Article

International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer

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Abstract

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Reference

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ORIGINAL ARTICLE

International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer

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Summary. *Background:* Guidelines addressing the management of venous thromboembolism (VTE) in cancer patients are heterogeneous and their implementation has been suboptimal worldwide. *Objectives:* To establish a common international consensus addressing practical, clinically relevant questions in this setting. *Methods:* An international consensus working group of experts was set up to develop guidelines according to an evidence-based medicine approach, using the GRADE system. *Results:* For the initial treatment of established VTE: low-molecular-weight heparin (LMWH) is recommended [1B]; fondaparinux and unfractionated heparin (UFH) can be also used [2D]; thrombolysis may only be considered on a case-by-case basis [Best clinical practice (Guidance)]; vena cava filters (VCF) may be considered if contraindication to anticoagulation or pulmonary embolism recurrence under optimal anticoagu-

lation; periodic reassessment of contraindications to anticoagulation is recommended and anticoagulation should be resumed when safe; VCF are not recommended for primary VTE prophylaxis in cancer patients [Guidance]. For the early maintenance (10 days to 3 months) and long-term (beyond 3 months) treatment of established VTE, LMWH for a minimum of 3 months is preferred over vitamin K antagonists (VKA) [1A]; idraparinux is not recommended [2C]; after 3–6 months, LMWH or VKA continuation should be based on individual evaluation of the benefit-risk ratio, tolerability, patient preference and cancer activity [Guidance]. For the treatment of VTE recurrence in cancer patients under anticoagulation, three options can be considered: (i) switch from VKA to LMWH when treated with VKA; (ii) increase in LMWH dose when treated with LMWH, and (iii) VCF insertion [Guidance]. For the prophylaxis of postoperative VTE in surgical cancer patients, use of LMWH o.d. or low dose of UFH t.i.d. is recommended; pharmacological prophylaxis should be started 12–2 h preoperatively and continued for at least 7–10 days; there are no data allowing conclusion that one type of LMWH is superior to another [1A]; there is no evidence to support fondaparinux as an alternative to LMWH [2C]; use of the highest prophylactic dose of LMWH is recommended [1A]; extended prophylaxis (4 weeks) after major laparotomy may be indicated in cancer patients with a high risk of VTE and low risk of bleeding [2B]; the use of LMWH for VTE prevention in cancer patients undergoing laparoscopic surgery may be recommended as for laparotomy [Guidance]; mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated [2C]. For the prophylaxis of VTE in hospitalized medical patients with cancer and reduced mobility, we recommend prophylaxis with LMWH, UFH or fondaparinux [1B]; for children and adults with acute lymphocytic leukemia treated with ʟ-asparaginase, depending on local policy and patient characteristics, prophylaxis may be considered in some patients [Guidance]; in patients receiving chemotherapy, prophylaxis is not recommended routinely [1B]; primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic [1B] or lung [2B] cancer treated with chemotherapy and having a low risk of bleeding; in patients treated with thalidomide or lenalidomide combined with steroids and/or chemotherapy, VTE prophylaxis is recommended; in this setting, VKA at low or therapeutic doses, LMWH at prophylactic doses and low-dose aspirin have shown similar effects; however, the efficacy of these regimens remains unclear [2C]. Special situations include brain tumors, severe renal failure (CrCl < 30 mL min^{-1}), thrombocytopenia and pregnancy. Guidances are provided in these contexts. *Conclusions:* Dissemination and implementation of good clinical practice for the management of VTE, the second cause of death in cancer patients, is a major public health priority.

Introduction

Cancer is an independent and major risk factor for venous thromboembolism (VTE) [1,2]. VTE, defined as deep-vein thrombosis (DVT) or pulmonary embolism (PE), is reported in up to 20% of patients with cancer [3]. Although the association between cancer and thrombosis has been known since Trousseau's first report [4], cancer care providers now have increased awareness of the impact of thrombotic complications in their patients. Several factors have contributed to this heightened awareness. First, cancer-associated VTE is increasingly prevalent. In an analysis of more than one million hospitalized patients with cancer, the rate of VTE increased by 28% from 1995 to 2003 ($P < 0.0001$) [5]. Second, the consequences of VTE are better understood. Thrombosis is the second leading cause of death in patients with cancer [6]. Furthermore, VTE is an independent prognostic factor of mortality in cancer patients. Cancer patients with VTE have a shorter overall survival than cancer patients without VTE at the same tumor stage and receiving the same anti-cancer treatment [1,3]. In addition, patients with cancer who also suffer from VTE have an increased risk of recurrent VTE, bleeding complications, morbidity, and utilization of health care resources [7,8].

