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Review

Management of cancer-associated thromboembolism in vulnerable population

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ABSTRACT

Although all patients with cancer-associated thrombosis (CAT) have a high morbidity and mortality risk, certain groups of patients are particularly vulnerable. This may expose the patient to an increased risk of thrombotic recurrence or bleeding (or both), as the benefit-risk ratio of anticoagulant treatment may be modified. Treatment thus needs to be chosen with care. Such vulnerable groups include older patients, patients with renal impairment or thrombocytopenia, and underweight and obese patients. However, these patient groups are poorly represented in clinical trials, limiting the available data, on which treatment decisions can be based. Meta-analysis of data from randomised clinical trials suggests that the relative treatment effect of direct oral factor Xa inhibitors (DXIs) and low molecular weight heparin (LMWH) with respect to major bleeding could be affected by advanced age. No evidence was obtained for a change in the relative risk-benefit profile of DXIs compared to LMWH in patients with renal impairment or of low body weight. The available, albeit limited, data do not support restricting the use of DXIs in patients with CAT on the basis of renal impairment or low body weight. In older patients, age is not itself a critical factor for choice of treatment, but frailty is such a factor. Patients over 70 years of age with CAT should undergo a systematic frailty evaluation before choosing treatment and modifiable bleeding risk factors should be addressed. In patients with renal impairment, creatine clearance should be assessed and monitored regularly thereafter. In patients with an eGFR < 30 mL/min/1.72 m^2, the anticoagulant treatment may need to be adapted. Similarly, platelet count should be assessed prior to treatment and monitored regularly. In patients with grade 3-4, thrombocytopenia (< 50,000 platelets/μL) treatment with a LMWH at a reduced dose should be considered. For patients with CAT and low body weight, standard anticoagulant treatment recommendations are appropriate, whereas in obese patients, apixaban may be preferred.

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Abbreviations

AKI	acute kidney injury
BMI	body mass index
CAT	cancer-associated thromboembolism
Cc_r	creatinine clearance
CI	confidence interval
CKD	chronic kidney disease
CG	Cockroft-Gault formula
CRB	clinically relevant bleeding
CrCl	creatinine clearance
CVC	central venous catheter
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
DXI	direct-acting oral factor Xa inhibitors
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
GFR	glomerular filtration rate
HR	hazard ratio
IRR	incidence rate ratio
IU	international unit
LMWH	low-molecular weight heparin
MB	major bleeding
MMSE	Mini-Mental State Examination
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PE	pulmonary embolism
RHR	ratio of hazard ratios
RI	renal impairment
RR	relative risk
RCT	randomised clinical trial
ULN	upper limit of normal
VKA	vitamin k antagonist
VTE	venous thromboembolism

1. Introduction

This chapter concerns patients with cancer-associated thromboembolism (CAT) for whom the benefit-risk ratio of anticoagulant therapy may be modified due to clinical or biological characteristics potentially associated with an increased risk of thrombotic recurrence or bleeding. In particular, this concerns older patients, patients with renal impairment or thrombocytopenia, and underweight and obese patients.

1.1. The notion of fragility

During certain phase III trials of direct factor Xa inhibitors (DXIs), certain patient subgroups, specifically patients aged ≥ 75 years, with renal impairment characterised by a creatinine clearance ≤ 50 mL/min or with a body weight ≤ 60 kg were observed to be at lower risk of bleeding under treatment with DXIs compared to low molecular-weight heparin (LMWH) [1–3]. These three patients groups were empirically grouped together under the label of 'fragile patients' [4] and have since been the subject of a number of other studies. Although the proportion of fragile patients enrolled in randomised clinical trials is low (for example, 17% in the Hokusai-VTE trial [2] and 21% in the EINSTEIN-PE study [3]), in everyday clinical practice, this proportion is much higher. In an analysis of 15,079 patients from the RIETE registry [5], 42% of patients experiencing a venous thromboembolism (VTE) fulfilled the fragility criteria, and these patients had a lower rate of VTE recurrence and a higher rate of bleeding than non-fragile patients. A subsequent study of the RIETE registry reiterated the findings from the clinical trials that the incidence of bleeding was lower in fragile patients receiving DXIs compared to those receiving LMWH or vitamin K antagonists (VKAs) [6].

1.2. Treatment effects in fragile patients with CAT from randomised clinical trials

Although numerous meta-analyses comparing DXIs with LMWH in patients with CAT have been published, none have evaluated whether fragility could have an impact on the efficacy and safety outcomes at the end of the treatment period. Moreover, no dedicated randomised clinical trials (RCTs) have been performed in fragile patients with CAT. Nonetheless, older patients represent between 15% and 35% of patients in recent RCTs of DXIs, patients with renal insufficiency between 7% and 27% and patients with low body weight between 10% and 27% (Table 1).

In this context, meta-analysis of data from subgroups of fragile patients included in these RCTs enables a gain in statistical power which makes it possible to compare the relative size of the treatment effect between patients with CAT treated with DXIs and those treated with LMWH. Such a meta-analysis has recently been carried out [11] and the results are presented as forest plots in Figs. 1 and 2.

In older patients, age (≥ 75 years old versus < 75 years) does not seem to influence the treatment effect with respect to VTE recurrence, the ratio of hazard ratios (RHR) for DXIs versus LMWH between the two age groups is close to unity (Fig. 1). In contrast, with respect to major bleeding, advanced age may be a possible modifier of the treatment effect, with a non-significant amplification of the treatment effect in favour of LMWH in patients aged ≥ 75 years compared to younger patients (Fig. 2). However, these data only allow comparison using the 75-year cut-off, which might not be appropriate, since, compared to VTE in patients without cancer, CAT typically occurs at a younger age. The cut-off point should preferably be 80 or even 85 years of age, as these age groups have the highest risk of VTE and major bleeding, irrespective of cancer.

Regarding VTE recurrence and major bleeding, creatinine clearance (≥ 50 mL/min versus < 50 mL/min) does not seem to influence the treatment effect, as the ratio of hazard ratios (RHR) for DXIs versus LMWH between patients with and without renal impairment is close to unity (Figs. 1 and 2).

Low body weight (≤ 60 kg) does not seem to have any impact on the treatment effect. The RHR for DXIs versus LMWH in patients with and without low body weight is close to unity for both VTE recurrence and major bleeding (Figs. 1 and 2). Nevertheless, the cut-off of 60 kg to identify underweight patients is too high and a cut-off of 50 kg would be more meaningful, although this would restrict considerably the number of patients available for analysis.

2. Older patients

2.1. Epidemiology

Age is the strongest risk factor for VTE, with incidence of thromboembolic disease reaching 1% per year in patients aged > 75 years and 60% of all VTEs occurring in patients in this age groups [12–14]. Moreover, individuals over the age of 75 years have a high burden of cancer as well as an increased risk of VTE [15,16].

The risk of VTE recurrence and the risk of major bleeding in CAT and older patients have been investigated in four epidemiological studies or subgroups of studies [17–20]. However, these studies are very heterogenous in design. Notably, they have a variable length of follow-up, use non-standardised definitions of outcome events and the data are derived either from prospectively collected clinical data or from retrospectively analysed medico-administrative data. In addition, the analysis of VTE outcomes does not always take into account the competing risk of death. Consequently, the estimation

Table 1
Randomised clinical trials of DXIs and LMWHs in patients with cancer.

