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Lessons from French national guidelines on the treatment of venous thrombosis and central venous catheter thrombosis in cancer patients

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ABSTRACT

Increased prevalence of Venous thromboembolism (VTE), as defined by deep-vein thrombosis (DVT), central venous catheter (CVC) related thrombosis or pulmonary embolism (PE) in cancer patients has become a major therapeutic issue. Considering the epidemiology and each national recommendations on the treatment of VTE in cancer patients, we analysed guidelines implementation in clinical practice. Thrombosis is the second-leading cause of death in cancer patients and cancer is a major risk factor of VTE, due to activation of coagulation, use of long-term CVC, the thrombogenic effects of chemotherapy and anti-angiogenic drugs. Three pivotal trials (CANTHANOX, LITE and CLOT) and several meta-analysis led to recommend the long term (3 to 6 months) use of LMWH during for treating VTE in cancer patients with a high level of evidence. The Italian Association of Medical Oncology (AIOM), the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), the French "Institut National du Cancer" (INCa), the European Society of Medical Oncology (ESMO) and the American College of Chest Physicians (ACCCP) have published specific guidelines for health care providers regarding the prevention and treatment of cancer-associated VTE. Critical appraisal of these guidelines, difficulties in implemenation of prophylaxis regimen, tolerance and cost effectiveness of long term use of LMWH may account for large heterogenity in daily clinical practice. Homogenization of these guidelines in international consensus using an adapted independent methodological approach followed by educational and active implementation strategies at each national level would be very valuable to improve the care of VTE in cancer patients.

Abbreviations

AIOM:	Italian Association of Medical Oncology
NCCN:	National Comprehensive Cancer Network
ASCO:	American Society of Clinical Oncology
INCa:	French "National Cancer Institute" INCa
ESMO:	European Society of Medical Oncology
ACCP:	American College of Chest Physicians
DVT:	deep venous thrombosis
VTE:	venous thromboembolism event
PE:	Pulmonary embolism
LMWH:	low molecular weight heparin
VKA:	vitamin K antagonist

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Introduction

Cancer is a major risk factor of venous thromboembolism (VTE) [1,2], as defined by deep-vein thrombosis (DVT) – including central venous catheter (CVC) related thrombosis – or pulmonary embolism (PE), which occur in 4 to 20% of cancer patients [3,4]. Although VTE is a preventable disease, today it is the second cause of death and a frequent cause of morbidity among medical and surgical cancer patients. Therefore, the prevention and the treatment of VTE in cancer patients represent a major therapeutic challenge since: (a) implementation of specific prophylactic regimen in onco-hematology has recently become an area of interest; (b) the care of established VTE in cancer patients has changed over the last ten years, given the results of comparisons between classical anticoagulation protocols using low-molecular-weight heparin (LMWH) and early VKA therapy as compared to the long-term use of LMWH for 3 to 6 months [5–7]. Indeed, three randomised clinical trials (CANTHANOX, CLOT and LITE) [5–7] have clearly demonstrated that long term use of LWMH is

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more efficient than VKA to treat VTE in cancer patients, leading to recommend the use of LMWH during 3 to 6 months for VTE treatment in cancer patients with a high level of evidence (grade A, level I). Since then, seven meta-analysis focused on the treatment of VTE in cancer patients have been made [8–14]. Because these patients often present with a variety of risk factors and co-morbidities, specific oncology guidelines on the subject were established using various methodological approaches. These national guidelines for the treatment of VTE in cancer patients were published first by the Italian Association of Medical Oncology (AIOM) in 2006 [15], then in the US by the National Comprehensive Cancer Network (NCCN) [16,17] and the American Society of Clinical Oncology (ASCO) [18] and in France by the French "National Cancer Institute" INCa (www.sor-cancer.fr) [19,20]. The latter recommendations also comprise the treatment of CVC related thrombosis. In addition, several scientific societies and organizations, including the American College of Chest Physicians (ACCP) [21,22] or the French Agency for Sécurité Sanitaire des Produits de Santé (AFPSSAPS) [23] issued detailed guidelines for the prevention and the treatment of VTE in the general population, with particular recommendations for cancer patients. Inspite of the paucity of evidence based data in haematology patients, recommendations were also written for the treatment of VTE in myeloma patients [24].

Many clinicians have not yet modified their clinical practice or still have doubt on the tolerability and acceptance of long term daily sub-cutaneous when applying standard therapeutic recommendations. A subset of patients with either life threatening thrombotic disease, advanced cancer disease, renal insufficiency or thrombocytopenia may require alternative therapeutic options, since specific precautions must be taken into consideration in the decision to anticoagulate. In addition, underuse of VTE prophylaxis still represents a major clinical challenge in the general population [25] and studies on clinical practice show that cancer appears as a strong obstacle for adapted prophylaxis of VTE [26–28].