Therefore, the prevention and treatment of VTE in cancer patients represent major challenges in daily practice. As cancer patients often present with a variety of risk factors and co-morbidities, specific oncology guidelines on the subject have been established using various methodological approaches. Several national and international guidelines for the prevention and treatment of VTE in cancer patients have been published in the past [9–18]. Their methodological quality varies widely. In addition, underuse of VTE prophylaxis represents a major problem in daily life, and use of adequate prophylaxis is even less frequent among cancer patients [19]. In view of these issues, an international multidisciplinary working group was set up, following the initiative of the 'Groupe Francophone Thrombose et Cancer' (GFTC), with the collaboration of the Academic Medical Centre (AMC) and the University Medical Center Groningen (UMCG), the Netherlands, to develop harmonized guidelines for cancer patients, using the GRADE system, an up-to-date evidence-based clinical practice guideline development approach, with the methodological support of the French Institute of Cancer (INCa). In this article, we present the results and conclusions of this working group on the prevention and treatment of VTE in cancer patients.

Methods

Working group

The working group comprised 24 experts from various specialties (oncology, hematology, internal medicine, vascular medicine, biology and epidemiology), including two methodologists (PD and MB) and two coordinators (DF and HRB), as well as one nurse.

Literature review and analysis

We searched MEDLINE® and several other databases (e.g. EMBASE, CCTR, etc.), including national guidelines and several evidence-based medicine sites (Table S1 of Supporting Information), for articles published in French or English between January 1996 and January 2011. This literature search was prospectively continued up to June 2011. The search terms were cancer, venous thromboembolism (VTE), anticoagulant drugs, unfractionated heparin, low-molecular-weight heparin and treatments, and therefore included vitamin K antagonists, new oral anticoagulants and external compression devices. Panelists who had participated in previous guideline working groups or who were authors of meta-analyses supplied further references not retrieved by the literature search, as well as data previously extracted [10–12,20].

We included in the analysis, meta-analyses, systematic reviews, randomized clinical trials, or non-randomized prospective or retrospective studies in the absence of randomized clinical trials, but excluded editorials, letters to the editor, case reports, publications without an abstract, press releases and animal studies. Abstracts were included only if the data had subsequently been presented in full in an article published in a peer-reviewed medical journal. If no specific studies in patients with cancer could be retrieved, we included in the analysis studies performed in the general population of VTE patients, but including patients with cancer. In this case, the results were extrapolated to cancer patients and methodological biases were taken into account.

For inclusion in the analysis, studies had to focus on the therapeutic management of confirmed VTE in cancer patients (including initial treatment, early maintenance and long-term treatment of established VTE, as well as treatment to prevent VTE recurrence) or the prophylaxis of VTE in cancer patients in the surgical and medical settings. Studies in patients with catheter-related thrombosis will be reported separately. Studies in patients with thrombosis related to tumor material or a history of cancer in remission for more than 5 years were excluded from the analysis. Studies which did not include as outcomes VTE or side-effects of anticoagulation were also excluded.

The main study outcomes were rates of VTE (first event or recurrence), major and minor bleeding, thrombocytopenia and death. Major bleeding was defined as fatal bleeding, bleeding into a critical organ, or clinically overt bleeding associated with a decrease in hemoglobin level of more than 2 g dL^{-1} or leading to the transfusion of two or more units of blood [21,22]. Minor bleeding was defined as all other bleeds.

Critical appraisal and data extraction

The quality of the studies was evaluated in a double-blind manner by the two methodologists (PD and MB) using validated critical appraisal (methodology and clinical relevance) and data extraction grids. Discrepancies in opinion between the two methodologists were resolved by discussion and, in the event of persisting disagreement, by a third expert (DF). Data were then extracted and entered in evidence tables, which were subsequently validated by all the working group members.

Consensus development

For each question, the results of the literature analysis were summarized and discussed by the whole working group taking into account the critical appraisal and data extraction grids. Overall conclusions with the corresponding levels of evidence were formulated on the basis of the pooled results and conclusions for each question and the degree of agreement between the studies, using the GRADE system [23,24].

The level of evidence (Table 1) depended on the study design as well as on study limitations, inconsistency, indirectness, imprecision and publication bias [23,24]. Recommendations were established based on these assessments and the corresponding levels of evidence, as well as the balance between desirable and undesirable effects, values and preferences, and costs. They were classified as 'Strong' (Grade 1 Guideline) or 'Weak' (Grade 2 Guideline) based on the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects (Table 2) [23,24]. In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the international experts within the working group and defined as 'Best Clinical Practice' (Guidance).

