and treatment-related factors (such as drug–drug interactions), which all potentially influence bleeding risk, and patient preference. These should be evaluated carefully for each patient during a multidisciplinary team meeting. For most patients, apixaban or a low molecular-weight heparin is the most appropriate initial choice for anticoagulant treatment. Such treatment should be offered to all patients with active cancer for at least six months. The patient and treatment should be re-evaluated regularly and anticoagulant treatment changed when necessary. Continued anticoagulant treatment beyond six months is justified if the cancer remains active or if the patient experienced recurrence of VTE in the first six months. In other cases, the interest of continued anticoagulant treatment may be considered on an individual patient basis in collaboration with oncologists.

1. Abbreviations

ACCP	American College of Chest Physicians
AUC	area under the curve
BCRP	breast cancer resistance protein
bid	twice daily
CAT	cancer-associated thromboembolism
CI	confidence interval
CRNMB	clinically relevant non-major bleeding
CYP450	Cytochrome P450

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DDI	drug–drug interaction
DVT	deep vein thrombosis
DXI	direct oral factor Xa inhibitor
ECOG	Eastern Cooperative Oncology Group
ERS	European Respiratory Society
ESC	European Society of Cardiology
GI	gastrointestinal
HR	hazard ratio
LMWH	low-molecular weight heparin
MB	major bleeding
MCM	multidisciplinary consultation meeting
OAT	organic anion transporter
PDC	proportion of days covered
PD-L1	programmed cell death ligand
PE	pulmonary embolism
PESI	Pulmonary Embolism Severity Index
P-gp	permeability glycoprotein
PS	performance status
PY	patient years
qd	once daily
RIETE	Registro Informatizado de Enfermedad TromboEmbólica
sPESI	simplified Pulmonary Embolism Severity Index
TKI	tyrosine kinase inhibitor
VKA	vitamin K antagonist
VTE	venous thromboembolism

2. Introduction

Venous thromboembolic disease is a frequently encountered and potentially fatal complication in patients with cancer. Cancer-associated thromboembolism (CAT) is the second most frequent cause of death in patients with cancer, after the cancer itself [1]. In addition, 20% of cases of venous thromboembolism (VTE) occur in patients with active cancer [2,3]. This is a growing medical problem since the incidence of cancer worldwide is increasing for the majority of primary cancer sites [4], leading to an increase in the incidence of CAT [5]. In parallel, prognosis for many cancers has improved over recent years, leading to increased survival and a longer period when the patient is exposed to a risk of CAT. For these reasons, optimal management of CAT is of major clinical importance. During the initial period after the thromboembolic event, a patient receiving anticoagulant treatment is exposed both to a risk of VTE recurrence and also to an elevated bleeding risk conferred by the treatment. However, the risk of VTE recurrence outweighs the risk of major bleeding by a factor of two, and the case fatality rate for VTE recurrence likewise exceeds that for major bleeding [6]. Given this risk profile, anticoagulant treatment should be offered to all patients experiencing CAT for at least three to six months [7–11]. The question thus arises as to the choice of the most appropriate initial anticoagulant treatment in these patients. A second question relates to the residual risk of VTE recurrence beyond six months after the initial CAT event. It is important to evaluate this risk appropriately in order to identify those patients for whom continued anticoagulant treatment would be justified and, which treatment should be offered. This article aims to review the available evidence addressing these two questions and to make proposals for improving the quality of care of patients who develop CAT.

3. Initial treatment

3.1. Treatment options

International and national clinical practice guidelines have been released, based on the results of available clinical trials and evidence-based medicine, to help clinicians in the management of CAT. They consider different options, which are classified according to the grade of evidence.

In the French guidelines updated in 2021, based on an adapted GRADE methodology (Grade 1: recommendation; Grade 2: suggestion) [12], long-term anticoagulant for at least six months is recommended (Grade 1+) in patients with a proximal DVT or PE and an active cancer.

Low molecular weight heparin (LMWH) and apixaban are the preferred options (Grade 1+), based on the design and results of prospective randomised controlled studies. As an alternative, edoxaban (Grade 2+) and rivaroxaban (Grade 2+) are suggested in patients without digestive and urologic cancer [10]. It should be noted that, of the directly-acting oral agents, only direct factor Xa inhibitors (DXIs), and not direct thrombin inhibitors such as dabigatran, have been evaluated in CAT.

3.2. Criteria for choosing the treatment strategy

When deciding how to treat a patient with cancer who has been newly diagnosed with a DVT or PE, the clinician must choose the most suitable anticoagulant from among the various approved options. This decision is complex and challenging: a large number of factors need to be taken into consideration, with their relative importance and pattern being specific for each patient.

Prospective clinical trials patients with active cancer have in general been conducted without any stratification according to cancer site, the nature of the VTE (PE or DVT; symptomatic or incidental) or patient characteristics such as age or renal function, and without defining the risk of bleeding. In practice, factors to consider for decision come from *post-hoc* analysis and can only be indicative.

A case-by-case evaluation of patient-related, cancer-related, and anticancer treatment-related factors is required to identify the best option for anticoagulant. The final step should be a process of shared decision-making between the patient and clinician [13]. We discuss below some of the important factors to consider when deciding anticoagulation therapy for a patient with CAT (Fig. 1).

3.2.1. Patient-related factors

Certain patient-related criteria need to be considered when deciding on initial treatment modalities. Firstly, the patient's general condition must be assessed, for example using the Eastern Cooperative Oncology Group (ECOG) performance status (PS) scale. As a reminder, patients with poor PS (ECOG 3-4) could not be included in most therapeutic trials evaluating DXIs, and patients with ECOG 0 or 1 represented about 80% of patients included in these trials. As a result, it remains uncertain whether therapeutic recommendations in the field of CAT are also appropriate for patients with poor PS.

The patient's weight may also be taken into consideration, particularly when prescribing an LMWH, at a dose adapted to the patient's weight. Data on extreme weights are limited, and the subject is addressed in the dedicated chapter on special populations [14]. In summary, low body weight (< 50 kg) appears to be associated with an increased risk of bleeding. These patients, as well as those with morbid obesity (BMI $\geq$ 40 kg/m^2), are very poorly represented in published interventional trials.

The average age of patients included in the trials was relatively young, under 70. Hence, data on very advanced age patients are limited in the field of CAT. A search for frailty factors, in particular those that can be optimised, should be carried out, using an appropriate screening tool such as the G-8 Geriatric screening scale [15,16], as described in the dedicated chapter on special populations [14].

Renal insufficiency increases the risk of bleeding, and may modify the pharmacological properties of anticoagulants, particularly in cases of severe renal insufficiency. Assessment of renal function is

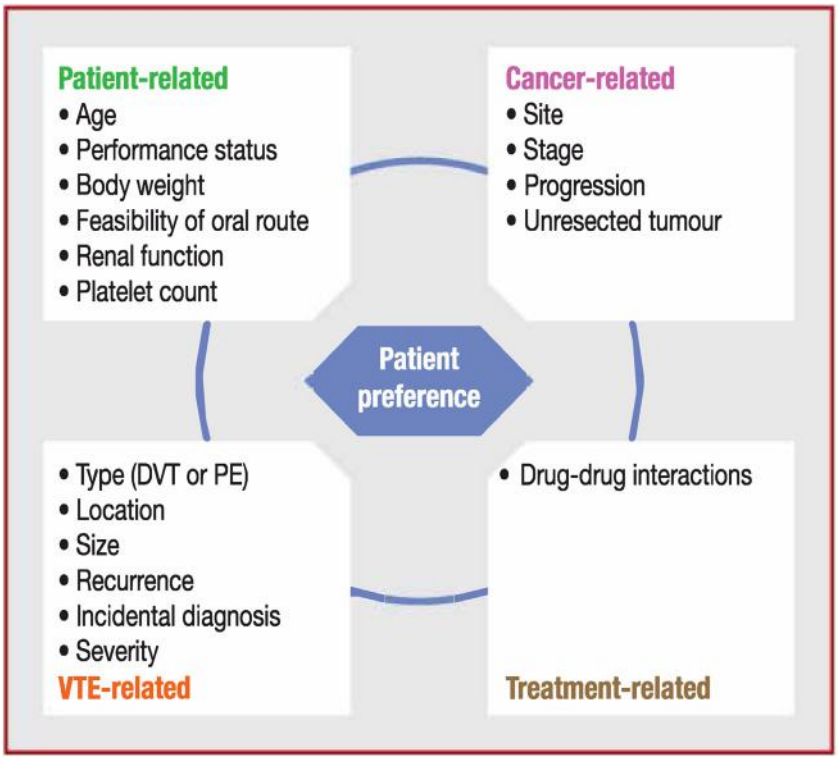


Fig. 1. Criteria to consider when evaluating a patient with cancer-associated thromboembolism for the choice of anticoagulant treatment.

recommended at the time of initial treatment, and during follow-up if eGFR deteriorates [14].

Anaemia and thrombocytopenia are common in cancer patients, and are associated with an increased risk of bleeding. Anaemia should be corrected whenever possible. In the case of thrombocytopenia, temporary adaptation of the anticoagulant may be proposed [14].