Study	*n*	Age ≥ 75 years	CrCL (CG) ≤ 50 mL/min	Body weight ≤ 60 kg
SELECT-D (Young et al.) [7]	406	83 (20%)	NA	62 (15%)
CASTA DIVA (Planquette et al.) [8]	158	55 (35%)	20 (13%)	43 (27%)
HOKUSAI CANCER (Raskob et al.) [9]	1050	176 (17%)	72 (7%)	159 (15%)
CARAVAGGIO (Agnelli et al.) [10]	1155	348 (30%)	314 (27%)	112 (10%)

CrCl: creatinine clearance; CG: Cockroft-Gault formula; NA: not available. Studies were only eligible if the rater of clinical outcome was blinded to the treatment assignment.

of the risk of recurrent VTE varies from 3 to 20% depending on the study and the duration of follow-up. In RCTs, the risk of recurrent VTE at six months when blindly assessed is quite similar and ranges from 3 to 14% in patients treated with DXIs or LMWH [7–10].

The risk of major bleeding in older patients treated for CAT would be 1 to 5% according to epidemiological studies, it varies from 2 to 6% in RCTs. These data show that, as in the generally CAT population, the risk of recurrence also outweighs the risk of major bleeding in the older, probably because older patients are intrinsically at greater risk of thrombosis, and also because they often receive less intensive treatment (reduced doses). For this reason, VTE recurrence and especially fatal pulmonary embolism (PE) is of more concern than bleeding, including fatal bleeding, in the older.

However, for older patients aged 80 years old or more, the incidence of any major bleeding seems to exceed the incidence of any VTE recurrence, although the incidence of fatal PE (3.7%) still exceeds that of fatal bleeding (0.8%) [21]. In a recent study from the RIETE registry, the risk of recurrence of VTE is estimated at nearly 4% in a sample of 3262 patients aged over 90, and the risk of major bleeding is much higher, estimated at over 17% in the same population [22]. These two studies were carried out in patients with VTE patients, not restricted to patients with CAT, and it is possible that the risk of VTE recurrence in these high age groups is underestimated in CAT, which increases the risk of VTE.

2.2. Frailty in older patients

Frailty refers to older people with a reduced physiological reserve associated with an increased susceptibility to disability, falls, hospitalisation, institutionalisation and mortality [23]. Several methods have been used to define frailty. The Fried criteria are one of the most widely used, corresponding to a phenotype that includes involuntary weight loss (weight loss > 5% in 1 year), reduced grip strength (dynamometer < 16 kg in women < 27 kg in men), reduced walking speed (< 0.8 m/sec), low level of physical activity and significant fatigue [24]. The presence of three or more of these factors defines frailty. On the other hand, Rockwood's definition, using the Clinical Frailty Scale [25], corresponds to an accumulation of deficits, integrating cognitive, social factors and comorbidities, of which cancer is one.

The prevalence of frailty in older patient with cancer is high, 45% in lung cancer and 43% in breast cancer, and represents a major risk factor for mortality in this population [26,27]. In this context, assessment of frailty is recommended in order to guide oncological care (curative or palliative, type and dose of chemotherapy) and to propose interventions to reduce frailty (such as management of malnutrition, sarcopenia, depression, neurocognitive disorders, iatrogenic risk and social isolation).

2.3. Oncogeriatric evaluation

Frailty in patients with cancer results from overlapping domains: Eastern Cooperative Oncology Group (ECOG) status, type of cancer, functional status, cognition, mood and emotional status, social support, financial concerns, nutritional status, comorbidities and polypharmacy, geriatric syndromes (fall risk, confusion, urinary incontinence, visual or hearing impairments), and reduced life expectancy. Frailty in community-dwelling adults increases with age, affecting 11% of the older over the age of 65 years and 25% of those over the age of 85 years [28]. The use of concomitant anti-cancer therapies (chemotherapy, hormones, immuno-modulatory or anti-angiogenic drugs), central venous catheter (CVC) placement, and invasive cancer surgery further increase the thrombotic risk and expose patients to potential drug interactions. Older patients (aged > 75) with cancer are at particularly high risk of bleeding not due only to age and renal dysfunction, but also to the more frequent side effects from cancer therapy and a generally frailer situation [29].

The identification of frailty, using the G-8 scale in older patients with CAT is critical to identify the need of a geriatric assessment [30] (Table 2). The rule of the 6 Cs (Table 3) (a useful checklist of geriatric features) is proposed to manage each component of frailty and minimise the risk of bleeding [29,31,32].

2.4. Treatment of CAT in older patients

There are no specific studies of anticoagulants in older populations, but older patients represent between 15% and 35% of patients in recent studies with DXIs (Table 1). In the meta-analysis of subgroups of patients aged ≥ 75 years described in Section 2.2 above, the choice of treatment between DXIs and LMWH does not seem to influence the treatment effect with respect to VTE recurrence [11], and the results are presented as forest plots in Figs. 1 and 2.

In older patients, age (≥ 75 years old versus < 75 years), the ratio of hazard ratios (RHR) for DXIs versus LMWH between the two age groups is close to unity (Fig. 1). In contrast, with respect to major bleeding, advanced age may be a possible modifier of the treatment effect, with a possible amplification of the bleeding risk associated with DXIs of 151% in patients aged (≥ 75 years compared to younger patients) (Fig. 2).

2.5. Proposals of the expert group

2.5.1. Oncogeriatric evaluation

- We recommend performing a frailty assessment using the G-8 scale for all cancer patients over the age of 70 to determine whether specialised geriatric assessment is indicated. Such a specialised geriatric evaluation should allow the clinician:

  - to direct oncological management towards therapeutic interventions or palliative care, and choose the appropriate treatment and dose,
  - to propose interventions to reduce frailty (such as management of malnutrition, sarcopenia, depression, neuro-cognitive disorders, social support or iatrogenic risk),
  - *expert panel ranking: 3.64 out of 4.00*;

- we recommend taking into account frailty features to reduce the risk of recurrence or bleeding complications by setting up a multidisciplinary oncogeriatric platform in all oncology centres. *Expert panel ranking: 3.74 out of 4.00.*