In the present paper, we aimed to review the various factors underlying the importance of improving the prevention and the treatment of established VTE in cancer patients. Therefore, we analysed the reasons for variations in practice at each national level in order to propose adapted strategy at the international level in light of each country specificity and complementary experience.

Epidemiology of VTE in cancer patients

The incidence of DVT and PE is 4- to 6-fold higher in patients with cancer than in those without this disease [1,2]. The risk of VTE is influenced by the characteristics of the underlying neoplasm (histological type, stage and site of cancer) and is higher in patients with mucinous adenocarcinoma of the digestive tract, pancreatic cancer, lung cancer, ovarian cancer, acute promyelocytic leukemia, or myeloproliferative disorders [29–31]. Furthermore, the likelihood of VTE recurrence increases in patients with active cancer or receiving antineoplastic treatments [4,32,33]. The association between cancer and thrombosis has been known for years [34], but several factors recently contributed to increased awareness of its importance.

First, cancer-associated VTE is increasingly prevalent. In a recent analysis of over 1 million hospitalized cancer patients, the rate of VTE increased from 3.6% per hospitalization in 1995–96 to 4.6% in 2002–03, an increase of 28% ($P < 0.0001$) including a near-doubling rate of PE from 0.8% to 1.5% ($P < 0.0001$) and a 47% increase in VTE among patients on chemotherapy [4]. During chemotherapy, the rate of VTE is quite heterogeneous according to the studied populations and the drugs used to treat the underlying cancer. It varied from 2.2% in a prospective study including more than 4,000 patients [4] to 7.3% (15/206) among various types of cancer patients [32] and 8.4% (15/179) in patients with germinal tumors [33]. Cancer patients undergoing surgery have a higher risk of VTE than those undergoing surgery for benign conditions. Their risk of a postoperative deep vein thrombosis (DVT) and fatal pulmonary embolism (PE) is increased by two to three compared to non-cancer patients. In the @ristos prospective study on VTE after cancer surgery, 2.1% of the VTE events – including 0.8% of lethal PE – were noted among 2,773 patients despite adapted VTE prophylaxis in 81% of hospitalised patients and in 31% of ambulatory patients [35]. VTE risk varies depending on the type of surgery. Among 1,375 patients operated on for a gynaecological tumour, the frequency of post-operative VTE was about 4% in the case of major cancer surgery, 0.4% in case of minor cancer surgery and only 0.3% in non-cancer surgery [36]. The rate of VTE among 3898 women with breast cancer surgery was 0.16% [37].

Second, the use of long-term central venous catheters (CVC) has increased in cancer patients, for the administration of intravenous chemotherapy and supportive care treatments. CVC placement may be complicated by CVC-associated thrombosis, defined as a mural thrombus extending from the catheter into the vessel lumen, and leading to partial or total catheter occlusion with or without clinical symptoms. The incidence of CVC-associated thrombosis varies from 4 to 5% (0% to 28% depending on the study) for symptomatic events, to respectively 30% (27% to 66%) for the asymptomatic events detected by venography and 15% to 20% for those detected by ultrasound echography [38]. CVC-associated thrombosis may result in pulmonary embolism in 10 to 15% of patients and loss of central venous access in 10% of patients [38]. From an economic perspective, it also accounts for a significant increase in treatment-related and management costs [20].

Third, the consequences of VTE are better understood. In patients treated for VTE, cancer increases both the risk of treatment failure and the risk of a severe hemorrhagic event. Thrombosis has become the second-leading cause of death in cancer patients, and is associated with increased mortality as well [39–41]. Importantly, VTE is responsible for the death of one out of seven hospitalized cancer patients [39] and the most common cause of death at 30 days for surgical cancer patients [42]. It is also an independent risk factor for death in cancer patients [3,40,41]. Pulmonary embolism is the leading cause of non-cancer death in cancer patients receiving chemotherapy and of particular importance in individual cancers types such as colorectal, lung, and ovary cancer [42–44]. Additionally, cancer patients who suffer VTE have an increased risk of recurrent VTE, bleeding complications, morbidity and utilization of healthcare resources contributing to increased awareness of the problem amongst both patients and clinicians [45,46].

Finally, newer anti-cancer agents particularly anti-angiogenic drugs, appear to be more thrombogenic than conventional chemotherapy [24,47,48].