The Guidelines were then peer-reviewed in February 2012 by 42 independent experts worldwide encompassing all medical and surgical specialties involved in the management of patients with cancer, and by three volunteer patient representatives selected from each panelist's patient population or from the patient associations with which the panelists were in contact. The peer review was performed according to a grid allowing quantitative and qualitative appraisal of the draft Guidelines. This process enabled us to consider both practioners' and

Table 1 Definition of levels of evidence according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) scale [GUYATT2008] [GUYATT2008A]

Level	Definition
High (A)	Further research is very unlikely to change our confidence in the estimate of effect
Moderate (B)	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low (C)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low (D)	Any estimate of effect is very uncertain

Table 2 Classification of recommendations

Recommendation	Definition
Strong (Grade 1)	The panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects
Weak (Grade 2)	The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident
Best clinical practice (Guidance)	In the absence of any clear scientific evidence and because of undetermined balance between desirable and undesirable effects, judgment was based on the professional experience and consensus of the international experts within the working group

patients' values and preferences. Discrepancies in opinion between the reviewers and the members of the working group were resolved by consensus during a final meeting.

Results

Treatment of established VTE

Several retrospective [8,25–31] and prospective [7,32–35] cohort studies showed that the rates of VTE recurrence and major bleeding are particularly high in cancer patients with VTE receiving anticoagulant therapy (Tables S2 and S3 of Supporting Information). Prospective studies reported a 2 to 5-fold increase in the rate of VTE recurrence and a 2 to 6-fold increase in the rate of major bleeding in cancer patients compared with non-cancer patients (Table S3 of Supporting Information) [7,32–35]. In addition, VTE recurrence and bleeding rates appear to correlate with cancer stage [7].

Initial treatment of established VTE

The definition of initial treatment corresponds to the first 10 days of anticoagulation.

Short-term unfractionated heparin (UFH) followed by vitamin K antagonists (VKA). The literature search failed to retrieve any randomized study evaluating the benefit-risk ratio of short-term UFH followed by VKA for VTE treatment in cancer patients. We identified six retrospective studies in cancer patients treated for VTE with UFH + VKA, showing high rates of recurrent VTE (11–38%) and major bleeding (8–35%) up to 10 months of follow-up (Table S2 of Supporting Information) [8,25,26,28–30]. In the control arms of two randomized studies comparing short-term UFH + VKA with short-term low-molecular-weight heparins (LMWHs) + VKA or fondaparinux + VKA, the rates of VTE recurrence and major bleeding after 3 months of treatment were 10–17.2% and 6.3–7%, respectively, in the subgroups of cancer patients (Table S4 of Supporting Information) [36,37]. In conclusion, the treatment of VTE in cancer patients with UFH followed by VKA is associated with a high rate of recurrence and bleeding.

Short-term LMWH followed by VKA. The literature search did not retrieve any randomized study or meta-analysis evaluating the benefit-risk ratio of short-term

LMWH followed by VKA for VTE treatment in cancer patients. Five randomized studies were performed in patients with cancer and used short-term LMWH followed by VKA as one of the treatments compared (Table S4 of Supporting Information) [37–41]. In these studies, including a total of 628 cancer patients, the rate of recurrent VTE was 6.7–16.9% and that of major bleeding was 2.9–16% after 6 months follow-up. In conclusion, the treatment of VTE in cancer patients with LMWH followed by VKA is associated with high rates of both relapse and bleeding.

Short-term LMWH vs. short-term UFH followed by VKA. Eight meta-analyses were identified that compared short-term LMWH with short-term UFH in the initial treatment of VTE, both drugs being then switched to VKA, in populations including patients with cancer (the proportion of these patients, when specified, ranging from 5% to 23%) (Table S5 of Supporting Information) [42–49]. In the general population, LMWHs were more effective than (in three meta-analyses [42,43,47]) or at least as effective as (in the five remaining meta-analyses) UFH. LMWHs were associated with a significantly lower risk of bleeding than UFH in five meta-analyses [42–45,47], and significantly reduced overall mortality in the six meta-analyses in which death rates were reported [42–47].

In two meta-analyses specifically performed in cancer patients, the rates of recurrence did not differ statistically between LMWH and UFH [50,51]; the relative effect regarding bleeding was not reported. Interestingly, a beneficial effect of LMWH vs. UFH was observed on the risk of death [50,51]: in the most recent meta-analysis in 801 cancer patients, the death rate was reduced from 18.9% with UFH to 13.1% with LMWH [relative risk (95% confidence interval), 0.71 (0.52–0.98)] [51].