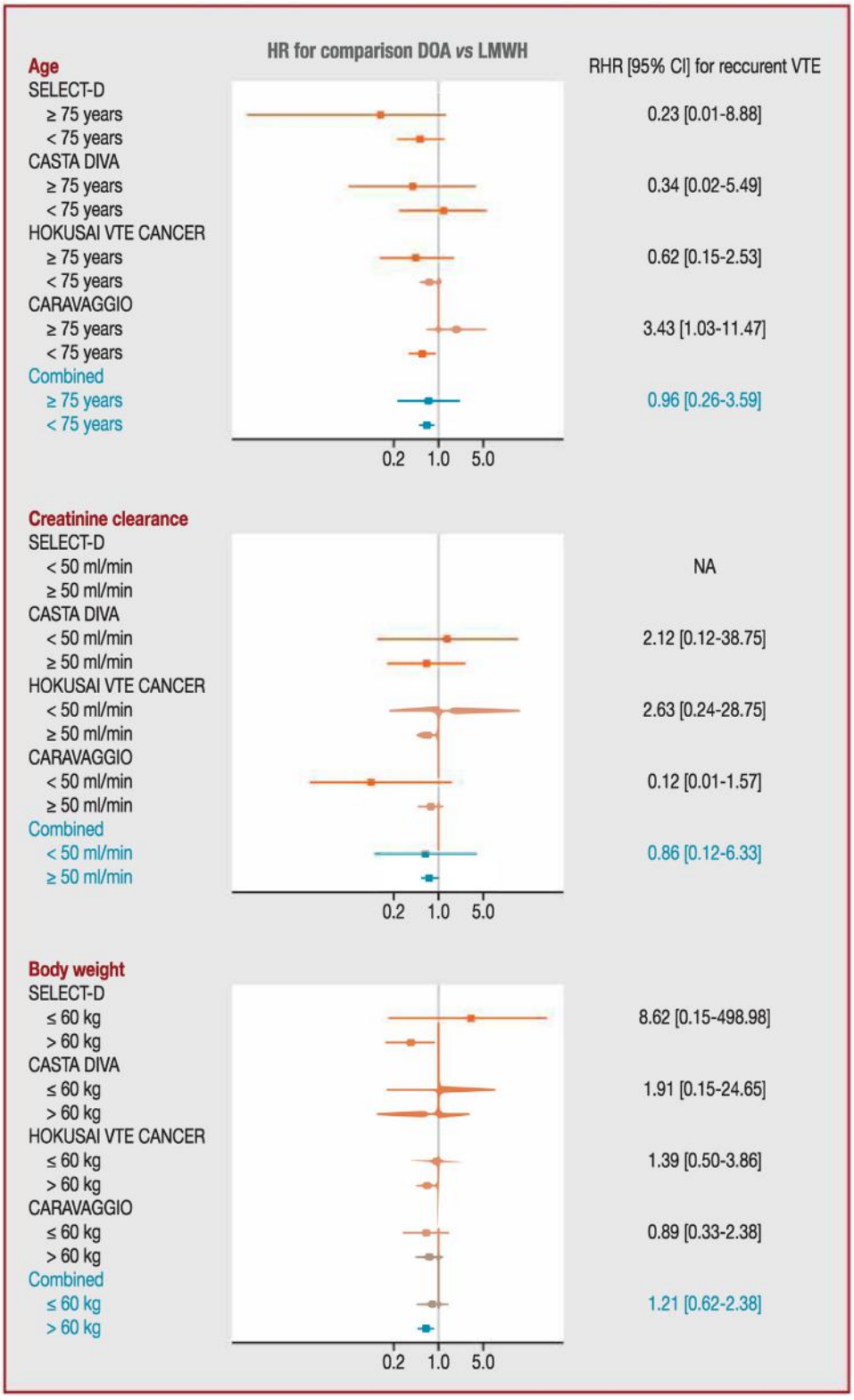


Fig. 1. Comparison of DXIs and LMWH on the risk of VTE recurrence by study for each fragility characteristic. For each study, the relative efficacy of the DXI versus the LMWH is expressed as a hazard ratio (HR) in patients with and without the fragility feature. The ratio of hazard ratios (RHR) compares the relative efficacy of the two treatments between patients with and without the fragility feature. A RHR < 1 means that the relative efficacy of the DXI versus the LMWH is greater in patients with the fragility characteristic, a RHR ≥ 1 means that the relative efficacy is greater in patients without the fragility characteristic.

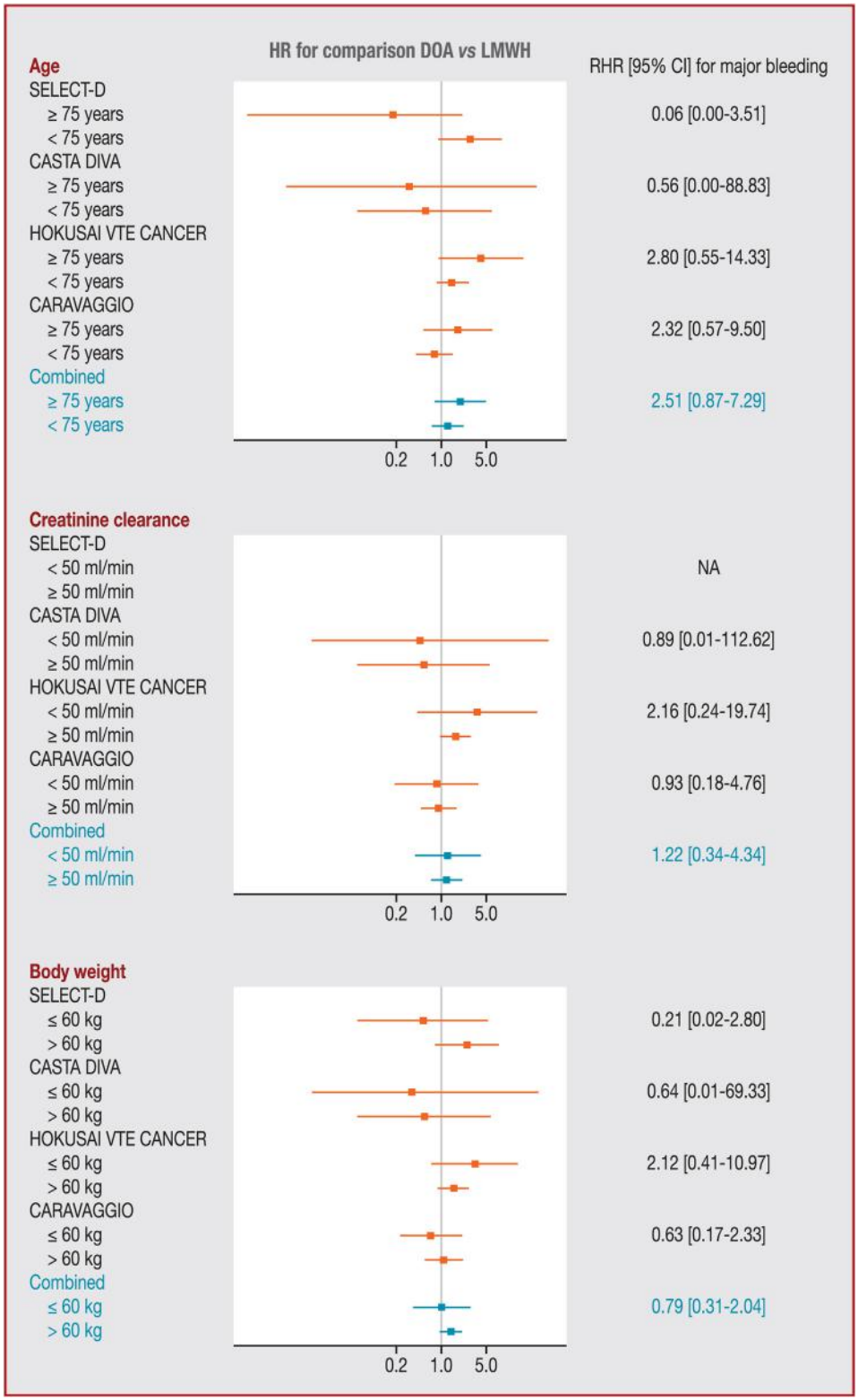


Fig. 2. Comparison of DXIs and LMWH on the risk of major bleeding by study for each fragility characteristic. For each study, the relative efficacy of the DXI versus the LMWH is expressed as a hazard ratio (HR) in patients with and without the fragility feature. The ratio of hazard ratios (RHR) compares the relative efficacy of the two treatments between patients with and without the fragility feature. A RHR < 1 means that the relative efficacy of the DXI versus the LMWH is greater in patients with the fragility characteristic, a RHR ≥ 1 means that the relative efficacy is greater in patients without the fragility characteristic.

Table 2
G-8 geriatric screening scale.

Item	Question	Score
A. Food intake	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0: severe decrease in food intake 1: moderate decrease in food intake 2: no decrease in food intake
B. Weight loss	Weight loss during the last 3 months?	0: weight loss > 3 kg 1: does not know 2: weight loss between 1 and 3 kg
C. Mobility	What is the person's mobility?	0: bed or chair bound 1: able to get out of bed or chair, but does not go out 2: goes out
E. Neuropsychological problems	What, if any, are the person's neuropsychological problems?	0: severe dementia or depression 1: mild dementia or depression 2: no psychological problems
F. Body mass index	What is the person's BMI in kg/m^2?	0: < 18.5 1: ≥ 18.5 but < 23.0 2: ≥ 23
H. Medication	Does the person take more than three prescription drugs per day?	0: Yes 1: No
P. Overall health state	In comparison with other people of the same age, how does the patient consider his/her health status?	0.5: does not know 1: as good 2: better

The G-8 scale is designed to be used in individuals > 70 years of age. The total G-8 score may lie between 0 and 17 with a higher score indicating a better health status. A threshold is suggested at 14 points meaning that a patient with a score of 14 or lower should undergo full geriatric evaluation.