Various national guidelines on thrombosis and cancer

The Italian Association of Medical Oncology (AIOM) [15], the National Comprehensive Cancer Network (NCCN) [16,17], the American Society of Clinical Oncology (ASCO) [18], the French "National Cancer Institute" (INCa) [19,20], the European Society of Medical Oncology (ESMO) [49] and the American College of Chest Physicians (ACCCP) [21,22] have successively issued specific guidelines for health care providers regarding the prevention and treatment of cancer-associated VTE. Each working groups included experts from the vascular and the oncology field, who had already contributed to analyse the impact of VTE on cancer morbidity and mortality. Various methodological approaches were used for the development, the dissemination and the evaluation processes of each clinical guidelines, which can be summarized below.

The AIOM guidelines [15]

The expert panel included 3 academically affiliated and 4 community-based practicing hematology/oncology specialists. The guidelines were focused on distinct issues: (i) VTE and occult cancer; (ii) prophylaxis of VTE in cancer surgery, during chemotherapy or hormonal therapy, and with central venous catheters; (iii) anticoagulation and prognosis of cancer patients. The methodology used a systematic review of the evidence as a basis for making the recommendations. This process included adjudicating the strength of each recommendation after a systematic weighting and grading of the level of evidence. Greater weight was given to well-designed randomized controlled trials and meta-analyses than to studies with weaker internal validity. The panel scored as high quality recommendations those that were derived from studies with false-positive rates of ≤5% and false-negative rates of ≤20%. When evidence was lacking, the panel determined that it was inappropriate to reach conclusions based on expert opinion. The strength of evidence and grade of recommendations were identical to that in use by the ASCO and the ESMO. The AIOM guidelines were published in May 2006 [15].

The NCCN guidelines [16,17]

A multidisciplinary panel of expert members from the NCCC consortium of 21 US leading academic cancer institutes was organized in 2005. An evidence-based guideline was developed on diagnosis, prevention and management of VTE in cancer patients. Comprehensive search of the English language literature performed by network staff was provided to panel members, who could supplement the literature review if they considered other data important in the guideline development process. Recommendations were graded according to the level of evidence and the degree of consensus among panel members. The first version of the guideline was presented at the NCCN Annual Meeting in March 2006 and subsequently published [16,50].

The ASCO guidelines [18]

The expert panel consisted of clinicians and researchers VTE and cancer including medical and surgical oncologists, academic and community practitioners, an oncology fellow, and a patient representative. Five questions were addressed: (1) Should hospitalized cancer patients receive anticoagulation for VTE prophylaxis?; (2) Should ambulatory cancer patients receive anticoagulation for VTE prophylaxis during systemic chemotherapy?; (3) Should cancer patients undergoing surgery receive perioperative VTE prophylaxis?; (4) What is the best method for treatment of cancer patients with established VTE to prevent recurrence? and (5) Should cancer patients receive anticoagulants in the absence of established VTE to improve survival? A comprehensive systematic review of published and unpublished randomized controlled clinical trials of anticoagulation therapy in medical and surgical oncology patients was performed. The entire Panel met twice to discuss the results of the systematic review, resolve differences in the interpretation of the results and elaborate practice recommendations, which were published in 2007 [18].

SOR guidelines [19,20]

The SOR (Standards, Options: Recommendations) guidelines department from the French National Cancer Institute since May 2008, conducted the program. Clinical guidelines for the standardization of 'good clinical practice' throughout the various disciplines involved in cancer care were developed on the treatment of VTE and of central venous catheter (CVC)-related thrombosis in cancer patients. The methodology was based on a systematic literature review by 2 full time independent methodologists and a critical appraisal performed by the multidisciplinary working group of experts using successive meetings over a 13 months working process. The panel included 22 French clinicians from various medical specialities, using a collaborative effort from the French National Institute of Cancer (INCa) and three other scientific societies of Internal Medicine (Société Francaise de Médecine Interne), of Vascular Diseases (SFMV, Société Française de Médecine Vasculaire) and of anesthesiology (SFAR, Société Française d'Anesthésie-Réanimation). The level of evidence depended not only on the type and quality of the studies reviewed, but also on the consistency of the data (Table 1). In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the expert group ('expert agreement'). Recommendations were classified as Standards (defined as a clinical pathway unanimously recognized as the "gold standard" by clinical practitioners) or Options (where many clinical pathways may be appropriate and one of the Options can be preferred). Studies taken into account encompassed the therapeutic management of established VTE in adults and children patients with solid tumors or hematologic malignancies and a CVC with or without a history of thrombo-embolic events. The document was then peer-reviewed by 65 other independent experts and their comments were integrated in the final version and published on line first in February 2008 (www.e-cancer.fr or www.sor-cancer.fr) and in two independent reviews thereafter [19,20].

The ESMO guidelines [49]

The ESMO Clinical Recommendations (CRs) are based on a narrative platform that briefly summarize the state of the art. The panel, similar to the AIOM panel, used a systematic review of the evidence as a basis for recommendations, which was established in parallel with the elaboration of ACCP guidelines. The ESMO guidelines were first published in 2008 [51].