Patient history may also strongly influence the selection, for example, those with absorption issue, because of anorexia, dysphagia, or extensive gastrointestinal resections. In these situations, parenteral treatment may be the preferred option, particularly to cover the initial high-risk period for VTE recurrence.

The existence (and even accumulation) of risk factors for bleeding should prompt vigilance, and the correction of modifiable factors (for example, co-medication with antiplatelet or non-steroidal anti-inflammatory drugs), but does not justify prescribing an anticoagulant outside the validated dose regimen. These factors may, however, influence the choice of one molecule over another one.

3.2.2. *VTE-related factors*

In the majority of cohorts and clinical trials in CAT patients, little information is available regarding the influence of the initial clinical presentation of VTE in cancer patients on the risk of recurrent VTE under anticoagulation and mortality and the implications of this in terms of antithrombotic management.

However, one of the most investigated issues is the impact of whether VTE was clinically suspected (on the basis of symptoms) or not (termed incidental, which may be symptomatic or asymptomatic). In a recent meta-analysis including three randomised trials comparing patients with incidental CAT (defined as asymptomatic CAT, not clinically suspected) versus symptomatic (i.e., clinically suspected CAT), the risk of recurrence under anticoagulation was reduced by 40% in the group with incidental VTE compared to those with symptomatic VTE (relative risk of 0.62, 95% CI: 0.44–0.87) [17]. In the RIETE registry, the 3-month mortality in patients with incidental PE was lower than in patients with clinically suspected PE (11% versus 22%; odds ratio of 0.43, 95% CI: 0.34–0.54) [18]. However, the prognosis of incidental VTE in cancer patients remains poor. In a case-control study including 904 cancer patients with incidental PE and 1808 controls with cancer and no PE, the mortality rate was increased by approximately twofold in patients with incidental PE as compared to controls (hazard ratio of 1.93, 95% CI: 1.74–2.14) [19]. In a prospective cohort of 695 patients with incidental PE, the 12-month cumulative incidence of recurrent VTE was 6.0% (95% CI: 4.4–8.1) [20]. These observations suggest that physicians should prescribe anticoagulant treatment in cancer patients presenting with incidental or asymptomatic PE or proximal DVT.

Regarding the thrombus location, patients with proximal DVT in the lower limbs were found to have a higher risk of recurrence under anticoagulation (hazard ratio of 1.78, 95% CI: 1.08–2.89) as compared to patients with isolated PE or PE associated with DVT in a large cohort of 1812 CAT patients [21]. However, the overall mortality appeared similar. Regarding splanchnic VTE, a similar rate of recurrent VTE rate and mortality have been reported as compared to other sites (PE or DVT) [22]. In an individual patient data meta-analysis on 1635 unselected patients with splanchnic vein thrombosis, the risk of recurrent VTE and of all-cause mortality was increased in patients with solid cancers as compared to others (hazard ratios: 2.02 [95% CI: 1.35–3.04] and 8.68 [95% CI: 6.24–12.07] respectively); the incidence rate of recurrent VTE was 11.2% [95% CI: 10.2–12.3] during a median follow-up duration 442 days (range: 7–730 days) [23].

A retrospective case-control study reported a moderate increase in the risk of recurrent VTE under treatment in patients with incidental truncular PE (odds ratio: 1.28 [95% CI: 1.08–1.53] with respect to incidental distal PE) [19]. However, in the prospective study of Kraaijpoel et al. patients with cancer with incidental PE, the thrombus size was not found to influence the risk of recurrent VTE under anticoagulation: patients with sub-segmental PE were found to have a similar 12-month cumulative rate of recurrent VTE

Table 1
Incidence of VTE recurrence or major bleeding in patients with CAT treated with tinzaparin.

	GI[a] [*n* = 382]	Lung [*n* = 254]	Genitourinary[b] [*n* = 199]	Gynecological[c] [*n* = 198]	Breast [*n* = 166]	Haematological [*n* = 104]	Other [*n* = 110]	Total [*n* = 1413]
VTE recurrence, number of events	23	20	18	17	1	4	2	85
Cumulative incidence [95% CI]	6.3% [4.1–9.7]	8.1% [5.3–12.3]	9.2% [6.4–13.1]	9.1% [5.9–14.0]	0.6% [0.1–4.7]	3.9% [1.5–9.9]	1.8% [0.6–6.1]	6.2% [5.0–7.7]
Time of occurrence (days), median [IQR]	29 [17–54]	36 [25.5–132]	31.5 [9–71]	57 [25–126]	–	32 [25–36.5]	48.5 [8–89]	35 [19–81]
Major bleeding, number of events	14	6	7	4	7	3	6	47
Cumulative incidence [95% CI]	3.8% [2.1–6.6]	2.4% [1.2–4.9]	3.6% [1.9–6.9]	2.1% [0.8–6.0]	4.2% [2.1–8.5]	3.1% [1.0–9.1]	5.5% [2.7–11.3]	3.4% [2.7–4.5]
Time of occurrence (days), median [IQR]	88.5 [15–128]	62.5 [38–150]	85 [28–110]	115.5 [57.5–121.5]	70 [9–112]	20 [15–185]	26.5 [7–63]	64 [15–118]
Deaths, number of events	132	109	51	56	29	18	31	426
Cumulative incidence [95% CI]	35.8 [30.8–40.7]	45.2% [38.8–51.7]	26.7% [20.4–33.0]	30.0% [23.4–36.7]	17.7% [11.8–23.5]	18.0% [10.4–25.6]	29.2% [20.5–37.9]	31.3% [28.9–33.8]
Time of occurrence (days), median [IQR]	57 [31–108.5]	68 [34–108]	73 [28–128]	76 [36–121]	63 [25–97]	56 [36–103]	73 [44–117]	68 [32–114]

CAT: cancer-associated thromboembolism; CI: confidence interval; VTE: venous thromboembolism. Data are taken from prospective studies evaluated VTE recurrence and bleeding outcomes in patients with CAT treated with tinzaparin [34].

[a] Colorectum (*n* = 214), pancreas (*n* = 59), stomach (*n* = 50), hepatobiliary (*n* = 37), œsophagus (*n* = 13), other intestinal (*n* = 4), peritoneum (*n* = 3), hepatopancreatic ampulloma (*n* = 1), jejunum (*n* = 1).

[b] Prostate (*n* = 74), renal carcinoma (*n* = 53), bladder (*n* = 49), testicle (*n* = 19), penis (*n* = 3), ureter (*n* = 1).

[c] Ovary (*n* = 85), cervix (*n* = 46), uterus (*n* = 38), other (*n* = 29), vagina (*n* = 3), vulva (*n* = 2) + *n* = 24 cervix, uterus, ovary combined in CATCH.

of 6% as compared to segmental, lobar or truncular PE and mortality was also similar [20]. In addition, the risk of recurrence was also similar according to whether sub-segmental PE was isolated or multiple [20]. Thus, thrombus site for PE patients does not appear to influence either the risk of recurrence or mortality. Furthermore, these observations suggest that sub-segmental PE, even incidental, should be treated similarly to more proximal PE. Of course, given the high proportion of false positive CTPA, it is very important to confirm sub-segmental PE by well-trained radiologists [10].

In a cohort of 1922 patients with isolated distal or proximal DVT, the risk of recurrent VTE under anticoagulation (4.60 vs. 5.77 per 100 person-years, respectively) and mortality (31.89 and 28.36 per 100 person-years, respectively) were found to be similar between these two groups [24]. The high risk of recurrent VTE in patient with cancer and distal DVT is also supported by the results of a recent meta-analysis, which found an annual incidence rate of recurrent VTE of 5.65% (95% CI: 2.09–15.30) per 100 patient-years regardless of type and duration of anticoagulant therapy [25].

Regarding severity of PE, it is well established that, in unselected patients with PE, prognosis is influenced by the occurrence of circulatory shock (systolic blood pressure < 90 mmHg), clinical severity [in the European Society of Cardiology (ESC) guidelines, the simplified pulmonary embolism severity index (sPESI) is the reference metric for determining this], the presence of right ventricular dysfunction (identified using computed tomography pulmonary angiography or trans-thoracic echography) and elevated troponin levels. These observations have led to the development of a risk stratification algorithm, which was proposed in the ESC/European Respiratory Society (ERS) consensus guidelines [26]. This risk stratification should be applied to cancer patients with PE in order to determine the setting of PE management and antithrombotic treatment regimen. By using sPESI score in haemodynamically stable patients, as recommended by ESC/ERS consensus, all patients with PE and cancer are classified as having PE at intermediate risk of death and, therefore, they should be hospitalized for initiation of anticoagulant treatment. However, limited data suggest that patients with cancer and "low risk" PE defined by either no HESTIA criteria or no other sPESI criteria than cancer itself and no other medical or social reason justifying hospitalization could be treated at home with a low risk of complication [27]. In high-risk PE patients with cancer, there is evidence that a reperfusion strategy should be implemented, given the major risk of death in this context [26,28]. At this time, there is no data suggesting that high-risk PE cancer patients should be treated differently than high-risk PE patients without cancer.

Regarding the case-fatality rate of recurrent VTE, in a large cohort of 1812 CAT patients, the overall case fatality rate for recurrent VTE while on anticoagulant therapy was 12.1% and was higher for recurrent PE (18.5%) as compared to recurrent DVT (6.3%) [21]. In a prospective cohort of 695 patients with incidental PE, the case-fatality rate of recurrence was also found to be high (20%, whether the index PE was sub-segmental or not) [20].