Table 3
6 Cs checklist: features to be taken into account in older patients receiving therapeutic anticoagulant therapy.

Geriatric features	Evaluation	Management	Anticoagulant treatment	Treatment proposal[a]
Cachexia (malnutrition)	Weight loss > 5% in 1 month or > 10% en 6 months OR Albuminaemia < 35 g/L	Dietary advice Oral nutritional supplements (energy intake of 30 to 40 kcal/kg/d, protein intake: 1.2 to 1.5 g/kg/day)	If hypoalbuminaemia is present, bleeding risk may be increased during DXI treatment	Prefer LMWH throughout malnutrition period
Cognition (neuro-cognitive disorders)	MMSE < 24/30 Memory impairment screen (forgetting a word after 10 minutes in spite of prompting) [33,34]	Pill organiser Home nurse visits		If adherence is an issue, LMWH administered by a nurse at the patient's home may be of interest
Coming a cropper (falls)	Risk of falls in case of Standing on one foot < 10 sec Timed up and go test > 20 sec Five times sit to stand test > 15 sec	Physiotherapy Vitamin D Mobility aids Home improvement Remote assistance	Falls are not a contraindication to anticoagulants	No impact on medication choice
Comedication	Check for drug interactions	Medication reconciliation Shared medication audit	Beware interactions between chemotherapy and DXIs No risk of interaction with LMWHs	Prefer LMWH
Comorbidities	Charlson Comorbidity Index [35]	Treatment of comorbidities		No impact on medication choice
Creatinine clearance	Cockcroft formula	Monitoring every 3 months or following acute illness such as infection, dehydration or acute heart failure	If C_{Cr} < 15 mL/min, DXIs and LMWH are both contra-indicated	Prefer LMWH if C_{Cr} 15–30 mL/min

C_{Cr}: creatinine clearance; DXI: direct-acting oral factor Xa inhibitors; LMWH: low-molecular weight heparin; MMSE: Mini-mental state examination.
[a] Low level of evidence.

2.5.2. Treatment recommendations

- We recommend treating elderly patients with cancer who present a VTE with an anticoagulant at standard full therapeutic dose. *Expert panel ranking: 3.92 out of 4.00.*
- We recommend not taking into account age *per se* in the choice of anticoagulant treatment between DXIs and LMWH. *Expert panel ranking: 3.78 out of 4.00.*
- We recommend assessing and taking into account frailty factors with the rule of the 6 Cs:

  - to choose the anticoagulant treatment (DXI or LMWH),
  - to eliminate risk factors for bleeding, when possible,
  - *expert panel ranking: 3.81 out of 4.00.*

3. Patients with impaired renal function

3.1. Epidemiology

The abundant literature on CAT and renal impairment mainly covers chronic kidney disease (CKD), although recent work points to a link between VTE and acute kidney injury (AKI) as well. Patients with CKD, defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, account for 20% of all cancer patients [36] and these patients present an increased risk of CAT [37]. In CAT, the proportion of patients with renal impairment was historically very high [38] with 16% of CAT patients having severe renal impairment (defined as a creatinine clearance < 30 mL/min by the Cockcroft and Gault formula) in the RIETE registry [39]. Despite

Table 4
Renal impairment in pivotal randomised clinical trials of treatment of cancer-associated thromboembolism.

Trial	ARMS	Patients (*n*)	Exclusion criteria regarding RI	Post-hoc analysis in mild RI
CLOT [50]	Dalteparin VKA	676	Serum creatinine level ≥3 × ULN	147 patients with eGFR between 30 and 60 mL/min/1.73m^2, and 15 with eGFR < 30 mL/min/1.73m^2 Findings consistent with those of the principal analysis Lower rates of recurrent VTE with dalteparin HR: 0.15 [95%CI: 0.03–0.65]) No significant increase in MB HR: 1.29 [95%CI: 0.43–3.83])
CANTHANOX [53]	Enoxaparin VKA		Severe renal failure (serum creatinine level of > 2.04 mg/dL [> 180 μmol/L])	
CATCH [51]	Tinzaparin VKA	864	GFR ≤ 20 mL/min/1.73m^2 (as estimated by the Modification of Diet in Renal Disease [MDRD] equation)	131 patients with GFR < 60 mL/min/1.73m^2 Increased risk of recurrent VTE in RI RR: 1.74 [95%CI: 1.06, 2.85] Increased risk of MB in patients with RI RR: 2.98 [95%CI: 1.29–6.90] No difference between tinzaparin and VKA
HOKUSAI-VTE cancer [9]	Edoxaban Dalteparin	1046	CrCl < 30 mL/min	72 patients with CrCl < 50 mL/min Pre-specified dose reduction in the edoxaban (30 mg) arm Subanalyses do not suggest findings different to those of the principal analysis, but interpretation limited by the low number of patients
CARAVAGGIO [52]	Apixaban Dalteparin	1155	CrCl < 25 mL/min	275 patients with CrCl 30–59 mL/min and 444 patients with CrCl 60–89 mL/min Findings consistent with those of the principal analysis, particularly no difference in rates of MB between apixaban and dalteparin A lower rate of recurrent VTE was described under apixaban in patients with CrCl 30–59 mL/min (HR: 0.27 [95%CI: 0.08–0.96])

CI: confidence interval; CrCl: creatinine clearance; GFR: glomerular filtration rate; HR: hazard ratio; MB: major bleeding; RI: renal impairment; RR: relative risk; ULN: upper limit of normal; VKA: vitamin K antagonist; VTE: venous thromboembolism.

a significant decrease over the past decade, the prevalence of renal impairment (regardless of severity) remains elevated, concerning around one-quarter of CAT patients seen in everyday clinical practice [40].

Renal impairment can have an impact on the evolution, overall management and treatment of patients with CAT [41,42]. Renal impairment *per se* is associated with an increased risk of bleeding, which may be amplified by a factor ranging from 1.5 to 3, depending on the degree of renal impairment, by anticoagulant therapy [43]. In epidemiological studies of patients with CAT, patients with comorbid renal impairment have been reported to be at increased risk of both fatal PE and bleeding, including fatal bleeding (an increase by a factor ranging from 3 to 15, depending on the degree of renal impairment) [38,39,43]. Renal impairment can also be associated with other cardiovascular comorbidities, such as hypertension and diabetes, and with a history of adverse cardiovascular events. The benefit/risk ratio of antiplatelet co-prescription must be adequately evaluated in patients with renal impairment [44].

Renal impairment may alter drug pharmacokinetics, which can affect the clearance of many drugs, increasing the risk of drug-drug interactions [42]. In particular, renal impairment directly reduces the clearance of anticoagulant drugs currently used for the treatment of CAT, such as LMWH or DXIs. In this respect, molecules in the same pharmacological class may not all be interchangeable; for example, data suggest a more favourable pharmacokinetic profile for tinzaparin among LMWHs [45–47] and apixaban among DXIs [48].