The ACCP guidelines [21,22]

The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines (8th Edition in 2008) were built on the innovations of prior conferences. The expert panel (88 members) included multidisciplinary physician, researchers, information scientists and guideline methodologists. Among all the other questions covered by the ACCCP process, the following ones were assessed in cancer patients: (A) thromboprophylaxis when (a) undergoing surgical procedures, (b) being bedridden with medical illness, (c) having a CVC to prevent catheter-related thrombosis, (d) receiving chemotherapy or hormonotherapy; (B) prophylactic anticoagulation and improved survival; (C) treatment in established VTE. The McMaster University Evidence-Based Practice Center, in collaboration with the guideline authors and methodologists, developped strategies and executed systematic searches for evidence Authors defined one question for each recommendation. For each question provided, comprehensive search of the English language literature between 2002 and May 2006 was performed by the librarians. Chapter authors revised previous chapters or wrote new chapters in close collaboration with all editors and other authors. Recommendations were graded according to the balance between the desirable and undesirable effects (1 and 2) and the methodologic quality (A to C).

Implementation of guidelines in daily clinical practice

Despite convincing data and increased awareness of clinicians on this subject, there is still large heterogeneity in daily clinical practice for the treatment of established VTE in oncology or haematology patients and implementation of the guidelines appears still low.

Table 1
Comparison of guidelines recommendations for the treatment and the prophylaxis of DeepVeinous Thrombosis (DVT) and Pulmonary Embolism (PE) in cancer patients

	NCCN [16,17]	ASCO [18]	AIOM [15]	ACCP [21,22]	SOR [19,20]
Prophylaxis of DVT and PE					
Hospitalized medical patients	VTE prophylaxis with anticoagulants if no contra indication from admission to discharge	VTE prophylaxis with anticoagulants if no contra indication or bleeding	Prophylaxis in patients confined to bed with an acute medical complication	Prophylaxis in bedridden patient with an acute illness	Not mentioned in the guideline
Ambulatory patients receiving chemotherapy	Not mentioned in the guideline	No routine prophylaxis	No routine prophylaxis	No routine prophylaxis	Not mentioned in the guideline
Surgical patients – prophylaxis	VTE prophylaxis with anticoagulants if no contra indication	UFH or LMWH if laparotomy, laparoscopy or throracotomy >30 mn	VTE prophylaxis for major surgery of neurosurgery	UFH 3/d, fondaparinux or LMWH in high risk patients with a major surgery for cancer. In other cases prophylaxis appropriate for the type of surgery	Not mentioned in the guideline
Surgical patients – duration of prophylaxis	From admission to discharge in non high risk patients For 4 weeks in high risk patients (abdominal, pelvic surgery, previous VTE, anesthesia >2 h, age >60 yrs, advanced disease, bed rest >4 d)	7 to 10 days for non high risk patients For 4 weeks in high risk patients (major pelvic or abdominal surgery, previous VTE, obesity, residual malignant disease	For up to 28–35 days after surgery in patients undergoing elective major abdominal or pelvis surgery	For up to 28 days for high risk patients (major cancer surgery, previous VTE)	Not mentioned in the guideline
Mechanical devices	Intermittent pneumatic venous device or graduated cpmpressive stockings for inpatients	To be used as monotherapy in case of contra indication of pharmacologic methods	Not mentioned in the guideline	Not mentioned in the guideline	Not mentioned in the guideline
Treatment of DVT and PE					
VTE treatment – acute	LMWH	LMWH	LMWH	UFH, LMWH or fondaparinux	UFH, LMWH or fondaparinux
VTE treatment – long term	LMWH or VKA 3–6 months for DVT 6–12 months for PE indefinite anticoagulation if active cancer or persistent risk factors	LMWH for at least 6 months	LMWH for 3 to 6 months Then LMWH indefinitely or until cancer is resolved	LMWH for 3 to 6 months Then VKA or LMWH indefinitely or until cancer is resolved	LMWH for 3 to 6 months Then VKA or LMWH indefinitely or until cancer is resolved and without anti cancer therapy
Vena cava filter	Failure or contra indication to anticoagulants. Patient non compliance In case of a recurrent PE could be life threatening	Contra indications to anticoagulant therapy or recurrent VTE despite adequate treatment	Contra indications to anticoagulant therapy or recurrent VTE despite adequate treatment. Anticoagulation is recommended if no CI	Contra indications to anticoagulant therapy.	Contra indications to anticoagulant therapy or recurrent VTE despite adequate treatment. Anticoagulation is recommended if no CI
Renal insufficiency	UFH + VKA	Not mentioned in the guideline	UFH + VKA or long term LMWH with anti Xa monitoring	No specific recommendation for cancer patients	UFH + VKA
Cerebral tumor	Same anticoagulation therapy except for recent central nervous system bleed, intracranial or spinal lesion at high risk for bleeding	Same anticoagulation therapy except for central nervous system bleed, recent cerebral surgery and platelets <50 G/L	Not mentioned in the guideline	Not mentioned in the guideline	Same anticoagulation therapy
Thrombolytic therapy	Massive or sub massive PE with right ventricular dysfunction or enlargement	Not mentioned in the guideline	Not mentioned in the guideline	In non cancer patients: hemodynamic failure, to discuss in high risk patients	Restricted to patients with PE and hemodynamic failure