Consequently, it appears that VTE-related characteristics (the presence of symptoms suggestive of VTE or not, thrombus site or severity of VTE) have little impact on CAT management: the risk of recurrence and death are increased in these patients as compared to non-cancer patients with VTE and the vast majority of these patients should be treated by anticoagulant therapy. In case of high-risk PE in cancer patients, reperfusion strategy remains indicated.

3.2.3. *Cancer-related factors*

In the different clinical trials, DXIs have been proven to be at least as effective as LMWH, and even more effective than LMWH for VTE recurrence prevention when meta-analysing all available studies (HR: 0.63; 95% CI: 0.47–0.86) [29]. However, potential safety issues should be noted, with a variable risk of bleeding between studies and between individual DXIs. Compared with dalteparin, an excess incidence of major bleeding (MB) was observed in patients treated with edoxaban or rivaroxaban, mostly corresponding to gastrointestinal (GI) bleeding in patients with GI cancer. However, only half of MB were related to the site of cancer in the HOKUSAI cancer study [30].

In the CARAVAGGIO Study, no difference was found in MB between the dalteparin and apixaban arms, including GI bleeding, also in patients with digestive cancer [31,32]. When considering clinically relevant non-major bleeding (CRNMB), there was a non-significant difference between arms, and no difference in the risk of GI bleeding [31,32]. In patients included in CARAVAGGIO, situations associated with a higher risk of VTE recurrence were pancreatic or

Table 2
Elimination half-lives of anticoagulants in healthy adults.

Anticoagulant	Elimination half-life
Parenteral (subcutaneous)	
LMWHs	3–6 hours
Fondaparinux	17 hours
Danaparoid	25 hours
Oral	
Warfarin	36–42 hours
Apixaban	10–14 hours
Dabigatran	14–17 hours
Edoxaban	9–11 hours
Rivaroxaban	7–11 hours

Data are taken from the ACCP and ESC anticoagulation guidelines [86,87].

Table 4
Transport and metabolism of oral anticoagulants used in the treatment of CAT.

	Apixaban	Rivaroxaban	Edoxaban	Warfarin
Transporters	**P-gp**	**P-gp**	**P-gp**	
	BCRP	**BCRP**		
		OAT3		
Metabolism	**3A4**	**3A4**	**Non-CYP**	**2C9**
	1A2, 2J2	**2J2**		
	2C8, 2C9, 2C19	not CYP	3A4 (< 4%)	1A2, 2C19, 3A4

Pathways in bold indicate the principal elimination pathways for the anticoagulant. CYP: cytochrome P450; P-gp: permeability glycoprotein; BCRP: breast cancer resistance protein; OAT: organic anion transporter.

hepatobiliary cancer site (HR: 2.20, 95% CI: 1.19–4.06), and concomitant anticancer treatment (HR: 1.98, 95% CI: 1.03–3.81) [33]. Situations associated with a higher risk of MB were genitourinary cancer (HR: 2.72; $P = 0.009$), non-resected luminal GI tract cancer (HR: 2.77; $P = 0.004$), and upper GI tract cancer (HR: 3.17; $P = 0.018$) [33]. In the CARAVAGGIO study, despite apparent differences in event rates according to the site of cancer, no significant difference was found between apixaban and dalteparin in terms of VTE recurrence and MB, with a dose regimen using a loading dose for each treatment (10 mg *bid* for seven days and then 5 mg *bid* for apixaban, 200 mg/kg/day for one month and then 150 mg/kg/day for dalteparin).

A meta-analysis based on individual patient data from prospective studies evaluated VTE recurrence and bleeding outcomes in patients with CAT treated with tinzaparin [34]. A total of 1413 patients (median age 65.0 [IQR: 56.0–73.5], 51.9% female) were included. At six months after tinzaparin initiation, 74 patients had experienced a recurrent VTE (cumulative incidence: 5.4% [95% CI: 4.3%–6.7%]), while 47 patients had experienced a major bleeding event (cumulative incidence: 3.4% [95% CI: 2.6%–4.6%]). The cumulative incidence of VTE recurrence was highest in patients with genitourinary, lung and gynecological cancers, while that of major bleeding incidence was highest in patients with breast, gastrointestinal and genitourinary cancers (Table 1).

Therefore, as no identified clinical risk factors can inform the choice between LMWHs and apixaban as the initial treatment, even in patients with a perceived or proven high risk of major bleeding, the only criterion of choice in this context could be the pharmacokinetic profile of the treatment (Table 2). In situations where major bleeding may be considered easier to manage when using an anticoagulant with a shorter half-life, then LMWHs might be preferred over apixaban (Table 3). The special situation of patients with brain tumours is discussed in a dedicated chapter [35].

3.2.4. Criteria for choosing VTE treatment related to anticancer therapy: drug interactions

The effect of anticoagulants used in the treatment of VTE may be altered by two kinds of drug-drug interactions (DDIs), namely pharmacodynamic and pharmacokinetic interactions.

3.2.4.1. Pharmacodynamic drug interactions. Pharmacodynamic drug interactions arise as a consequence of interference of the co-prescribed drug with either haemostasis or the vascular endothelium (or both), thereby modifying the bleeding risk or thrombotic risk associated with anticoagulants, although in principle the thrombotic risk should be at least in part controlled by anticoagulant treatment. A drug interaction increasing the bleeding risk has been described with certain small-molecule or monoclonal antibody tyrosine kinase inhibitors (TKIs) [36].

These pharmacodynamic DDIs are not specific for the type of anticoagulant, and increase the risk of haemorrhage whatever the anticoagulant used. In this case, a LMWH is preferred for the initial phase of treatment, given that its elimination half-life is shorter than that of a DXI. After six months of treatment, if anticoagulant treatment is to be continued, two options can be discussed: LMWH or a reduced dose of DXI.

3.2.4.2. Pharmacokinetic drug interactions. These are principally important for DXIs and vitamin K antagonists (VKAs) since their absorption, distribution and elimination depend on transmembrane transporters or cytochrome P450 (CYP450) and non-CYP drug metabolizing enzymes (Table 4). Many anticancer drugs can interfere with the activity of these transporters or enzymes, with inhibition causing an increase in anticoagulant levels and induction leading to a decrease in anticoagulant concentrations.

These DDI PKs are specific to each anticancer agent and each anticoagulant, depending on the metabolic pathways and transporters involved (Table 4). Thus, within the same class of anticancer drugs, there may be molecules with no modulating effect, enzyme inducers or inhibitors and/or transporters.

To date, the most relevant pharmacokinetic DDIs relate to interactions with drugs that affect the activity of CYP3A4 and permeability glycoprotein (P-gp). DXIs are substrates for these proteins, although they do not interfere with the activity of CYP3A4 or P-gp at clinically relevant concentrations. In theory, DXIs can only modify the pharmacokinetics of anticancer agents through competitive inhibition. However, no competitive inhibition by DXIs of the metabolism of sensitive substrates of CYP3A4 (simvastatin) and P-gp (digoxin) at clinical doses [37] and such interactions are improbable with anticancer drugs.

Table 3
Situations where an LMWH may be preferred over a DXI as initial CAT treatment.

Tumour site	Clinical setting
0esogastric tumour or non-resected colorectal tumour	With anaemia identified by iron deficiency or history of recent bleeding
Non-resected urothelial or gynaecological (especially cervical) cancer	With anaemia identified by iron deficiency or history of recent bleeding
Metastasis of renal carcinoma or melanoma	If appearance on imaging is indicative of a risk of bleeding (hypervascularisation+++)
Primary or secondary location close to large pulmonary vessels	All clinical settings
Inoperable locally advanced breast cancer with skin involvement.	With anaemia identified by iron deficiency or history of recent bleeding
Primary or secondary location of cutaneous tumours or sarcoma	With anaemia identified by iron deficiency or history of recent bleeding

LWMH: low molecular weight heparin; CAT: cancer-associated thromboembolism.
The table illustrates settings where it may be more difficult to stop or control a major or clinically relevant bleed.

Table 5
Number and importance of DDIs identified with anticoagulants.

	DDI (all types)	Major DDI	Moderate DDI	Minor DDI
VKA (warfarin)	625	141	414	70
LMWH	191	94	91	6
Apixaban	359	120	231	8
Rivaroxaban	353	124	221	8
Edoxaban	259	161	92	6

LMWH: low molecular weight heparin; VKA: vitamin K antagonist.
Data taken from https://www.drugs.com/drug-interactions.html.

3.2.4.3. Overview of potential drug–drug interactions with anticoagulants. The number of potential DDIs between anticoagulants and other drugs is significant (Table 5) and warrants specific discussion in these guidelines given the potential haemorrhagic or thrombotic risk. In a digital database (https://www.drugs.com/drug-interactions.html), 625 such DDIs were identified. Of these, 36% were considered to be major, and two-thirds of the so-called major DDIs were pharmacodynamic drug interactions (Table 5). For example, of the 120 major DDIs listed for apixaban, 68 corresponded to pharmacodynamic interactions, 46 to inhibition of transporter proteins or CYP450 and eight to induction of transporter proteins or CYP450. Of the 46 inhibitors of CYP3A4 or P-gp resulting in a major DDI with apixaban, 20 concerned cancer therapies.