Short-term fondaparinux vs. short-term LMWH or UFH followed by VKA. In *post-hoc* analyses of the subgroups of cancer patients in two randomized controlled trials comparing fondaparinux with LMWH for the treatment of DVT ($n = 237$) and with UFH for the treatment of PE ($n = 240$), the rate of VTE recurrence after 3 months was lower with fondaparinux than with UFH, but higher than with enoxaparin, with no difference between fondaparinux and the comparators in the risk of bleeding or death (Tables S5 and S6 of Supporting Information) [37,51].

Table 3 LMWH used in studies comparing early maintenance treatment (10 days to 3 months) and long-term (beyond 3 months) treatment by LMWH alone with short-term heparin followed by VKA

Drug	Dosage and duration	Study
Enoxaparin	1.5 mg kg^{-1} per day for 3 months	CANTHANOX [MEYER2002]
Dalteparin	200 IU kg^{-1} per day for 1 month, 150 IU kg^{-1} per day for 5 months	CLOT [LEE2003]
Tinzaparin	175 IU kg^{-1} per day for 3 months	LITE [HULL2006]
Idraparinux	2.5 mg per week first dose, then 2.5 mg per week or 1.5 mg per week if creatinine clearance < 30 mL min^{-1} for 3 or 6 months	VANGOGH subgroup [VANDOORMAAL2010]

Thrombolytics. The use of thrombolytic drugs in cancer patients with VTE was evaluated in only one study retrieved, a retrospective multicenter cohort study comprising patients from five randomized studies (Table S7 of Supporting Information) [52]. In this study, 57 cancer patients with PE were treated first with tissue plasminogen activator or urokinase and then by intravenous UFH. The rate of recurrent VTE within 14 days after treatment administration was 6%, the rate of major bleeding within 72 h after treatment administration being 12%.

Vena cava filters. Data on the use of vena cava filters in cancer patients with VTE are scarce. Fourteen retrospective cohort studies including 29–308 patients [28,53–65] were identified (Table S8 of Supporting Information). Among these studies, 11 were non-comparative and three compared the efficacy of vena cava filters with that of heparin followed by VKA. Contraindication for anticoagulant treatment was the principal reason for vena cava filter placement. The heterogeneity of the results can probably be ascribed to differences in the type of recurrent VTE analyzed and concomitant treatment with an anticoagulant (when specified).

Recommendations.
1 LMWH is recommended for the initial treatment of established VTE in cancer patients [Grade 1B].
   Values and preferences: LMWHs are easier to use than UFH.
2 Fondaparinux and UFH can be also used for the initial treatment of established VTE in cancer patients [Grade 2D].
   Values and preferences: fondaparinux is easier to use than UFH.

3 Thrombolysis in cancer patients with established VTE may only be considered on a case-by-case basis, with specific attention paid to contraindications, especially bleeding risk (brain metastasis) [Best clinical practice, based on evidence of very low quality and the high bleeding risk of thrombolytic therapy].
   Values and preferences: an expert opinion is recommended before using thrombolytics.
4 In the initial treatment of VTE, vena cava filters may be considered in the case of contraindication for anticoagulation or in the case of PE recurrence under optimal anticoagulation. Periodic reassessment of contraindications for anticoagulation is recommended and anticoagulation should be resumed when safe. Vena cava filters are not recommended for primary VTE prophylaxis in cancer patients. [Best clinical practice, based on evidence of very low quality and an unknown balance between desirable and undesirable effects].

Early maintenance and long-term treatment of established VTE

The early maintenance treatment period corresponds to the time beyond the tenth day up to the third month of anticoagulation, long-term treatment of VTE corresponding to treatment indicated beyond the third month of anticoagulation (Table 3).