3.2. Treatment of CAT in patients with renal impairment

Severe renal impairment has been an exclusion criterion of the pivotal RCTs in the field of treatment of CAT (Table 4). For this reason, less than ten percent of included patients had an abnormal renal function, and less than two percent had a creatinine clearance below 30 mL/min [49]. No patient had a creatinine clearance < 15 mL/min or was under dialysis. A small number of *post-hoc* analyses of patients with moderate renal impairment have been published (Table 4). For LMWH, *post-hoc* subgroup analyses of the CLOT and CATCH trials comparing an LMWH to a vitamin K antagonist (VKA) reported an increased risk of recurrent VTE and bleeding in patients with moderate renal impairment, when compared to patients without renal impairment, without any difference between treatment arms [50,51]. For DXIs, a subgroup analysis of the CARAVAGGIO trial reported similar rates of major bleeding between apixaban and dalteparin, but a lower risk of recurrent VTE with apixaban in patients with creatinine clearance between 30 and 59 mL/min [52]. Although proposed in other anticoagulation indications such as atrial fibrillation, reduced doses of DXIs are not currently validated in the treatment of CAT in patients with renal impairment. The meta-analysis described above in Section 2.2 indicated that renal impairment did not affect the relative incidence of recurrent VTE or major bleeding in patients receiving DXIs or LMWH [11].

Whatever the formula used to assess GFR, patients with severe renal impairment experience a very high rate of major bleeding during the three months of anticoagulation therapy [54]. In patients with severe renal impairment, particularly in those with eGFR < 15 mL/min/1.73 m^2 or under dialysis, the optimal management strategy is unclear. Some authors suggest using an LMWH, as some of these are licensed in patients with severe renal impairment [55]. Reduced doses of DXIs are not currently validated for the treatment of VTE in patients with severe renal impairment. Patients with CAT and severe renal impairment are probably best managed by a multidisciplinary team on a case-by-case basis, extrapolating

Table 5
Dosing recommendations for patients with renal impairment.

	Creatinine clearance (mL/min)			
	< 15 or dialysis	15–29	30–50	> 50
LMWH				
Dalteparin	Use not approved by health authorities	Dose reduction should be considered[a]	200 IU/kg once daily for 1 month and then 150 IU/kg	200 IU/kg once daily for 1 month and then 150 IU/kg
Enoxaparin	Use not approved by health authorities	100 IU/kg once daily	100 IU/kg twice daily	100 IU/kg twice daily
Tinzaparin	Use not approved by health authorities	175 IU/kg once daily[b]	175 IU/kg once daily	175 IU/kg once daily
DXI				
Apixaban	Use not approved by health authorities	10 mg twice daily for 7 days and then 5 mg twice daily[c]	10 mg twice daily for 7 days and then 5 mg twice daily	10 mg twice daily for 7 days and then 5 mg twice daily
Edoxaban	Use not approved by health authorities	Not recommended	30 mg once daily (following initial 5–10 days of LMWH)	60 mg once daily (following initial 5–10 days of LMWH)
Rivaroxaban	Use not approved by health authorities	15 mg twice daily for 3 weeks and then 20 mg once daily[c]	15 mg twice daily for 3 weeks and then 20 mg once daily	15 mg twice daily for 3 weeks and then 20 mg once daily

DXI: oral direct factor Xa inhibitor; LMWH: low molecular-weight heparin. Data from product monographs compiled by Carrier et al. (2020) [55].
[a] Use with caution when treating patients with creatinine clearance < 30 mL/min; see product monograph for dosing in haemodialysis and haemofiltration.
[b] Only in patients with a creatinine clearance ≥ 20 mL/min. Tinzaparin is not recommended in patients with a creatinine clearance below 20 m /min.
[c] Must be used with caution in patients with creatinine clearance 15–29 mL/min due to the potentially elevated bleeding risk.

the available data on anticoagulation of patients with severe renal impairment to cancer patients.

Concerns have been raised regarding acute kidney injury (AKI) in the setting of cancer [56]. *Per se*, PE may lead to AKI, in around one in three patients [57], with AKI being associated with an increased risk of death and bleeding [58]. While the majority of patients improve their renal function after AKI, the existence of cancer seems to be associated with a reduced chance of recovering renal function [59]. Therefore, close monitoring of renal function and adjustment of the type of anticoagulation therapy may be necessary to manage patients with CAT and renal impairment effectively [41,47].

Recommended dosing regimens for LMWH and DXIs according to creatinine clearance [55] are provided in Table 5.

3.3. Proposals of the expert group

- At the time of CAT diagnosis, we recommend assessing renal function by evaluation of the glomerular filtration rate using a validated formula. *Expert panel ranking: 3.88 out of 4.00*.
- We suggest monitoring renal function throughout follow-up, in particular in case of acute kidney injury due to PE or when the patient is treated with drugs with known renal toxicity. *Expert panel ranking: 3.89 out of 4.00*.
- In patients with renal impairment, we suggest evaluating and eliminating, if possible, modifiable bleeding risk factors, such as co-prescription of drugs (for example antiplatelet agents) or with a risk of drug-drug interactions. *Expert panel ranking: 3.85 out of 4.00*.
- In patients with mild-to-moderate renal impairment (eGFR 30–60 mL/min/1.72 m^2), we recommend prescribing the standard full therapeutic dose of LMWH or DXIs for the acute treatment of CAT [60]. *Expert panel ranking: 3.92 out of 4.00*.
- In patients with eGFR < 30 mL/min/1.72 m^2, we suggest to adapt the anticoagulant strategy as needed:

  - in patients with eGFR between 15 and 30 mL/min/1.72 m^2, we suggest prescribing LMWH rather than an oral anticoagulant (DXI or VKA) for the acute treatment of CAT. *Expert panel ranking: 3.88 out of 4.00*,
  - in patients with eGFR <15 mL/min/1.72 m^2, or under dialysis, we suggest discussing the choice of treatment with the nephrologist on a patient-by-patient basis, from the following options: UFH or VKA. *Expert panel ranking: 3.63 out of 4.00*

Table 6
Grades of thrombocytopenia.

Grades of thrombocytopenia	Platelet count
Grade 1	75,000 to < 100,000/μL
Grade 2	50,000 to < 75,000/μL
Grade 3	25,000 to < 50,000/μL
Grade 4	< 25,000/μL

According to the classification of the National Cancer Institute Common Terminology Criteria for adverse events [61].

4. Patients with thrombocytopenia

4.1. Epidemiology

Thrombocytopenia is generally defined as a platelet count below 100,000/μL (100 G/L). Severity of thrombocytopenia is further stratified according to the National Cancer Institute Common Terminology Criteria for Adverse Events [61] (Table 6).

Cancer patients may develop thrombocytopenia through various mechanisms, including myelotoxic effects of chemotherapy, infiltration of the bone marrow by malignant cells, immune-mediated destruction of platelets, and consumption of platelets due to hypersplenism or disseminated intravascular coagulation (DIC).

Data on the prevalence of thrombocytopenia in patients with CAT are sparse. In a retrospective cohort of 3635 patients with CAT, the prevalence of thrombocytopenia was 22% [95%CI: 21–24%] in those with solid tumours and 47% [95%CI: 43–51%] (in patients with haematological malignancies. Grade 3-4 thrombocytopenia occurred in 7% [95%CI: 6–8%] of patients with solid tumours and in 30% [95%CI: 27–34%] of those with haematological malignancies [62].

Cancer patients with thrombocytopenia receiving anticoagulation are at high risk of bleeding [63]. The severity of thrombocytopenia correlates with the bleeding risk, with platelet counts below 50,000/μL associated with a higher risk. Nevertheless, thrombocytopenia does not protect against VTE, particularly in the first month of anticoagulation [64]. In a systematic review which included 93 patients with CAT and thrombocytopenia who

Table 7
Exclusion criteria regarding thrombocytopenia in pivotal randomised controlled trials assessing the efficacy and safety of anticoagulants for the treatment of cancer-associated thrombosis.