As a result, there is an abundant literature on the subject. A search of the PubMed database using the key words “drug interaction” and “anticoagulant” identified over 13,000 publications and more than 2100 reviews, with a marked increase since the introduction of DXIs. However, only 241 of the publications relating to DDIs described randomised clinical trials. The aim here is not to provide an exhaustive review, but to explain why, in spite of the abundant literature, analysis of DDIs remains complex. There are several reasons for this including the following:

- a drug may interfere with several CYP450 isoenzymes to varying degrees. For example, tamoxifen is a strong inhibitor of CYP3A4 and CYP2C19 but a moderate inhibitor of CYP2C9 and P-gp;
- a drug may interfere in one direction on CYP450 isoenzymes and in the opposite direction on transmembrane transporters. For example, enzalutamide is a strong inducer of CYP3A4 but an inhibitor of P-gp;
- the mechanisms of inhibition are complex and variable including competitive and non-competitive reversible inhibition and direct or metabolic irreversible inhibition [38]. For this reason, the interaction may vary according to the doses of the two interacting drugs.

Demonstration of DDIs is based essentially on *in vitro* models, with clinical confirmation in healthy volunteers in the event of a significant effect being observed *in vitro*. However, the reproducibility of the models used is questionable. For this reason, guidelines for drug developers have been drawn up by regulatory authorities. The inter-individual variability in plasma levels of DXIs and VKAs is very large, and only very pronounced DDIs will have a clinically relevant impact on anticoagulant exposure *in vivo*. In addition, the extrapolation of results obtained *in vitro* and in healthy volunteers to patients with cancer and other chronic diseases remains uncertain. For example, although amiodarone is a weak inhibitor of CYP3A4 and a moderate P-gp inhibitor and, on this basis, might be expected to interact with apixaban, such an interaction was not confirmed in a Phase III trial in atrial fibrillation [39]. Most anticancer drugs cannot be evaluated in healthy volunteers, and it is virtually impossible to use randomised studies in cancer patients in order to identify DDIs, given the limited number of patients studied for each potentially interacting drug [40]. Exploration of potential DDIs from real-life data appears to be a useful approach but the interpretation of such data is complex and subject to confounding bias. For example, two studies of interactions between amidodarone and apixaban using data from health insurance claims databases yielded contradictory results, with no interaction being observed in the French SNDS database [41], and a significant interaction with an increased risk of haemorrhage in a US database [42].

Given this complexity and the sometimes conflicting results obtained, it is not surprising to observe significant discrepancies from one DDI database to another, even for drugs with very well-characterised DDIs such as anti-epileptics [43]. It is therefore necessary to use several sources to identify potential DDIs, with a preference for databases established by professional associations in onco-cardiology (e.g. [44,45]) or recent systematic reviews of the literature by experts in the field (e.g. [46–48]). A list of reliable DDI databases available on-line is proposed in Table 6.

For anticancer drugs, almost 85% of the drugs used do not interfere with anticoagulants. However, the remaining 15% may be associated with an increased risk of haemorrhage or thrombosis, justifying an adjusted therapeutic strategy. With this in mind, the latest ESC onco-cardiology recommendations identify ten drugs with proven pharmacokinetic DDIs that should not be used in combination with anticoagulants, and ten other drugs with pharmacodynamic DDI PD that require frequent clinical and haematological monitoring [45].

Finally, DDIs are classified as mild, moderate and major, but this classification is based essentially on pharmacokinetic considerations and very rarely on the basis of clinical consequences. The definition of a major DDI also varies from one source of information to another. Empirically, it is proposed that a pharmacokinetic DDI should be defined as major when there is a twofold change in the area under the plasma concentration-time curve (AUC), i.e. a halving in the case of major induction and a doubling in the case of major inhibition [49]. This classification is illustrated by the effect of co-administration of apixaban with ketoconazole (a strong inhibitor of 3A4 and P-gp) and rifampicin (a strong inducer of 3A4 and P-gp) [50]. It should be noted, however, that a moderate DDI in the presence of at least two other pharmacokinetic variability factors (age > 80 years, body weight < 60 kg and creati-

Table 6
Non-exhaustive list of on-line databases containing information on DDIs.

Name	Support	DDIs included	Access	Mobile App
DDI predictor®	Academic (France)	General	Free	No
Cancer ichart®	Academic (UK)	Cancer	Free	Yes
MedScape®/webMD®	Private – (US)	General	Free	Yes
Drugs.com	Mixed (US)	General	Free	No
UpToDate/Lexi-Comp®	Private	General	For pay	Yes
Micromedex/Drugdex®	Private	General	For pay	No

nine > 133 μmol/L) may have consequences identical to a major DDI in terms of AUC.

Proposals of the expert group for assessing and managing potential drug-drug interactions between anticoagulants and anticancer therapies

- We recommend that any combination of anticoagulant and anticancer drug should be investigated for potential drug-drug interactions (DDIs). This search should be extended to any other co-prescribed drugs. *Expert panel ranking: 3.89 out of 4.00*
- Given that discrepancies between databases are sometimes significant, we recommend using multiple sources of information to identify these DDIs, giving preference to regularly updated sources. *Expert panel ranking: 3.57 out of 4.00*
- Concerning the various possible sources of information:
  - We recommend using the information provided in the summary of product characteristics for each molecule prescribed. We suggest to use the DDI thesauri of the registration authorities (ANSM, France [51], British National Formulary [52], fda.gov, USA. . .). *Expert panel ranking: 3.67 out of 4.00*
  - We suggest using one or more databases established by professional associations in onco-cardiology. *Expert panel ranking: 3.67 out of 4.00*
  - We suggest using systematic reviews of the literature by experts in the field, ensuring that they are recently updated. *Expert panel ranking: 3.71 out of 4.00*
  - We suggest using at least one digital database. *Expert panel ranking: 3.64 out of 4.00*
  - We suggest considering a pharmacokinetic DDI to be major if the area under the curve of DXI concentrations is significantly modified by a factor of two. The presence of other pharmacokinetic variability factors (age, body weight and creatinine levels) should be taken into account in the case of a moderate DDI. *Expert panel ranking: 3.58 out of 4.00*
- If no major DDI is identified, the usual recommendations apply. *Expert panel ranking: 3.81 out of 4.00*
- If there is a discrepancy between the different sources used regarding the existence of a major DDI, we suggest that the case be discussed at a multidisciplinary consultation meeting involving an expert pharmacist or pharmacologist. *Expert panel ranking: 3.76 out of 4.00*
- If a major pharmacodynamic or pharmacokinetic (strong 3A4 or P-gp inhibition) DDI is identified with increased DXI concentrations and an increased risk of haemorrhage, we recommend using an LMWH for the initial phase of treatment. After six months of treatment, we recommend assessing the need to continue anticoagulant treatment. If necessary, treatment with LMWH should be continued. Alternatively, and after discussion in a multidisciplinary consultation meeting (MCM), a reduced dose of DXI may be suggested in the absence of additional bleeding risk factors such as severe renal or hepatic failure. *Expert panel ranking: 3.82 out of 4.00.* Alternatively, and after discussion in a MCM, we suggest considering VKAs. *Expert panel ranking: 3.33 out of 4.00*
- If a major pharmacokinetic DDI is identified with reduced DXI concentrations (strong induction of 3A4 and/or P-gp), we recommend using an LMWH for the initial phase of treatment. After six months of treatment, we recommend assessing the need to continue anticoagulant treatment. If necessary, treatment with LMWH should be continued. Alternatively, and after discussion with the MCM, a full dose of DXI may be suggested, in the absence of additional thrombotic risk factors. *Expert panel ranking: 3.52 out of 4.00.* Alternatively, and after discussion in a MCM, we suggest considering VKAs. *Expert panel ranking: 3.33 out of 4.00*
- We suggest using edoxaban in cases of induction or strong 3A4 inhibition contraindicating the use of rivaroxaban or apixaban. *Expert panel ranking: 3.35 out of 4.00*
- If a major pharmacokinetic or pharmacodynamic DDI is identified, we recommend giving priority to the anticancer treatment. However, we suggest that the MCM discuss the possibility of an alternative to the current anticancer therapy. *Expert panel ranking: 3.79 out of 4.00*
- We recommend checking with the patient about any nutritional or health supplements that they may be taking and informing them of any potential interactions with anticoagulants or anticancer drugs. *Expert panel ranking: 3.89 out of 4.00*

3.2.5. Patient preference

Patient adherence, referring to the extent to which patients take the prescribed treatment, is the most important condition to make the treatment of CAT effective. For this reason, patients should be involved in the treatment decision process when choosing between LMWH and DOACs [13]. Each patient will have their own unique set of values and preferences resulting from personal views, VTE experience, and history. Previous qualitative studies have shown that the most important criterion for patients is that anticoagulant treatment should have minimal interference with their anticancer treatment, over that of the route of administration, even in the form of daily injections [53,54].