Early maintenance treatment and long-term treatment by use of LMWH. We identified one prospective cohort study evaluating early maintenance treatment by LMWH [66], and six randomized studies comparing the benefit-risk ratio of early

Table 4 Dosage regimen evaluated in clinical trials of thromboprophylaxis in surgical cancer patients

LMWH	Dalteparin 5000 IU per day for 8–9 days	3 studies
	Dalteparin 2500 IU per day for 7 days	1 study
	Nadroparin 2850 IU per day for 7–11 days	1 study
	Enoxaparin 40 mg per day for 10 ± 2 days	3 studies
	Enoxaparin 25 mg per day for 10 ± 2 days	1 study
Factor Xa inhibitors	Fondaparinux 2.5 mg per day for 5–9 days	1 study
LMWH extended use	Tinzaparin 3500 IU per day for 3 weeks (after 7 days postoperatively)	1 study
	Enoxaparin 40 mg per day for 25–31 days (28 days)	1 study
	Dalteparin 5000 IU per day for 21 days (after 7 days postoperatively)	1 study
	Bemiparin sodium 3500 IU per day for 28 days	1 study
LMWH for brain tumors during hospitalization *	Nadroparin 7500 IU per day	1 study
	Dalteparin	1
	Enoxaparin	2
	Enoxaparin	1
	Enoxaparin	1

maintenance and long-term treatment by LMWH with that of short-term heparin followed by VKA, four in patients with cancer [36,38–40] and two in the general population including cancer patients [41,67] (Table S9 of Supporting Information). In one of these randomized studies [36], the heparin used in the control group was UFH, whereas it was an LMWH in the five remaining studies. Anticoagulant treatment lasted 3–6 months. Three of the randomized trials showed a significant benefit of extended LMWH treatment in terms of VTE recurrence [36,39,41]. In the five randomized trials for which the information was provided, the safety, in terms of bleeding risk, of extended LMWH treatment was at least as good as that of short-term heparin followed by VKA. The CANTHANOX study showed that LMWH was more effective than VKA in reducing the risk of the composite of major bleeding or recurrent VTE at 3 months ($P = 0.04$; logrank test) [38].

Five meta-analyses were performed on studies comparing extended LMWH treatment with short-term heparin followed by VKA, two concerning the general population [68,69], including cancer patients, and three specifically focusing on cancer patients [20,70–72] (Table S10 of Supporting Information). All but one [68] concluded that early maintenance treatment (10 days to 3 months) and long-term treatment (beyond 3 months) by LMWH alone vs. heparin (UFH or LMWH) followed by VKA in cancer patients with VTE decreased the VTE recurrence rate by 50% [20,69–72], with no increase in bleeding risk or any effect on the mortality rate [20,70–72]. The remaining meta-analysis included seven studies totaling 1379 patients [68], of which only one had enrolled cancer patients. In the overall population, the rates of clinical events (VTE recurrence, major bleeding or death) were comparable in the LMWH extended treatment group and the VKA group [68].

In conclusion, in cancer patients with VTE, early maintenance treatment (10 days to 3 months) and long-term treatment (beyond 3 months) with LMWH significantly reduced the risk of VTE recurrence by approximately 50% vs. short-term heparin followed by VKA, with no increase in bleeding risk, but did not decrease mortality.

Long-term use of idraparinux. One randomized trial (VANGOGH-DVT), not specific to cancer patients, compared the efficacy and safety of idraparinux with those of heparin (LMWH or UFH) + VKA administered for 3–6 months to patients with DVT (92% of patients received 6-month therapy) [73] (Table S11 of Supporting Information). *Post-hoc* analysis of the subgroup of patients with active cancer ($n = 421$) showed that idraparinux was as effective as VKA, with the same rate of bleeding events.

Duration of anticoagulation. Only one specific study on the duration of anticoagulation was identified [74] (Table S12 of supporting information). In this study, 409 patients with active cancer and a first episode of DVT received LMWH for 6 months and were then divided into three groups on the basis of the results of a duplex ultrasound examination: patients with

residual venous thrombosis were randomized to continuation (Group A1) or discontinuation of anticoagulation therapy (Group A2), and those without residual venous thrombosis were to discontinue anticoagulant therapy (Group B). Rates of VTE recurrence were 14.2%, 21.9% and 2.8% in Groups A1, A2 and B, respectively (A1 vs. B, $P = 0.03$; A2 vs. B, $P = 0.01$; A1 vs. A2, $P = 0.73$). Corresponding rates of major bleeding were 4.2%, 1.6% and 1.9%.

So far, no study has compared 3 vs. 6 months of LMWH. Four clinical trials investigating VTE treatment in cancer patients, although not specifically designed to evaluate the duration of anticoagulation, showed a benefit of early maintenance treatment (10 days to 3 months) and long-term treatment with LMWH alone (beyond 3 months) compared with short-term heparin followed by VKA [36,38–40] (Table S9 of Supporting Information). Two of these studies used a 6-month LMWH regimen.

Recommendations.

1 LMWHs are preferred over VKA for the early maintenance treatment (10 days to 3 months) and long-term treatment (beyond 3 months) of VTE in cancer patients [Grade 1A].