Study name, year	Study design	Anticoagulant used		Total number of patients analysed		Exclusion criterion for platelet count
		Intervention	Control	Intervention	Control	
CLOT [50]	Randomised, open label, trial	Dalteparin 200 U/kg once daily for 1 month followed by 150 IU/kg once daily	Dalteparin 200 IU/kg once daily for five to seven days and followed by a VKA	338	333	< 75,000/μL
CATCH [51]	Randomised, active-controlled, open-label superiority trial	Tinzaparin 175 IU/kg once daily	Tinzaparin 175 IU/kg once daily for five to ten days followed by a VKA	351	307	< 50,000/μL
HOKUSAI-VTE CANCER [9]	Randomised, open label, non-inferiority trial with blinded central outcome adjudication	Therapeutic dose of LMWH for at least 5 days followed by edoxaban 60 or 30 mg once daily	Dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily	522	524	< 50,000/μL
SELECT-D [7]	Randomised, open-label, pilot trial with blinded central outcome adjudication	Rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily	Dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily	203	203	< 100,000/μL
ADAM-VTE [68]	Randomised, open label, superiority trial with blinded central outcome adjudication	Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily	Dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily	145	142	< 50,000/μL
CARAVAGGIO [10]	Randomised, open label, non-inferiority trial with blinded central outcome adjudication	Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily	Dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily	576	579	< 75,000/μL
CASTA-DIVA [8]	Randomised, open label, non-inferiority trial with blinded central outcome adjudication	Rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily	Dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily	74	84	< 50,000/μL

LMWH: low molecular-weight heparin; VKA: vitamin K antagonist.

received full-dose or dose-modified anticoagulation, 24% developed recurrent VTE and 17% developed major bleeding [65].

4.2. Treatment of CAT in patients with thrombocytopenia

Pivotal RCTs comparing the efficacy and safety of LMWH versus VKAs for the treatment of CAT have excluded patients with baseline platelet counts < 75,000 μL (Table 7) [66,67]. In the CLOT trial, dalteparin was reduced by ~25% in patients with a platelet count ranging from 50,000 to 100,000/μL, and anticoagulation was withheld in patients with a platelet count below 50,000/μL [6]. Similarly, recent RCTs comparing the efficacy and safety of DXIs versus LMWH for the treatment of CAT excluded patients with thrombocytopenia (Table 7) [7–10,68]. Results from these trials cannot therefore be extrapolated to patients with grade 3-4 thrombocytopenia.

Numerous retrospective studies [69–84] and two prospective studies [85,86] have reported the outcomes of patients with CAT and thrombocytopenia who received different anticoagulation management strategies. Most patients included in these studies had haematological malignancies or had undergone stem cell transplantation and were treated with LMWH. Anticoagulation management strategies included full-dose anticoagulation with or without transfusion support, dose reduction including intermediate dose LMWH (for example, 150 IU/kg enoxaparin once daily, or 50 IU/kg enoxaparin twice daily) or prophylactic fixed dose (for example, enoxaparin 4000 U once daily) or temporary withholding of anticoagulation, depending on platelet count. Rates of recurrent VTE, major bleeding and total bleeding varied widely between these studies [69–86].

Data regarding the use of DXIs in patients with severe thrombocytopenia are sparse. Only sixteen patients in the TROVE study [86] and four in the CAVEaT study [85] were receiving DXIs, and bleeding rates were particularly high in these patients.

A recent meta-analysis of ten studies assessed the rates of recurrent VTE and bleeding complications in patients with CAT and thrombocytopenia [87]. The pooled incidence rate of recurrent VTE was 2.65 per 100 patient-months [95%CI: 1.62–4.32] in patients receiving full-dose anticoagulation, 3.51 per 100 patient-months [95%CI: 1.00–12.39] in those receiving modified-dose anticoagulation and 3.68 per 100 patient-months [95%CI: 1.23–10.94] in those who did not receive anticoagulation. Compared to patients receiving full dose anticoagulation, those receiving modified dose anticoagulation had an incidence rate ratio (IRR) of recurrent VTE of 2.01 [95%CI: 0.56–6.41], while those who did not receive anticoagulation had an IRR of recurrent VTE of 1.78 [95%CI: 0.46–5.89]. The pooled incidence rate of major bleeding was 4.45 per 100 patient-months [95%CI: 2.80–7.06] in patients receiving full dose anticoagulation, 4.16 per 100 patient-months [95%CI: 2.24–7.74] in those receiving modified-dose anticoagulation and 2.20 per 100 patient-months [95%CI: 0.71–6.82] in those who did not receive anticoagulation. Compared to patients receiving full dose anticoagulation, those receiving modified dose anticoagulation had an IRR of major bleeding of 0.93 [95%CI: 0.39–2.15], while those who did not receive anticoagulation had an IRR of major bleeding of 0.49 [95%CI: 0.11–1.47].

Individualised approaches are necessary to balance the risk of bleeding with the need for effective anticoagulation therapy in these patients. In patients with grade 1-2 thrombocytopenia, using full-dose anticoagulation appears safe [74]. In patients with grade 3-4 thrombocytopenia, timing of onset and risk of thrombus propagation should be considered. In patients with acute VTE at high risk of thrombus propagation defined as segmental or more proximal PE, proximal deep vein thrombosis (DVT), or a history of

recurrent VTE, full dose anticoagulation is required with transfusion support to maintain a platelet count of > 40,000-50,000/μL. Maintaining an adequate platelet count is crucial in minimising bleeding risk during anticoagulation therapy. However, the decision to transfuse should be based on careful consideration of the patient's overall clinical profile, including the risk of thrombosis and the presence of other comorbidities. In patients with grade 3 thrombocytopenia and acute VTE at low risk of thrombus propagation defined as distal DVT or catheter-related upper extremity DVT, and in those with subacute VTE, a reduced dose of LMWH may be considered to minimise the bleeding risk while maintaining adequate anticoagulation efficacy. In patients with grade 4 thrombocytopenia and acute VTE at low risk of thrombus propagation or those with subacute VTE, anticoagulation should be withheld to avoid bleeding. This strategy is supported by the results of a quality assessment initiative in which 99 patients with 140 episodes of platelet counts ≤ 50,000/μL lasting at least seven days were managed according to this approach. No episodes of recurrent VTE or major bleeding occurred when the LMWH dose was decreased or withheld [79].

4.3. Proposals of the expert group

- We recommend close monitoring of platelet count in patients receiving anticancer regimens who have a moderate-to-high risk of developing chemotherapy-induced thrombocytopenia in order to assess the need for anticoagulant dose adjustment. *Expert panel ranking: 3.93 out of 4.00*.
- We suggest using standard therapeutic anticoagulation (LMWH or DXI) in patients with grade 1 (75,000–100,000/μL) or grade 2 (50,000–75,000/μL) thrombocytopenia. *Expert panel ranking: 3.92 out of 4.00*.
- In patients with acute VTE (first 30 days) and grade 3-4 thrombocytopenia (< 50,000/μL):

  - we suggest using dose-modified LMWH (25% dose reduction) in those with a platelet count between 30,000 and 50,000/μL,
  - we suggest using prophylactic dose LMWH with platelet transfusion support in those patients with a platelet count < 30,000/μL,
  - *expert panel ranking: 3.62 out of 4.00*.

- We suggest considering placement of a removable inferior vena cava filter on a case-by-case basis in those with persistent grade 3-4 thrombocytopenia (< 50,000 μL). *Expert panel ranking: 3.48 out of 4.00*.
- In patients with acute VTE (beyond 30 days) with grade 3-4 thrombocytopenia (< 50,000/μL):

  - we suggest using dose-modified LMWH (50% dose reduction) in those patients with a platelet count between 30,000 and 50,000/μL,
  - we suggest using prophylactic dose LMWH in those with a platelet count < 30,000/μL, except in case of active bleeding; we suggest platelet transfusion support in those with persistent thrombocytopenia,
  - *expert panel ranking: 3.33 out of 4.00*.