DOACs may provide a more convenient option than LMWHs, associated with similar efficacy for CAT. Indeed, an increased treatment satisfaction was observed with DOACs compared to LMWHs in naturalistic studies [55,56] and randomised controlled trials [57,58]. However, adherence, defined as medication adherence with a proportion of days covered (PDC) ≥ 80% before discontinuation, has been reported to be high with both DXIs and LMWH and comparable with both treatment classes, both in observational studies [59] and in clinical trials [31,60,61].

In contrast, patient persistence, the duration a patient continues a prescribed anticoagulant, may be shorter with LMWH than with DXIs, although published data is variable between studies. In general, more than half of patients initially managed with LMWH will have switched to another anticoagulant class by three months [62–64]. In the CANVAS Study, most of the patients (80%) declining randomisation who chose to receive DXIs, and persistence at six months was better than in those who chose to receive LMWH (74.3 vs. 60.2%), while it was similar at three months (86.7 vs. 79.5%) [62].

Overall, the choice of anticoagulant class should be made after a clinician-patient discussion as a shared decision in order to optimise adherence [13]. Regular discussions with patients during follow-up should take place, as many patients may wish to discontinue the anticoagulant option after a few weeks. A transition to another anticoagulant should be considered at this time in order to keep adherence as high as possible, this being the key to achieving the desired results of treatment.

3.3. Switching between anticoagulants

3.3.1. Situations where switching may be desirable

The most suitable anticoagulant therapeutic regimen may change as patients continue along their journey through cancer. In the COSIMO study [55], designed to assess patient-reported treatment satisfaction following a planned change from standard therapy (principally LMWH) to rivaroxaban for the treatment of CAT, patients received a median of 100 days (3.3 months) of anticoagulant therapy before switching to rivaroxaban. The most

Situations associated with a low risk of VTE recurrence

- Patients with cancer who had undergone successful cancer surgery within the three months prior to the VTE index event and not requiring adjuvant therapy (*ie*, the main risk factor for VTE could be surgery rather than cancer)

Situations associated with an intermediate risk of VTE recurrence

- Patients with a history of cancer

Situations associated with a high risk of VTE recurrence

- Patients with active cancer

  As the definition of "active cancer" varies across studies, the ISTH proposed a consensual definition[a]:

  Cancer is considered active if any of the following apply:

  - No potentially curative treatment has been received
  - Evidence that curative treatment has not been effective (e.g. recurrent or progressive disease)
  - Ongoing treatment

Fig. 2. Cancer activity and the risk of VTE recurrence. [a]Taken from Kearon et al., 2016 [74]

common reasons for changing to rivaroxaban were patient-related, including fatigue with parenteral administration ($n = 136$, 26.9%), improved quality of life ($n = 94$, 18.6%) and general patient preference ($n = 76$, 15.0%); for 174 (34.5%) patients, the it was physician who decided to change their therapy.

A transition from one anticoagulant option to another can be considered durinthe follow-up for different reasons (see Box 1). A flexible approach to therapy should always be taken. As a general rule, the route, dose and duration of anticoagulant treatment for CAT should thus be periodically reassessed on a case-by-case basis, and chosen to ensure both optimal patient adherence and continued treatment relevance in terms of efficacy and tolerability.

3.4. Switching modalities

If a switch is considered, the initial drug should be replaced by the other directly. Both classes should never be taken by the patient simultaneously. This is the case both for switching from an LMWH to a DXI (Fig. 3) and for switching from a DXI to an LMWH.

3.5. Treatment duration

3.5.1. Continuation or discontinuation of treatment beyond six months

Consistent data from prospective cohort studies and retrospective analyses of health insurance claims databases indicate that the majority of patients diagnosed with CAT survive for at least six months [65–68]. This thus raises the question of whether anticoagulant treatment should be continued beyond the minimum recommended duration of six months for all patients with CAT [67]. The decision should be based on available guidelines and take into account the patient's clinical status at the time, as evaluated by the oncologist, vascular specialist, nurse and any other relevant caregiver. The decision should be taken by the multidisciplinary team, after discussion with the patient, and the information shared with all other healthcare professionals involved. Continuation of treatment should be the most appropriate strategy when the risk of VTE recurrence remains elevated and outweighs any risk of bleeding associated with anticoagulant use. Several factors enter into this risk assessment, in particular, the activity of the cancer and the site of the primary cancers (see Sections 3.5.3 and 3.5.4 below).

Apart from the Cancer-DACUS study (discussed below in Section 3.5.2), no randomised clinical trials have evaluated the risk of VTE recurrence or bleeding in patients with CAT treated with anticoagulants beyond six months. For example, the long-term extension of the SELECT-D trial of rivaroxaban in CAT was closed prematurely because of low recruitment. However, numerous observational studies have addressed this issue. For example, in a prospective observational study involving 6592 patients with CAT, the cumulative incidence of VTE recurrence was 22.1/100 patient-year [95% CI: 19.9–24.4] during the first six months and 7.9/100 patient-year [95% CI: 6.2–9.8] between 6 and 12 months [69]. Nonetheless, these observational studies have reported highly variable rates of VTE recurrence and bleeding complications.

A meta-analysis of available data, from observational studies and follow-up of patients with CAT included in clinical studies, demonstrated a persistent risk of VTE recurrence and bleeding between 6 and 12 months after the index VTE [70]. The event rate was extremely heterogenous between studies, and it was not possible to generate an overall estimate of event rates. However, in the individual studies, the risk of VTE recurrence between 6 and 12 months was systematically lower than that observed during the first six months.

3.5.2. VTE recurrence following discontinuation of anticoagulant treatment

Limited data is available from clinical trials on outcomes between patients continuing or stopping anticoagulant treatment beyond six months after the initial CAT, and the available information cannot be used to provide robust guidance for routine clinical practice. The Cancer-DACUS trial compared outcomes (VTE recurrence and major bleeding) between two randomised groups of patients treated for CAT with LWMH for six months who displayed residual vein thrombosis [71]. In the group who continued anticoagulant treatment, the 12-month cumulative VTE recurrence rate was lower than in the group who discontinued. However, the patients included in this study were principally post-cancer surgery patients with localized disease and not requiring chemotherapy (which may explain the relatively low event rates observed) and the findings may not be readily extrapolatable to all patients with cancers.

Moreover, in the long-term extension of the SELECT-D study, where patients with CAT completing six months of anticoagulant treatment were re-randomised to continuing rivaroxaban or switching to a placebo was insufficiently powered to provide useful information on the risk of discontinuing anticoagulant since the trial was stopped prematurely due to difficulty with recruitment [72]. Such study protocols have not been attempted for other DXIs.

A meta-analysis including published data from 14 randomised trials or cohort studies, (excluded case-control studies, cross-sectional studies, case series, case reports), that includes data on over 1900 patients with several types of cancer has recently been published [73]. This meta-analysis provides an estimate of the rate of recurrent VTE after discontinuation of anticoagulant therapy in