Values and preferences: daily subcutaneous injection may represent a burden for patients.

2 Idraparinux is not recommended for the early maintenance treatment (10 days to 3 months) and the long-term treatment (beyond 3 months) of VTE in cancer patients; idraparinux is currently not available on the market [Grade 2C].

Values and preferences: idraparinux once weekly is easier to use than UFH or LMWH.

3 LMWH should be used for a minimum of 3 months to treat established VTE in cancer patients; however, patients were treated for 6 months in the largest study in this setting [Grade 1A].

Values and preferences: daily subcutaneous injection may represent a burden for patients.

4 After 3–6 months, termination or continuation of anticoagulation (LMWH or VKA) should be based on individual evaluation of the benefit-risk ratio, tolerability, patients' preference and cancer activity [Best clinical practice, in the absence of data].

Treatment of VTE recurrence in cancer patients under anticoagulation

We identified one retrospective cohort study specifically designed to evaluate the treatment of VTE recurrence in 70 cancer patients who experienced recurrence while receiving an anticoagulant [75] (Table S13 of Supporting Information). At the time of the recurrence, 67% of patients were receiving LMWH and 33% were receiving a VKA. VTE recurrence was treated with either dose escalation of LMWH in patients already receiving LMWH (increase of the weight-adjusted dose by 20–25% for at least 4 weeks or to the therapeutic range), or

initiation of LMWH treatment at a therapeutic dose in patients who were on VKA. All patients were followed-up for a minimum of 3 months after the index VTE recurrence. A total of six patients (8.6%) experienced a second recurrence of VTE during the follow-up period. Three patients (4.3%) had bleeding complications. The median time between the index VTE recurrence to death was 11.4 months (range, 0–83.9 months; death rate, 36/70). The authors concluded that cancer patients with recurrent VTE have a short median survival and that escalating the dose of LMWH can be effective for treating cases that are resistant to standard, weight-adjusted doses of LMWH or a VKA.

In the 14 retrospective cohort studies of vena cava filters in cancer patients, a substantial proportion of patients received these filters to prevent VTE recurrence [28,53–65] (Table S8 of Supporting Information). However, no data are available regarding this subset of patients.

Recommendation. In the event of VTE recurrence, three options can be considered: (i) switch from VKA to LMWH in patients treated with VKA; (ii) increase in LMWH dose in patients treated with LMWH, and (iii) vena cava filter insertion [Best clinical practice, based on evidence of very low quality and an unknown balance between desirable and undesirable effects].

Values and preferences: individual decision.

New oral anticoagulant agents (NOAC)

The experts of the working group acknowledge the potential benefit of new oral anticoagulant agents for the treatment of VTE in cancer patients. However, the group considered it was premature to issue recommendations or guidance on the use of these new agents in this setting in view of the absence of specific data, and considering that none of these products had yet been approved for use for VTE treatment at the time this document was prepared and none of the experts had enough clinical experience with their use to give any meaningful 'best practice advice'.

Prophylaxis of VTE in cancer patients

Prophylaxis of VTE in surgical cancer patients. *LMWH or UFH compared with placebo or no treatment.* Only one randomized controlled study in 99 Indian patients undergoing colorectal surgery for cancer, comparing LMWH for 6 days with no prophylaxis, has been published since January 1996 [76] (Table S13 of Supporting Information). No postoperative VTE occurred in either group and there was no difference in the rate of bleeding events between the two groups.

Three meta-analyses of older randomized studies were identified, one conducted in general surgery patients [77], and two focusing on patients undergoing gynecologic surgery [78,79] (Table S14 of Supporting Information). Overall, LMWH and UFH were superior to placebo or no prophylaxis

in preventing postoperative VTE in cancer patients. In one meta-analysis [77], the rate of any bleeding was higher with LMWH than with placebo or no treatment.

LMWH vs. UFH. Three randomized double-blind studies comparing LMWH with UFH for the prevention of VTE in surgical patients were identified, two conducted specifically in cancer patients [80,81] and one in patients undergoing colorectal surgery (35.2% for cancer) [82] (Table S13 of Supporting Information). In these studies, LMWH and UFH showed similar efficacy with a trend towards less bleeding with LMWH.

In three meta-analyses [77,79,83], including studies published before January 1996, UFH given three times a day was as effective as LMWH once a day, but LMWH once a day appeared to be superior to UFH twice a day (Table S14 of Supporting Information). The rate of bleeding was the same with UFH and LMWH.