Table 2
Comparison of guidelines recommendations for the treatment and the prophylaxis of catheter related thrombosis

	NCCN [16,17]	ASCO [18]	AIOM [15]	ACCP [21,22]	SOR [19,20]
Treatment of catheter related thrombosis				Recommendations are made for non cancer patients and for upper limb DVT	Recommendations are specific for cancer patients and catheter related thrombosis
Initial and long term treatment	Initial treatment with UFH, LMWH or fondaparinux then VKA or long term LMWH	Not mentioned in the guideline	Not mentioned in the guideline	Initial treatment with UFH, LMWH or fondaparinux then VKA	Long term LMWH
Duration of treatment	As long as catheter is in place 1 to 3 months after catheter removal	Not mentioned in the guideline	Not mentioned in the guideline	>3 months	As long as catheter is in place, anticancer therapy is maintained or cancer is active. 6 weeks after catheter removal if no active cancer nor anti cancer therapy
Thrombolytic therapy	Consider catheter-directed thrombolytic therapy for massive DVT	Not mentioned in the guideline	Not mentioned in the guideline	Catheter-directed thrombolytic therapy in patients with low risk of bleeding and severe symptoms of recent onset	Systemic or catheter-directed thrombolytic therapy in patients with poorly tolerated vena cava syndrome
Catheter removal	If symptoms or clot persist Catheter not required	Not mentioned in the guideline	Not mentioned in the guideline	No removal if mandatory and functional catheter Unfavorable clinical evolution under anticoagulation	Non functional catheter Distal catheter tip not in the right position Non mandatory catheter Infected thrombophlebitis Unfavorable clinical evolution under anticoagulation
Prophylaxis of catheter related thrombosis					
Pharmacological prophylaxis	Not recommended for VTE and mentioned in the guideline for catheter related thrombosis	Not mentioned in the guideline	Prophylactic doses of LMWH or low dose warfarin is not recommended	Prophylactic doses of LMWH or low dose warfarin is not recommended	Prophylactic doses of LMWH or low dose warfarin is not recommended
Mechanical prophylaxis	Not mentioned in the guideline	Not mentioned in the guideline	Not mentioned in the guideline	Not mentioned in the guideline	The distal tip of CVC should be placed at the junction between the superior vena cava and the right atrium. Right-sided insertion and placement of the CVC in a specialized unit should be favored.

Critical appraisal of the guidelines

Results from comparative analysis of the various guidelines subjects, as assessed by each national working group, are shown in tables 1 and 2. Similar questions were treated, apart from the prophylaxis and treatment of CVC-associated thrombosis in cancer patients (including the role of placement techniques), which were specifically evaluated only by the French recommendations [20]. Overall, each working group produced similar recommendations for a single question, although some guidelines recommend specific generic entities, dose, dosing interval and duration of therapy, whereas others give predominant drug class recommendations for the treatment of established VTE in cancer patient.

Methodological assessement of these guidelines was performed using the Appraisal of Guidelines Research & Evaluation (AGREE) Instrument [52]. The quality of clinical practice guidelines is generally defined as the confidence that the potential biases of guidelines development have been addressed adequately and that the recommendations are both internally and externally valid, as well as feasible for practice. This process involves taking into account the benefits, harms and costs of the recommendations, plus the practical issues attached to them. Therefore the assessment includes judgements about the methods used for developing the guidelines, the content of the final recommendations, and the factors linked to their uptake. The AGREE Instrument provides an assessment of the predicted validity of a guideline, that is the likelihood that it will achieve its intended outcome. Criteria contained in the AGREE Instrument have been developed through discussions between researchers from several countries who have extensive experience and knowledge of clinical guidelines. The AGREE Instrument consists of 23 key items organised in six domains. Each domain is intended to capture a separate dimension of guideline quality: (1) **Scope and purpose** (items 1–3) is concerned with the overall aim of the guidelines, the specific clinical questions and the target patient population; (2) **Stakeholder involvement** (items 4–7) focuses on the extent to which the guideline represents the views of its intended users; (3) **Rigour of development** (items 8–14) relates to the process used to gather and synthesize the evidence, the methods to formulate the recommendations and to update them; (4) **Clarity and**