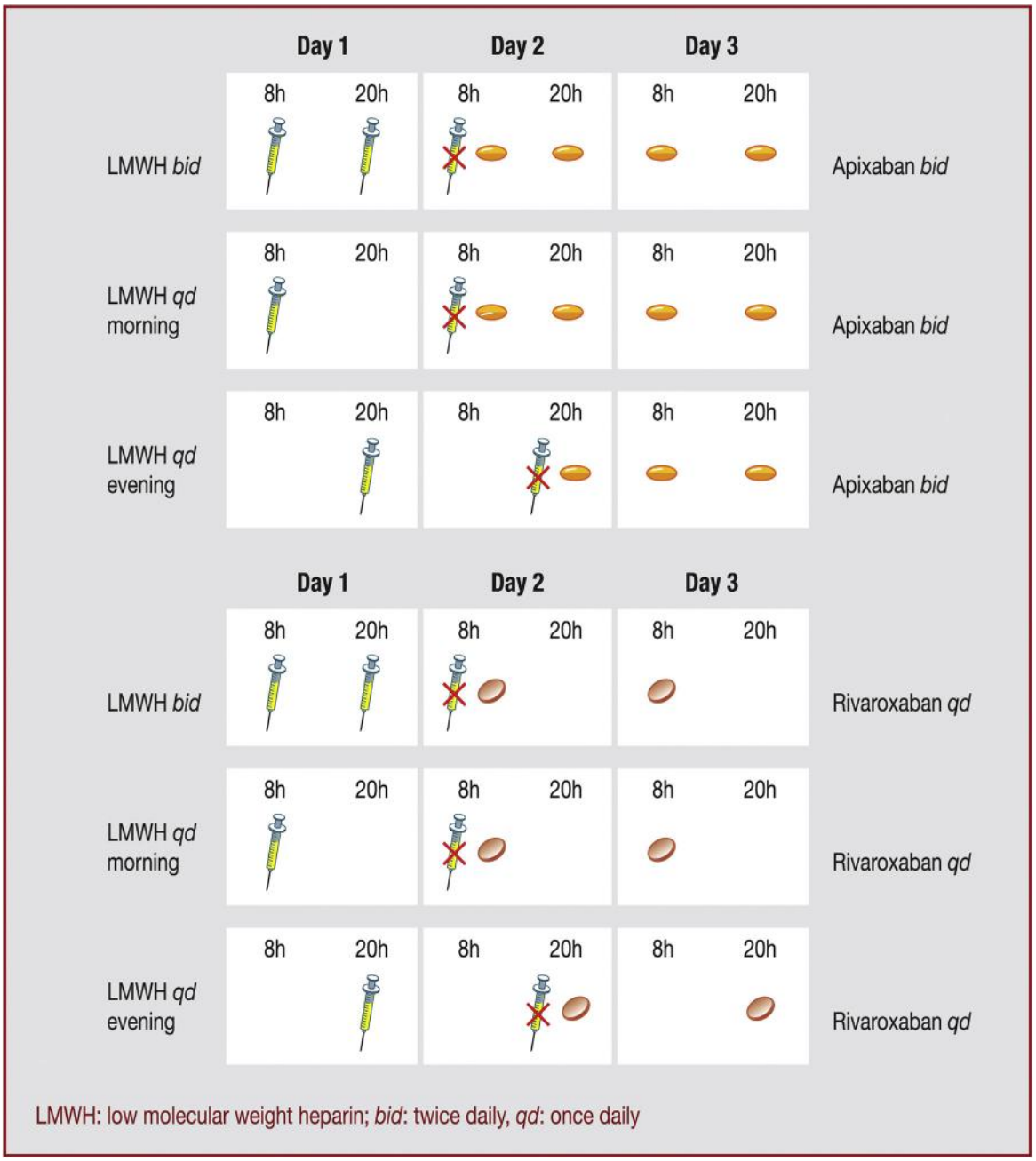


Fig. 3. Dosing sequence for switching from an LMWH to a DXI. LWMH: low molecular weight heparin; *bid*: twice daily, *q*d: once daily.

patients with CAT, who had completed at least three months of anticoagulant therapy (LMWH, VKAs or DXIs), and were followed-up thereafter for at least three months. It should be noted that only half of the eligible studies were included in the final meta-analysis, due to lack of complete key data in the source publication. The pooled rate of recurrent VTE per 100 person-years after discontinuation of anticoagulant therapy was 14.6 events [95% CI: 6.5–22.8] in the first three months, decreasing to 1.1 events [95% CI: 0.3–2.1] in years 2–3, and 2.2 events [95% CI: 0.0 to 4.4] in years 3–5. The cumulative VTE recurrence rate was 28.3% [95% CI: 15.6–39.6%] at year 1, 31.1% [95% CI: 16.5–43.8%] at year 2, 31.9% [95% CI: 16.8–45.0%] at year 3 and 35.0% [95% CI: 16.8–47.4%] at year 5. The results show that the rate of recurrent VTE after discontinuation of anticoagulant therapy over time in patients with CAT remains high, especially in the first few months after discontinuation [73].

3.5.3. *Cancer activity and the risk of VTE recurrence*

The activity of the cancer is an important determinant of the risk of VTE recurrence (Table 7), as well as of major bleeding. The evidence for this association has come from several large patient registries and prospective observational studies (Table 7). Patients with an active cancer (as defined in the ISTH practice guidelines [74]) have the highest risk of VTE recurrence, whether they are receiving anticoagulant treatment or not.

Early evidence for a role of cancer activity as a risk factor for VTE recurrence was provided by the Olmstead County study [75], a large long-term hospital database study from the United States. The study investigated long-term outcome in 3385 patients enrolled over a 35-year period, treated principally with VKAs and UFH. Patients with active cancer were compared to those with prior cancer that was inactive at the time of recurrence. The cumulative incidence curves for VTE recurrence in patients with active cancer

Table 7
Studies of VTE recurrence as a function of cancer activity.

GARFIELD-VTE [76]				
Study type:	Prospectively-collected data from 358 consecutive patients with CAT treated with anticoagulants			
Key finding(s):		Active cancer (high risk)	History of cancer (intermediate risk)	No cancer (low risk)
	Event rates (%) [95% confidence interval]			
	VTE recurrence	9.3 [7.4–11.8]	6.0 [4.3–8.4]	4.6 [4.2–5.1]
	Major bleeding	9.7 [7.7–12.2]	2.7 [1. 7–4.4]	2.0 [1.7–2.3]
	All-cause mortality	48.1 [43.4–53.2]	13.2 [10.6–16.4]	3.2 [2.9–3.6]
	Hazard ratios [95% confidence interval]			
		Active cancer vs. history of cancer		Active cancer vs. no cancer
	VTE recurrence	1.3 [0.9–1.9]		1.57 [1.2–2.0]
	Major bleeding	2.9 [1.7–5.0]		3.78 [2.9–5.0]
	All-cause mortality	3.5 [2.7–4.5]		14.19 [12.1–16.6]
van der Hulle et al., 2016 [77]				
Study type:	Prospectively-collected data from 358 consecutive patients with CAT treated with anticoagulants			
Key finding(s):	139 patients (38.8%) discontinued anticoagulant treatment after a median period of 6 months			
	Cumulative VTE recurrence rate following discontinuation:			
	19/100 PY [95% CI: 9.3–33] in patients whose cancer was still active			
	3.2/100 PY [95% CI: 1.5–5.9] in patients whose cancer had been cured			
USCAT [66]				
Study type:	Prospectively-collected data from 432 patients with CAT initially treated with tinzaparin for six months			
Key finding(s):	Cumulative incidence of clinical outcomes during the 7–12-month period following the index CAT event			
		All patients	Cancer progression	Metastatic disease
		n = 432	*n* = 217	*n* = 320
	VTE recurrence	8.0 [4.2–15.1]	10.6 [5.3–21.2]	8.7 [5.1–14.9]
	Clinically relevant bleeding	4.9 [3.2–7.4]	8.8 [5.6–13.7]	5.3 [3.2–8.8]
	Major bleeding	2.6 [1.3–5.1]	5.1 [2.8–9.1]	2.8 [1.4–5.6]
	Death	30.7 [22.8–38.6]	52.9 [41.0–64.8]	36.7 [27.6–45.7]
Barca-Hernando et al., 2023 [78]				
Study type:	Prospectively-collected data from 311 patients with CAT discontinuing anticoagulant treatment at least six months after the index CAT.			
Key finding(s):	Recurrent VTE at 6 months post-discontinuation: 6.1% [95% CI: 3.5–9.4%]			
	Recurrent VTE at 12 months post-discontinuation: 8.7% [95% CI: 5.8–12.4%]			
	Death post-discontinuation: 32.6%			
	Hazard ratio in patients with metastatic disease (vs. localised disease) – Fine-Gray model			
	Recurrent VTE at 6 months post-discontinuation: 3.83 [95% CI: 1.54–9.52]			
	Recurrent VTE at 12 months post-discontinuation: 5.00 [95% CI: 2.2–11.5]			
Schmidt et al., 2022 [65]				
Study type:	Retrospective survey of 585 consecutive patients with CAT followed for up to 24 months after the index VTE event			
Key finding(s):	The overall 1-year cumulative incidence of VTE recurrence was 8.2% [95%CI: 5.5%–11.6%]			
	VTE recurrence rate between 6 and 12 months after the index VTE event:			
	1.28% [95% CI: 0.13–5.81] in patients with cancer surgery during 3 months before index VTE			
	10.0% [95% CI: 6.7–14.1] in patients with no cancer surgery during 3 months before index VTE			
RIETE registry [79]				
Study type:	International, prospective cohort study of patients diagnosed with VTE			
Key finding(s):	14,318 patients CAT were evaluated, of whom 3414 had received anticoagulants for ≥ 3 months			
	The cumulative incidence of recurrent VTE was 10.2% [95% CI: 9.1–11.5] at 1 year			
	Surgery during the 2 months before the index VTE was associated with a low risk of recurrence (hazard ratio: 0.60 [95% CI: 0.40–0.92])			

CAT: cancer-associated thromboembolism; CI: confidence interval; VTE: venous thromboembolism.

and in those with prior, cured cancer continued to diverge beyond six months after the index VTE event, suggesting that patients with CAT remain at elevated risk for VTE recurrence beyond the recommended six-month period of anticoagulant treatment.

The GARFIELD-VTE study [76] was a prospective observational study of 10,684 patients with objectively diagnosed VTE involving 1075 patients with active cancer, 674 patients with a history of cancer, and 8935 patients without cancer. In this study, active cancer was an important risk factor for VTE recurrence and major bleeding as compared to patients with no cancer (Table 7).

A cohort study conducted in 358 consecutive patients with CAT supports the discontinuation of anticoagulant treatment in patients cured of cancer but not in those with active cancer [77]. In this study, the cumulative VTE recurrence rate was six-fold higher in patients whose cancer was still active when anticoagulants were discontinued (19/100 patient-years) than in those in whom the cancer had been cured (3.2/100 patient-years) (Table 7). Of interest, 70% of this group of patients with recurrent VTE also experienced a cancer recurrence during the follow-up period.

The influence of metastatic disease or cancer progression on VTE events occurring in CAT patients after the initial anticoagulant period has also been evaluated recently. In the USCAT study, both metastatic disease and cancer progression were reported to increase the risk of both VTE recurrence and bleeding between 6 and 12 months after the index VTE (Table 7) [66]. A retrospective analysis reported post-treatment outcomes in 311 patients with CAT included in three prospective studies, who discontinued anticoagulant after a median duration of anticoagulant therapy of 10.6 months [IQR: 6.5–19]. In this study, recurrent VTE at six and twelve months post-discontinuation was more frequent in patients with metastatic disease (Table 7) [78]. Whether the cancer is still "active" should thus be at the centre of discussion on whether to pursue anticoagulant treatment beyond six months, since these patients remain at particularly high risk for VTE recurrence.