5. Patients with low body weight

5.1. Epidemiology

In adult patients aged ≥ 20 years, low body weight is commonly defined as a body mass index (BMI) below 18.5 kg/m^2 among. Results from the 2015–2016 National Health and Nutrition Examination Survey (NHANES) indicate that approximately 1.5% of American adults ≥ 20 years are underweight. In the EDITH study, a case-control study designed to test interactions between genetic and environmental risk factors for VTE, low body weight was associated with a statistically significant reduction in risk for VTE compared to individuals with normal weight (OR: 0.55 [95%CI: 0.33–0.91]) [88]. This population also presents challenges for anticoagulation management since underweight patients have reduced adipose tissue, which may alter the volume of distribution and renal clearance of certain anticoagulant drugs and thus lead to a higher incidence of bleeding.

Compared with the general population, patients with cancer, especially in those with advanced cancer, frequently present with low body weight and cachexia. On the other hand, the proportion of underweight patients who develop CAT is not known with accuracy [89]. To date, only very limited data from clinical trials are available in this population because the number of underweight patients enrolled in most clinical studies was very low (for example, about 10% in the CARAVAGGIO study [10] (Table 1).

The major concern is not low body weight as such, but rather patients weighing less than 50 kg, because the data available for these patients is very limited, since they were excluded from clinical trials. Only data from patient registries are available. For example, a study from the RIETE REGISTRY was performed in order to assess the risk of bleeding in 8845 patients within the first 15 days of anticoagulation for VTE as a function of weight [90]. In this study, 169 patients weighing < 50 kg had a significantly higher rate of bleeding complications than patients weighing 50–100 kg (OR: 2.2 [95% CI: 1.2–4.0]).

5.2. Treatment of CAT in underweight patients

A recent cross-sectional study of 61 treated patients with CAT has compared plasma levels of apixaban in three groups of patients according to their body weight (patients > 60 kg treated with apixaban 5 mg *bid*, patients ≤ 60 kg treated with apixaban 5 mg *bid*, and patients ≤60 kg treated with half-dose apixaban 2.5 mg *bid*). The mean apixaban plasma trough levels in low weight patients receiving half-dose apixaban were similar to those in patients weighing > 60 kg receiving the full dose of 5 mg *bid*. However, in low-weight patients treated with apixaban 5 mg *bid*, mean values tended to be higher than in patients weighing > 60 kg, although the difference was not statistically significant. Further research is needed on the utility of weight-based adjustments in apixaban dosing in low-weight patients with cancer [91]. It should be noted that, to date, practice guidelines do not recommend these weight-adjusted regimens for DXIs.

For LMWH, a secondary analysis of the CATCH study which assessed characteristics of patients with clinically relevant bleeding (CRB) showed that the proportion of patients with a BMI < 18.5 kg/m^2 who developed a CRB was 8.9% compared to 15.9% in patients with BMI ≥ 18.5 kg/m^2. Univariate and multivariate analyses identify did not any association between BMI and the occurrence of CRB [92].

The meta-analysis described above in Section 2.2 indicates that body weight ≤ 60 kg does not seem to have any impact on the relationship between treatment class (DXIs or LMWH) and the incidence of recurrent VTE or major bleeding [11]. Until further data are obtained to explore a possible association, there is no reason to restrict the indications of DXIs in patients with low body weight.

5.3. Proposals of the expert group

- We recommend using an anticoagulant at standard full therapeutic dose in underweight patients with CAT using the same

regimens as in other patients experiencing a VTE. *Expert panel ranking: 3.60 out of 4.00*:

- the available data do not permit recommending a DXI over an LMWH or vice versa in underweight patients. We suggest using either of these drug classes in function of the overall risk profile of the patient and not taking into account low body weight per se in the choice of anticoagulant treatment between DXIs and LMWH [60]. *Expert panel ranking: 3.58 out of 4.00*.

- We suggest not following peak or trough levels of DXIs because these data cannot currently be used in informing treatment decisions. *Expert panel ranking: 3.69 out of 4.00*

6. Obese patients

6.1. Epidemiology

Obesity is defined as a body mass index (BMI) of $\geq 30\ kg/m^2$. Already a common condition with more than 650 million adults obese in 2016 worldwide. For the United States, it is projected that 51% of the population will be obese and one in four adults will have a BMI $\geq 35\ kg/m^2$ by 2030 [93]. In addition, it is estimated that obesity attributes to about 4–8% of all cancers worldwide [94,95]. In the United States, it has been estimated that 4.7% of new cases of cancer in men and 9.6% new cases of cancer in women are attributable to obesity [96]. The World Health Organization predicts that the number of new cancer cases will rise by approximately 70% over the next 20 years [97].

Many risk factors for VTE have been identified, notably obesity and cancer. Obesity, defined as a body mass index (BMI) of $\geq 30\ kg/m^2$, is associated with a two-to threefold increased risk of a first VTE compared to patients with BMI < $30\ kg/m^2$ [98]. Similarly, a BMI > $40\ kg/m^2$ is associated with an approximatively twofold increased risk of recurrent VTE, independently of age and sex [99]. Finally, BMI > $30\ kg/m^2$ has been included as of the four criteria of the HERDOO2 predictive model for VTE recurrence [100,101]. Although the question of appropriate treatment of VTE in obese patients is in itself crucial, is even more relevant in obese patients with cancer.

6.2. Estimation of treatment effect in obese patients in general

The major concern is the lack of clinical evidence available regarding the efficacy and safety of DXIs in obese patients since pivotal phase III RCTs comparing DXIs with warfarin for treatment of VTE included very few patients with obesity or weight > 100 kg, ranging from 12 to 20%. In addition, data from pharmacokinetic and pharmacodynamic studies suggest that variations in drug handling may occur in the setting of obesity by increasing the volume of distribution and drug clearance [102]. Therefore, in 2016, the ISTH SSC published guidance that suggested not using DXIs in patients with a BMI > $40\ kg/m^2$ or weight > 120 kg [103].

Nevertheless, since the publication of the ISTH guidance in 2016, new studies have been performed to assess the efficacy and safety of DXIs in patients with BMI > $40\ kg/m^2$ or weight > 120 kg. One large study integrating five United States healthcare claims databases was performed in order to compare the risk of recurrent VTE and major bleeding between apixaban and warfarin in obese patients with VTE. A total of 43,095 obese patients were identified, of whom 19,751 were morbidly obese ($\geq 40\ kg/m^2$). In obese and morbidly obese patients, apixaban was associated with a significantly lower risk of recurrent VTE (HR: 0.73 [95%CI: 0.64–0.84] for obese and 0.65 [95%CI: 0.53–0.80] for morbidly obese) and of major bleeding (HR: 0.73 [95%CI: 0.62–0.85] for obese and 0.68 [95%CI: 0.54–0.86] for morbidly obese) as compared with warfarin [104]. Finally, a recent systematic review and meta-analysis including RCTs and observational studies have found that DXIs were associated with a comparable risk of recurrent VTE and a lower risk of major bleeding events compared to VKA for the treatment of VTE in patients with morbid obesity [105]. Therefore, the ISTH SSC Subcommittee on Control of Anticoagulation recently updated their guidance on using DXIs in patients with obesity for treatment of VTE as follows: "For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA, weight-based LMWH (per manufacturers' recommendations) and fondaparinux are also options" [106].

Concerning the use of LMWH in obese patients, data on the safety of using a weight-adjusted LMWH dose for the treatment of VTE are also limited. Cohort studies evaluating enoxaparin and dalteparin have shown that LMWH should be weight-adjusted in patients over 90 kg [107,108]. A cohort study of 193 patients weighing between 91 and 182 kg, evaluated the rates of VTE recurrence and major bleeding in patients treated with dalteparin 200 international units (IU)/kg once daily for acute VTE; only two patients (1.0%) experienced major bleeding confirming the safety of dalteparin administration based on actual body weight in the obese population [108]. Nevertheless, the current French product monograph for dalteparin recommends capping the dose at a maximum of 18,000 IU daily, as is the case for tinzaparin.