Comparison of drugs (Table 4). Two randomized double-blind trials compared two anticoagulant agents for VTE prophylaxis after abdominal surgery [84,85] (Table S15 of Supporting Information).

In the first study in 2927 high-risk patients undergoing abdominal surgery, once-daily subcutaneous fondaparinux 2.5 mg and dalteparin 5000 IU administered for 5–9 days had comparable benefit-to-risk ratios [84]. In the subgroup of patients undergoing surgery for cancer ($n = 1941$, i.e. two-thirds of the study population), fondaparinux reduced by 38.6% (95% CI, 6.7–59.6) the risk of symptomatic VTE and asymptomatic DVT, with a trends towards an increase in bleeding risk; major bleeding was reported in 3.4% of patients with fondaparinux and in 2.5% with dalteparin ($P = 0.355$).

In the second study in 1296 patients undergoing elective resection of colorectal adenocarcinoma, the benefit-to-risk ratios of once-daily subcutaneous nadroparin 2850 anti-Xa IU and enoxaparin 4000 anti-Xa IU were compared [85]. Treatments were administered for 7–11 days. At day 12, the rate of symptomatic and asymptomatic VTE was 15.9% with nadroparin and 12.6% with enoxaparin (RR = 1.27; 95% CI, 0.93–1.74). Corresponding rates of symptomatic VTE were 0.2% vs. 1.4% (RR = 0.12; 95% CI, 0.01–0.92) at day 12 and 0.6% vs. 2.1% at day 60 (NS). Major bleeding occurred less frequently with nadroparin than with enoxaparin (7.3% vs. 11.5%, $P = 0.012$).

Dose of LMWH (Table 4). Only one double-blind trial has compared two doses of the same anticoagulant agent for VTE prophylaxis in a surgical context [86] (Table S15 of Supporting Information). Once daily subcutaneous dalteparin 2500 anti-Xa IU and dalteparin 5000 anti-Xa IU administered for 8 days were compared in 1375 patients undergoing major elective abdominal surgery, 70% of these patients undergoing this procedure for cancer. The high-dose dalteparin regimen was more effective than the low-dose dalteparin regimen (postoperative total VTE rate, 8.5% vs. 14.9%; $P < 0.001$),

with no statistically significant difference in terms of bleeding complications (4.6% vs. 3.6%, respectively).

Extended duration of prophylaxis. We identified four prospective randomized studies evaluating extended prophylaxis with LMWH, one specifically in cancer patients [87] and three in the general population including cancer patients [88–90] (Table S16 of Supporting Information), and one meta-analysis of extended LMWH prophylaxis in cancer patients [91] (Table S17 of Supporting Information). Although two of the randomized studies were negative (one was stopped before the calculated number of patients was achieved), two studies were positive and the meta-analysis showed a reduced risk of postoperative VTE after major laparotomy surgery in cancer patients, with a trend towards an increased bleeding risk in the extended prophylaxis group.

External compression devices (ECD). Three randomized studies in patients undergoing surgery for gynecologic [92] or brain [93,94] tumors (Table S18 of Supporting Information) and one meta-analysis of studies in mixed neurosurgical patients [95] (Table S19 of Supporting Information) were identified. Overall, ECD and LMWH appeared to be equally effective in preventing VTE in major abdominal or pelvic surgery for gynecologic malignancies. As regards prophylaxis after surgery for brain tumors, graduated compression stockings (GCS) + intermittent pneumatic compression (IPC) showed the same efficacy as GCS alone, and both ECD were superior to no prophylaxis; in neurosurgical patients, LMWH were superior to ECD despite an increase in minor bleeding, but with no increase in intracranial bleeding or in major bleeding.

Recommendations.

1 Use of LMWH once a day or a low dose of UFH three times a day is recommended to prevent postoperative VTE in cancer patients; pharmacological prophylaxis should be started 12–2 h preoperatively and continued for at least 7–10 days; there are no data allowing conclusions regarding the superiority of one type of LMWH over another [Grade 1A].

 Values and preferences: LMWH once a day is more convenient.

2 There is no evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in cancer patients [Grade 2C].

 Values and preferences: similar.

3 Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in cancer patients is recommended [Grade 1A].

 Values and preferences: equal.

4 Extended prophylaxis (4 weeks) to prevent postoperative VTE after major laparotomy in cancer patients may be indicated in patients with a high VTE risk and low bleeding risk [Grade 2B].

 Values and preferences: longer duration of injections.

5 The use of LMWH for the prevention of VTE in cancer patients undergoing laparoscopic surgery may be recommended in the same way as for laparotomy [Best clinical practice, based on a balance between desirable and undesirable effects indicating an increased bleeding risk].