Although patients with active cancer carry the highest risk if VTE recurrence, patients with a history of cancer that has been cured are also at increased risk of VTE. For example, the GARFIELD-VTE study showed that patients with a history of cancer had a significantly higher incidence of VTE recurrence than patients who had never had cancer [76] (Table 7).

In certain situations, the risk of VTE recurrence in patients with CAT appears to be relatively low and, in such situations, discontinuation of anticoagulant treatment after six months may be an option. In particular, patients with cancer having undergone can-

Proposals of the Expert Group

- We recommend treating patients with active cancer (as defined in Fig. 2) diagnosed with proximal DVT or PE for at least six months. *Expert panel ranking: 3.77 out of 4.00*
- In patients with active cancer diagnosed with proximal DVT or PE:
  - We recommend either apixaban or LMWH (without bridging with a VKA)
  - As an alternative, except for luminal GI tract cancer or urothelial cancer or renal cell carcinoma, we suggest edoxaban or rivaroxaban
  - *Expert panel ranking: 3.33 out of 4.00*
- When choosing the appropriate initial anticoagulant (LMWH or DXIs), we suggest considering the following, in collaboration with oncologists
  - Type and severity of index VTE event
  - Perceived risk of bleeding (prefer drugs with shorter half-life if high-risk)
  - Ongoing anticancer treatment
    - Check for drug-drug interactions (see Section 3.2.4 above).
    - Take into account planned surgery or invasive procedure.
  - Patient profile (age, platelet count, body weight, renal function, performance status)[4]
  - Patient preference.
  - *Expert panel ranking: 3.89 out of 4.00*
- In all patients with CAT, during cancer treatment, we suggest to re-consider the type of anticoagulant treatment (LMWH vs. DXI) periodically, taking into consideration the following, in collaboration with oncologists:
  - Type and severity of index VTE event
  - Perceived risk of bleeding (prefer drugs with shorter half-life if high-risk)
  - Ongoing anticancer treatment
    - Check for drug-drug interactions (see Section 3.2.4 below).
    - Take into account planned surgery or invasive procedure.
  - Patient profile (age, platelet count, body weight, renal function, performance status)[4]
  - Patient preference.
  - *Expert panel ranking: 3.82 out of 4.00*

[4]For treatment of patients aged > 70 years, with thrombocytopenia, with compromised renal function or at extremes of body mass index see chapter 'Special Populations' [14].

Box 1: Reasons for switching anticoagulant therapy

Initial decision by the clinician making the VTE diagnosis after discussion with the patient

Acceptability, adherence and persistence issues and patient preference (whatever the reason)

Intercurrent events during follow-up requiring specific management, such as surgery and other invasive procedures

Initiation of an anticancer treatment with a potential for DDI

VTE recurrence or bleeding

Changes in the patient risk profile

In case of regular nausea or vomiting

cer surgery within the three months prior to the VTE index event and not requiring adjuvant therapy appear to present a relatively low risk of VTE recurrence. In these patients, the principal risk factor for VTE could be surgery rather than cancer. For example, in a retrospective survey of 585 consecutive patients with CAT, the rate of VTE recurrence from 6 to 24 months following the index event in patients who had undergone cancer surgery in the three months prior to the index event (1.28%) was five times lower than that observed in the remaining patients (10.0%) (Table 7), and close to values observed in patients without cancer [65]. Similarly, in the RIETE registry, the one-year cumulative incidence for recurrent VTE in 3414 patients with CAT discontinuing anticoagulant treatment after at least three months was 10.2%. Surgery within the two months before the index VTE event was associated with a reduced risk of symptomatic PE or DVT during the one-year follow-up after anticoagulant discontinuation (hazard ratio: 0.60) (Table 7) [79].

3.5.4. Site of the primary cancer and the risk of VTE recurrence

During the initial anticoagulant treatment phase, both the risk of VTE recurrence and the risk of bleeding differ according to the site of cancer in patients with CAT. In a retrospective study of 3947 patients with symptomatic CAT from the RIETE patient registry, the rate of VTE, both the risk of VTE recurrence and the risk of bleeding during anticoagulant treatment differ between the four most frequent primary cancer sites (breast, prostate, colorectal or lung cancer) [80] (Table 8). The VTE recurrence rate ranged from 5.6/100 patient years (PY) in breast cancer to 27/100 PY in lung cancer and the major bleeding rate from 4.1/100 PY in breast cancer to 13/100 PY in prostate cancer. The risk of VTE recurrence outweighed the major bleeding risk in lung cancer, whereas the opposite was true in prostate cancer. In breast and colorectal cancer, the two risks were of similar magnitude. A subsequent analysis of predictors of VTE recurrence in the RIETE registry [79] extended the analysis to less common sites of primary cancer, including the pancreas, the biliary tract, the brain, the stomach, the oesophagus, the liver, or the ovary. Primary cancers in these sites were all associated with a higher risk of recurrence. In two other large patient registries, the Olmstead County project [75] and the UK CPRD [69], the pancreas, brain and ovaries were the solid tumour sites associated with the highest rate of VTE recurrence. A limitation is that those studies consider heterogeneous treatments and variable sample sizes representing various tumor sites. A meta-analysis of studies focusing on tinzaparin reported the highest risk in patients with genitourinary, lung and gynecological cancers [34].

Less information is available on outcomes during the continued (post-six months) treatment period in patient with different primary cancer sites. The USCAT study reported outcomes over 6 to 12 months follow-up in 432 patients with CAT still alive at six months, the majority of whom continued anticoagulant treatment [66]. This study demonstrated that the risk of VTE recurrence is higher in patients with colorectal cancer (12.6%) and lung cancer (13.8%) than in those with breast cancer (1.5%) while clinically relevant bleeding was more frequent in patients with colorectal cancer (5.8%) and breast cancer (4.5%) than in those with lung cancer (1.3%). These results are thus consistent with data reported from the initial treatment phase [80].

3.5.5. The decision to continue or withhold anticoagulant treatment beyond six months

In patients with a major risk factor for VTE other than cancer, such as surgery, who have completed six months of anticoagulant treatment, if the cancer is no longer active and has a good prognosis, anticoagulant treatment could be discontinued. On the other hand, when cancer remains the principal risk factor for VTE and is still active, anticoagulation should be continued. Outside these two extreme situations, the decision to continue or discontinue anticoagulation can only be made on a case-by-case basis, preferably during dedicated multidisciplinary discussions ("thrombosis board"), taking into account the risk of cancer recurrence, the frequency of cancer monitoring and the preference of the patient.

3.5.5.1. Drug and dose selection criteria. Given the persistent risk of VTE recurrence and the risk of bleeding after completing six

Table 8
Event rates during the course of anticoagulant therapy according to the primary cancer site.

RIETE registry 2017 [80]			
Study type:	RIETE international registry of patients with VTE: 3947 patients included and treated with anticoagulants for a mean duration of 139 days		
Key finding(s):	Event rates for VTE recurrence and major bleeding per 100 patient years	VTE recurrence (/100 PY)	Major bleeding (/100 PY)
	Primary cancer		
	Breast cancer	5.6 [95% CI: 3.8–8.1]	4.1 [95% CI: 2.7–5.9]
	Colorectal cancer	10 [95% CI: 7.6–13]	12 [95% CI: 9.4–15]
	Prostate cancer	6.9 [95% CI: 4.4–10]	13 [95% CI: 9.2–17]
	Lung cancer	27 [95% CI: 22–23]	11 [95% CI: 8.6–15]
RIETE registry 2023 [79]			
Study type:	RIETE international registry of patients with VTE: 3414 patients included and treated with anticoagulants for at least three months (median treatment duration: 187 days)		
Key finding(s):	Hazard ratio for VTE recurrence determined from Fine-Gray competitive risk analysis (reference: patients with cancer of the oropharynx or larynx, or melanoma)		
	Primary cancer		Hazard ratio
	Pancreatic or biliary cancer or carcinoma of unknown origin		6.86 [95% CI: 1.89–24.85]
	Lung, brain, stomach, oesophagus, liver or ovarian cancer		3.56 [95% CI: 1.07–11.80]
	Others (haematological, colorectal, uterine, bladder, kidney, prostate, breast or vulva cancer)		2.94 [95% CI: 0.91–9.52]
Olmstead County study [75]			
Study type:	RIETE international registry of patients with VTE: 3947 patients included and treated with anticoagulants for a mean duration of 139 days		
Key finding(s):	Hazard ratio for VTE recurrence determined from Cox analysis (reference: patients with other types/stages of primary cancer)		
	Primary cancer		Hazard ratio
	Stage IV pancreatic cancer		6.38 [95% CI: 2.69–15.13]
	Brain cancer		4.57 [95% CI: 2.07–10.09]
	Myeloproliferative or myelodysplastic disorder		3.49 [95% CI: 1.59–7.68]
	Ovarian cancer		3.22 [95% CI: 1.57–6.59]
	Stage IV cancer other than pancreas		2.85 [95% CI: 1.74–4.67]
	Lung cancer		2.73 [95% CI: 1.63–4.55]
UK CPRD study [69]			
Study type:	Retrospective analysis of 6592 patients with CAT in the UK Clinical Practice Research Datalink database		
Key finding(s):	Event rates for VTE recurrence per 100 patient years		
	Primary cancer		VTE recurrence (/100 PY)
	Pancreatic cancer		14.6 [12.9–16.5]
	Brain cancer		12.1 [10.3–14.0]
	Ovarian cancer		11.9 [10.6–13.2]
	Stomach cancer		10.8 [9.5–12.3]
	Lung cancer		10.1 [9.5–10.8]
	Uterine cancer		7.0 [5.9–8.3]
	Colon cancer		6.7 [6.3–7.2]
	Haematological malignancies		4.5 [4.1–4.8]
	Prostate cancer		4.4 [4.0–4.7]
	Breast cancer		3.2 [2.9–3.4]
	Bladder cancer		2.7 [2.4–3.0]