Table 3
Comparison of recommendations of guidelines for treatment and prophylaxis of catheter related thrombosis

	NCCN [16,17]	ASCO [18]	AIOM [15]	ACCP [21,22]	SOR [19,20]
Scope and purpose					
The overall objective(s) of the guideline are described in detail and the expected health benefits from the guideline should be specific to the clinical problem	Yes	Yes	Yes	Yes	Yes
A detailed description of the clinical questions covered by the guideline is provided	Yes	Yes	Yes	Yes	Yes
There is a clear description of the target population to be covered by a guideline. The age range, sex, clinical description, comorbidity are provided.	Yes	Yes	Yes	Yes	Yes
Stakeholder involvement					
The guideline development group includes individuals from all the relevant professional groups.	Yes	Yes	Yes	Yes	Yes
The patients' views and preferences have been sought	No	No	No	No	No
The target users of the guideline are clearly defined	No	Yes	No	Yes	Yes
The guideline has been piloted among target users.	No	No	No	No	No
Rigor of development					
Systematic methods were used to search for evidence.	Yes	Yes	Yes	Yes	Yes
The criteria for selecting the evidence are clearly described.	Yes	Yes	Yes	Yes	Yes
The methods used for formulating the recommendations are clearly described.	No	Yes	+/−	Yes	Yes
The health benefits, side effects and risks have been considered in formulating the recommendations.	+/−	+/−	+/−	+/−	+/−
There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes	Yes
The guideline has been externally reviewed by experts prior to its publication.	No	No	+/− (3 reviewers)	Yes	Yes
A procedure for updating the guideline is provided.	Yes	Yes	No	Yes	No
Clarity and presentation					
The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes	Yes
The different options for management of the condition are clearly presented.	Yes	Yes	Yes	Yes	Yes
Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes	Yes
The guideline is supported with tools for application.	Yes	Yes	Yes	Yes	Yes
Applicability					
The potential organizational barriers in applying the recommendations have been discussed.	No	+/−	No	+/−	+/−
The potential cost implications of applying the recommendations have been considered.	+/−	+/−	+/−	+/−	+/−
The guideline presents key review criteria for monitoring and/or audit purposes.	No	No	No	No	No
Organisational changes that may be needed in order to apply the recommendations are discussed	No	No	No	No	No
Editorial independence					
The guideline is editorially independent from the funding body.	Yes	Yes	Yes	Yes	Yes
Conflicts of interest of guideline development members have been recorded.	Yes	Yes	No	No	No

presentation (items 15–18) deals with the language and format of the guidelines; (5) **Applicability** (items 19–21) pertains to the likely organisational, behavioural and costs implications of applying the guidelines; (6) **Editorial independence** (items 22–23) is concerned with the independence of the recommendations and development group. This specific tool, providing a framework for assessing the quality of the guidelines, was used by four individual specialists of the subject who had not been involved in the development process. Such analysis (Table 3) revealed two main obstacles for the guidelines implementation.

First, upstream of the development of guidelines, none of the available guidelines on VTE and cancer have sought for patients' preferences. In addition, none of them were tested among target users, which could be detrimental for their conviviality and their uptake in clinical practice. Indeed, the guidelines development groups generally include individuals from all the relevant professional groups, but difficulties in identifying the most appropriate methods for doing so and lack of ressources for involving patients in the developpement process may have contributed to this finding. Second, and perhaps most importantly, downstream the guidelines publication, the potential organisational barriers in applying the recommendations have not been discussed. This point may be of a peculiar importance, since clinical management of VTE in cancer patients requires a multidisciplinary approach. The various treatment modalities (such as surgery, radiotherapy, chemotherapy, infectious disease, internal medicine …) cannot be provided by the same specialist. Indeed, many oncologists are still unfamiliar with the treatment of VTE, apart from the "Standard" approach and the use of several "Options". Severe cases, necessitating thrombolytic drugs or vena cava filters, require technical assistance and vascular experts in the field. These points may account for difficulties in compliance, especially when patients have to receive daily subcutaneous injection of LMWH for at least three months compared to oral drugs. The poor scores for the "applicability domain" emphasizes the need to anticipate the implementation of guidelines during their development process.