Fondaparinux is an interesting option in the treatment of VTE in obese subjects, especially when the maximum dose of LMWH is reached. The design of the Matisse trials of fondaparinux used a weight-adapted treatment regimen (10 mg subcutaneously once daily, for patients weighing > 100 kg). These trials this provides specific data in this population [109]. The effect of obesity on outcomes after fondaparinux, enoxaparin or UFH treatment for acute VTE in the Matisse trials was assessed in 24,218 patients, including 496 patients weighing > 100 kg and 1216 patients with a BMI $\geq 30\ kg/m^2$. The incidence of recurrence and major bleeding were similar for each patient subset of weight and BMI for both the fondaparinux and UFH treatment groups.

6.3. Treatment of CAT in obese patients

To date, data on the specific population of obese patients with CAT are limited due to the relatively small number of patients included in phase III RCTs [7–10]. The subgroup results presented in the published data from these studies only distinguish patients weighing ≥ 90 kg, which is insufficient to establish obesity. Few studies present data for patients with a BMI > $30\ kg/m^2$, and no information is available for higher BMI thresholds. There is clearly a lack of clinical evidence available regarding efficacy and safety in the obese population.

Similarly, data from trials using LWMH in obese patients with CAT are scarce. For example, in the CATCH study, comparing long-term tinzaparin to warfarin for the treatment of acute VTE in cancer patients, the mean weight in the group receiving tinzaparin was 67 ± 17.3 kg [67].

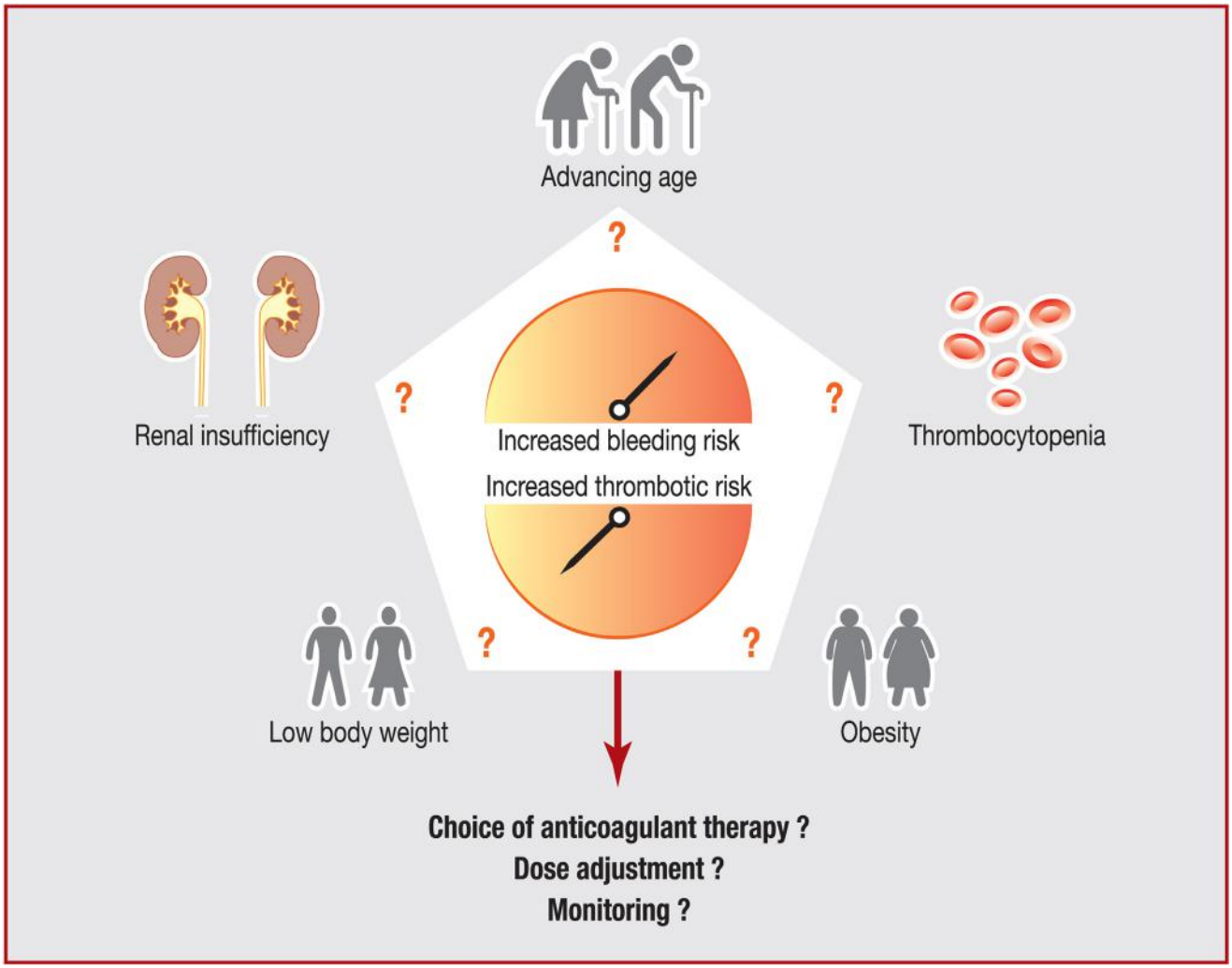
Interestingly, a *post-hoc* analysis of two RCTs comparing efficacy, safety and overall survival of fondaparinux to standard initial treatment (LMWH) in cancer patients with VTE was performed [110]. Two hundred thirty-seven cancer patients with DVT and 240 were initially treated with fondaparinux or enoxaparin and 240 cancer patients with PE received fondaparinux or UFH. In both studies, no difference in the incidence of bleeding or VTE recurrence, or in overall survival, was observed between fondaparinux and UFH or LMWH. In a meta-analysis assessing the first 5–10 days of anticoagulant therapy in patients with cancer, mortality at 3 months,

recurrent VTE or major bleeding rates did not differ significantly between fondaparinux on the one hand and LMWH or UFH on the other [111].

6.4. Proposals of the expert group

The available data do not permit the recommendation of a modified treatment regimen in obese patients with CAT. Therefore, in line with the 2021 ISTH SSC general recommendations for obese patients (BMI $\geq$ 35 kg/m^2) and the 2023 revised French recommendations for the treatment of VTE in cancer:

- we suggest using a standard dose of DXIs in obese patients with CAT, as in other patients experiencing VTE. Of these molecules, apixaban is preferable. As an alternative, for patients who are not at high risk of gastrointestinal or genitourinary bleeding, a rivaroxaban or edoxaban-based regimen may also be used (although the evidence base is limited for edoxaban). *Expert panel ranking: 3.74 out of 4.00*;
- we suggest that weight-based dose regimens of LMWH are also an option in accordance with the manufacturers' recommendations. *Expert panel ranking: 3.74 out of 4.00*;
- we suggest offering fondaparinux for initial treatment, if the administration of LMWH is limited by the recommendations in the product monograph to cap the dose at a maximum of 18,000 IU daily, in particular for dalteparin and tinzaparin. *Expert panel ranking: 3.56 out of 4.00*;
- we suggest not following peak or trough levels of DXIs because these data cannot currently be used in informing treatment decisions. *Expert panel ranking: 3.60 out of 4.00*



Central Illustration: The challenge of anticoagulation management in vulnerable patients.

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Appendix C. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2023.11.009.

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