CI: confidence interval; PY: patient years; RIETE: Registro Informatizado de Enfermedad TromboEmbólica; VTE: venous thromboembolism.

months of anticoagulant therapy for CAT, together with the risk of recurrence in case of anticoagulant discontinuation, current guidelines [7,9,11,81] recommend continuing anticoagulant therapy for as long as the cancer is active and considering a low dose anticoagulant regimen as an attractive option for extended treatment. However, the type of anticoagulant and the dose of anticoagulant warrant prospective assessment in randomised controlled trials.

The EVE trial [82], a prospective randomised study in patients with CAT completing 6–12 months of anticoagulation, failed to demonstrate any superiority of a low-dose regimen of apixaban as compared to a full-dose after a 12-months follow-up with respect to the risk of major bleeding and clinically relevant non-major bleeding (8.9 vs. 12.2%, $P = 0.39$). In contrast, a substantial decrease in major bleeding events and a slight increase in VTE recurrence was demonstrated in an observational study in patients with active cancer treated with low-dose apixaban compared to full dose apixaban as secondary prophylaxis [83].

The API-CAT study [84], a prospective randomised double-blind study including 1767 patients is underway and aims to demonstrate the non-inferiority of a low-dose regimen of apixaban as compared to a full-dose in patients with CAT and active cancer completing at least six months of anticoagulation with respect to VTE recurrence. Since, cancer site could influence prognosis or treatment responsiveness in terms of efficacy and safety, randomisation was stratified on cancer site. If non-inferiority is demonstrated, then superiority with respect to the risk of bleeding (major bleeds + clinically relevant non-major bleeds) will be tested.

Proposals of the Expert Group

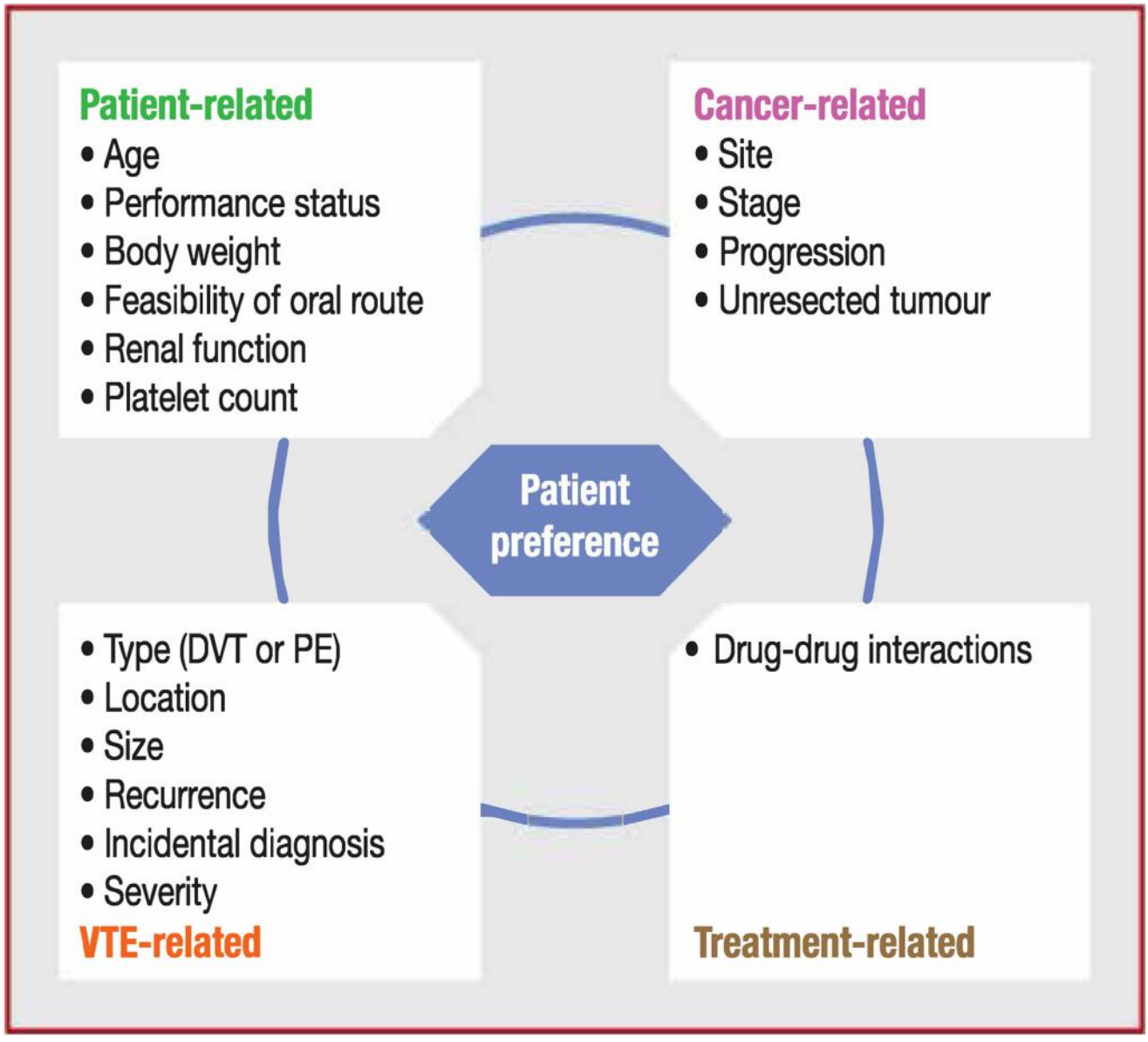
- Beyond six months of CAT treatment, we recommend anticoagulant treatment continuation:
  - EITHER In case of active cancer (as defined in Fig. 2), including increased biomarkers, and planned continuation of anticancer treatment (including hormonotherapy) for the next six months
  - OR In case of VTE recurrence during the first six months of treatment.
  - *Expert panel ranking: 3.63 out of 4.00*
- When anticoagulant treatment is continued beyond six months, we recommend using a DXI, or LMWH if well tolerated, effective and accepted by the patient.
  - Pending results of ongoing research, we suggest not using reduced doses of DXIs.
  - *Expert panel ranking: 3.60 out of 4.00*

- In patients who no longer have an active cancer (as defined in Fig. 2), we suggest considering the following when choosing the appropriate long-term anticoagulant strategy (stop, switch, reduced dose), in collaboration with oncologists
  - Risk of cancer recurrence, if in remission
  - Ongoing anticancer treatment, if any
  - Type, tolerability and acceptability of anticoagulant treatment during the first 6 months
  - Type and severity of index VTE event
  - Patient profile (age, platelet count, body weight, renal function)[5]
  - *Expert panel ranking: 3.70 out of 4.00*

3.5.5.2. Unresolved issues.

3.5.5.2.1. Thromboprophylaxis in cancer patients with a history of unprovoked VTE. The particular case of patients with active cancer and a history of VTE and no ongoing anticoagulant treatment is worth discussing, especially if they are receiving cancer chemotherapy. Indeed, the AVERT study showed that apixaban 2.5 mg bid reduced the risk of VTE compared with placebo (4.2% vs. 10.2%, HR 0.41; 95% CI: 0.26–0.65; $P < 0.001$) but with an increased risk of major bleeding (3.5 vs. 1.8, HR 2.00; 95% CI: 1.01–3.95; $P = 0.046$) [85]. However, only a minority (≈3% in both groups) of the patients included had previous VTE. It is questionable whether the benefit–risk ratio of this thromboprophylaxis could be optimized if it is prescribed in cancer patients at very high thromboembolic risk such as pancreatic cancers and/or patients with a history of unprovoked VTE.

3.5.5.2.2. Thromboprophylaxis in cancer patients with a history of CAT. Patients with a history of cancer have a higher risk of complications and VTE recurrence than patients without. This raises the question of the interest of restarting anticoagulant treatment (at prophylactic doses – "secondary" thromboprophylaxis) in patients with a history of CAT, for whom anticoagulant treatment was discontinued after cancer remission and who experienced a new cancer or recurrence of the index cancer. The results of the AVERT study cannot be extrapolated to this setting. Therefore, this question needs further dedicated studies (Central Illustration).



Central Illustration. Criteria to consider when evaluating a patient with cancer-associated thromboembolism for the choice of anticoagulant treatment.

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Appendix C. Supplementary material

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