Difficulties in implementing prophylaxis guidelines

Under use of VTE prophylaxis still represents a major clinical challenge in the general population. The ENDORSE study, a 41 multinational cross-sectional survey which included more than 68,000 patients, recently showed that only 59% of surgical and 40% of medical patients at risk received adapted VTE prophylaxis, with large heterogeneity in guidelines implementation from country to country [25]. In this survey, among medical patients with active malignancy and a high risk of VTE, only 37% received ACCP-recommended VTE prophylaxis. In the SWIss Venous Thromboembolim Registry (SWITTER), 567 patients with objectively confirmed acute DVT or PE were included. Within the 30 days prior to the VTE events, only 146 (48%) of medical patients received prophylaxis, and among the surgical patients, 183 (70%) received prophylaxis ($p < 0.001$) [26]. The MASTER registry enrolled 2119 patients, of whom 424 (20%) had cancer. Inferior vena cava filter implantation were more common in cancer patients (7.3% versus 4.1%; $p = 0.005$), whereas inferior cava filter indications do not differ between patients with or without cancer [27]. In this study, oral anticoagulants were used in 64% of patients with cancer, while all the guidelines recommend long term use of LMWH in this setting. Similarly, long term LMWH were prescribed in 50% of 2,945 cancer patients of the RIETE registry [28].

Tolerance of long term use of LMWH

The major adverse effect, which restrains clinicians from prescribing long-term LMWH, is the presumed intolerance and low acceptance of daily sub-cutaneous injections in cancer patients. Indeed, many oncologists still do not prescribe LMWH for 3 or 6 months, in order not to impose additionnal constraint on patients and to alter their patients' quality of life.

Pain and skin hematoma at the injection sites are common adverse side effects in daily practice, which may occur in 30 to 90% of subjects with subcutaneous administration [53]. However, these side effects have not been evaluated in randomized trials. They were only mentioned by Sideras, who reported a significant difference between the placebo (19%) and the LMWH group (50%) [54]. These side effects can be the source of discomfort for patients with prolonged treatment and could limit the number of available injection sites. In a series of subjects with chronic obstructive pulmonary disease, a prolonged 30 second injection or a 10 seconds wait before pulling the needle compared to an injection performed within 10 seconds allowed to observe less frequent and less pronounced indurations [55]. In two studies performed among 34 patients with stroke [56] and 50 hospitalized medical patients [57], an injection of LMWH performed over 30 seconds as compared to 10 seconds reduced the pain and the incidence of bruising. A lot of data on the influence of the needle size exists to, but results are non conclusive. Ice application after injecting the LMWH does not reduce the frequency and the size of skin induration although if it may have an analgesic effect [58,59].

Bleeding complications common to any type of anticoagulant treatment are identical in cancer patients with LMWH or VKA [5–7,11,60]. Theoretically, potential complications related to LMWH include thrombocytopenia, heparin-induced thrombocytopenia, allergic reactions, pain and bruising linked to the sub-cutaneous injection and the risk of fractures due to induced osteoporosis.

In cancer patients, the various prospective studies did not report any cases of **Heparin Induced Thrombocytopenia (HIT).** The incidence of thrombopenia was identical with long term use of LMWH and VKA as assessed in the LITE [7], the CANTHANOX [5] and in the Sideras [54] studies. A retrospective study of patients treated with UFH found 55 episodes of HIT, including 11 in the cancer patients, but did not allow for an estimation of the prevalence of HIT in cancer patients [61]. From two prospectively evaluated groups of 598 patients treated with UFH and 1754 patients under LMWH, extrapolation of the data estimated a HIT frequency of 1.5% (5/335) in the sub-group of cancer patients [62]. In the absence of specific studies and with a total of 16 HIT episodes reported (including 5 patients on LMWH), it was impossible to draw firm conclusion on the real frequency of HIT in cancer patients [62]. Nevertheless, it seems well established that thrombopenia is predominantly related to simultaneous use of chemotherapy and to bone marrow infiltration than heparin per se. In addition, thrombopenia related to heparin is less frequent with LMWH than with UFH [63]. Lastly, during prolonged use of LMWH, HIT is generally observed within the first month of treatment and infrequent thereafter [63].

The risk of bone fractures was not increased with LMWH (no case in either arms in the CANTHANOX study [5], 5% with VKA and 3% with long term LMWH in the LITE study [7] and appeared preferentially related to cancer than to LMWH. Allergic reactions were only documented in the MALT study and did not differ between the prophylactic use of LMWH and placebo [64].

Overall, the long term use of LMWH to treat VTE is well accepted in cancer patients and their use do not appear more detrimental than daily subcutaneous injections for other life long therapies, such as diabetes treatment. Two studies in palliative care performed by Noble reported the results of semi-directive 30 minute interviews with cancer patients treated worth long-term LMWH [65,66]. LMWH were well accepted and were even acknowledge to have a positive impact on the quality of life of patients. Constraints under LMWH were considered insignificant as compared with those occurring under chemotherapy or radiotherapy. Most patients, who were once treated by VKA, preferred LMWH, which allowed far less biological surveillance and therapeutic adaptation [65]. LMWH were also preferred to compression stockings, which patients found too difficult to wear [66]. This finding was not limited to palliative care patients and analysis of the CLOT study also showed improved quality of life in patients treated by LMWH (score of 0.66 for LMWH and 3.4 for VKA) [67].

Cost effectiveness of long term use of LMWH in cancer patients

The potential cost implications of applying the recommendations are poorly considered. Indeed, at the European level, use of LMWH vary from country, according to regulatory approval, cost, access to health care, opportunity for outpatient use, ease of administration and the need of monitoring. Because LMWH is more expensive than VKA, it is an important issue to point out since reimbursement may be a serious problem for people with a limited coverage. The cost effectiveness of treating established VTE has been studied in a canadian post hoc analysis of the CLOT study [67]. When all the components were combined for the entire population ($n = 676$), patients in the dalteparin group had a significantly higher cost overrun of $Can 2159. Drug acquisition contributed for 67% of the cost in the dalteparin group (vs 13% in the control), while VTE treatment and laboratory monitoring were the largest cost components in the oral anticoagulants group. A cost-utility analysis was then performed to estimate the incremental cost per QUALY (Quality of Life Adjusted Year) gained. Indeed a $Can 50,000 cost per QUALY has been suggested as a threshold, at or below which new medical interventions should be considered by health care systems with an 'acceptable' economic value [68]. When differences in treatment preferences and health utilities were combined, the additional cost with dalteparin was associated well-below the breakeven point mentioned. The same medico-economic analysis had been previously performed in the non-cancer population using six trials comparing LMWH and long-term VKA [69]. The cost of a year of life with maintained quality of life was estimated at a cot of $6,583 per QUALY based on the cost in Italy and $28,231 per QUALY

based on the costs in the United States. This figure is higher than noted in the cancer population by Dranitsakis [19]. However, LMWH appeared as cost effective drug for secondary prophylaxis of VTE, especially in patients at high risk of recurrence and in countries where the drug's cost is lower.

Conclusion: How to improve treatment of VTE in cancer

It appears important to identify organizational and individuals obstacles and the way to overcome these difficulties in order to contribute to improved acceptance and use of guidelines. Clinical pratice guidelines (CPGs) improve the quality of patient care, reducing practice variation and promoting more efficient use of health resources. They are contingent upon rigorous guideline development processes that include the best available evidence and successful implementation of guidelines into practice. In a recent Canadian survey analysis, Kryworuchko et al. compared 730 guidelines from 1994–1999 and 630 guidelines among 2000–2005 [70]. Given that guideline development processes have improved in some area over the past 12 years, yet not in other, ongoing monitoring of the guideline quality is required. Guideline dissemination and implementation activities have actually decreased which argues for a shared approach by various European and international groups. Unfortunately, the potential positive impact on patient health outcomes will not be realized until the recommendations are adopted and acted upon. A review of cluster randomized controlled trials revealed that passive strategies (mailings of printed educational material, publishing in newletters or journals, direct mailing to others, computer technology …), contrary to conventional wisdom, may actually be useful for promoting the uptake of guidelines on their own by about 8%. Educational strategies (providing guideline information to patients or consumers, educational or continuing medical education activities, organization of conferences) and active implementations strategies are more effective (training and support of people who have educational or administrative influence, face to face visits at practitioner's office, guideline reminder systems, training or support for audit and feedback, integration of guideline into recertification or licensing examinations, administrative strategies such as the design of laboratory or x ray forms …).

A need for international validated guidelines

Overall, the conclusions of these studies are concordant with the recommendations proposed by our SOR working group. In order to facilitate the implementation of the various guidelines for the treatment of VTE in cancer patients, the homogenization of all the various documents currently proposed by each national and European working groups would certainly be very valuable to the daily practice. An international consensus could be rapidly developped produced by a panel of national experts already involved in this field and validated by independant reviewers at each national level. In short an update of the current literature, which had been assessed for establishing the Italian (2006), the NCCP (2007), the French (2008) and the ACCP (2009) recommendations, could be performed using the Adapte methodology. The INCa has proposed its support to achieve the literature search according to a professional and exhaustive methodology, using an independant institutional approach. The INCa will provide several methodological tools to be used by the working group panel, including: a website dedicated to the project, critical appraisal grids or evidence tables. These international guidelines should be elaborated under the auspices of the International Society of Thrombosis and Hemostasis, and endorsed by national and European institutions through a specific procedure, while their dissemination, assessment of adhesion and compliance rely more on national groups because of linguistic and organizational considerations.

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Author's contributions

All authors made substantial contributions to all of the following: the conception and design of the study (DF and PD), acquisition of data (DF, CD, SV, AL, AM, PD), analysis and interpretation of data (DF, CD, MM, PD), drafting the article (DF, CD, MM and PD) or revising (SV, AL, AM) it critically for important intellectual content.

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