 Values and preferences: daily injections.

 Costs: In some countries, the price of LMWH may influence the choice.

6 Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated [Grade 2C].

 Values and preferences: no injection.

Prophylaxis of VTE in medical cancer patients

Hospitalized cancer patients. No study evaluated the benefit-risk ratio of thromboprophylaxis specifically in hospitalized medical cancer patients. We therefore selected the randomized clinical trials comparing LMWH with UFH in hospitalized medical patients with reduced mobility [96–99] included in the ACCP guidelines [12], which previously addressed this question (Table S20 of Supporting Information). All but one of these [98] were double-blind studies. In addition, four randomized double-blind studies comparing LMWH with placebo in comparable patients were considered [100–103] (Table S21 of Supporting Information). The percentage of cancer patients in the selected studies varied from 5% to 15%.

These studies showed that LMWH and fondaparinux were superior to placebo in preventing VTE, with a non-significant trend towards an increased bleeding risk (except for enoxaparin 40 mg and fondaparinux). LMWH and UFH showed similar efficacy and safety. No study reported a difference in efficacy between cancer and non-cancer patients.

Children with acute lymphocytic leukemia (ALL) treated with L-asparaginase. Two small studies conducted in children with acute lymphocytic leukemia (ALL) treated with L-asparaginase were identified [104,105] (Table S22 of Supporting Information). The first was a randomized study comparing antithrombin supplementation with no supplementation [105]. No differences were seen between the two groups in terms of either VTE events or bleeding complications. The second was a non-randomized prospective cohort study conducted during two periods, comparing antithrombin supplementation alone (1995–2000) with antithrombin supplementation + LMWH (2001–2006) [104]. The rates of thromboembolic events were 12.7% and 0% ($P = 0.02$), respectively, with no reports of bleeding complications. Overall, the rate of symptomatic VTE in children with ALL was around 5%.

Ambulatory patients treated with chemotherapy. We identified two prospective randomized studies comparing LMWH with no treatment [106,107], three randomized double-blind trials comparing LMWH with placebo [108–

110] and one analysis of pooled data from two randomized double-blind studies (PROTECH and TOPIC 2) comparing LMWH with placebo [111] (Table S23 of Supporting Information).

Overall, these studies showed that primary prophylaxis with LMWH in patients treated with chemotherapy non-significantly increased intracranial bleeding in patients with a brain tumor, decreased the rate of VTE without an excess of bleeding in patients with locally advanced or metastatic pancreatic cancers (at sub-therapeutic dosages) or locally advanced or metastatic lung cancers, but had no effect on VTE in patients with metastatic breast cancers. LMWH may increase the bleeding risk, particularly in the context of thrombocytopenia.

Patients treated with thalidomide or lenalidomide. We identified two retrospective studies of VTE prophylaxis in cancer patients treated with thalidomide [112,113], one prospective randomized study comparing aspirin, LMWH and warfarin in patients with myeloma [114] (Table S24 of Supporting Information) and two meta-analyses addressing the issue of anticoagulation in patients with myeloma [115,116] (Table S25 of Supporting Information). None of the studies included a placebo group.

These studies and meta-analyses showed that the rate of VTE in patients treated with IMiDs (thalidomide and lenalidomide) combined with steroids and/or chemotherapy (doxorubicin) is very high. Prophylactic doses of LMWH, aspirin (100 mg day^{-1}) or warfarin to maintain INR within the therapeutic range reduced the risk of thromboembolic events in multiple myeloma patients treated with lenalidomide or thalidomide with no increase in bleeding risk.

Recommendations.
1 We recommend prophylaxis with LMWH, UFH or fondaparinux in hospitalized medical patients with cancer and reduced mobility [Grade 1B].
   Values and preferences: subcutaneous injections.
   Costs: In some countries price differences between LMWH, UFH or fondaparinux may influence the choice.
2 For children with ALL treated with L-asparaginase, depending on local policy and individual patient characteristics (platelet count, kidney function, fibrinogen and antithrombin III levels, etc.), prophylaxis may be considered in some patients; the same therapeutic option can be considered for adults [Best clinical practice, based on evidence of very low quality and a balance between desirable and undesirable effect depending on individual patient characteristics].
   Values and preferences: subcutaneous injections.
3 In patients receiving chemotherapy, prophylaxis is not recommended routinely [Grade 1B].
   Values and preferences: subcutaneous injections.
4 Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic cancer treated with chemotherapy and having a low bleeding risk [Grade 1B].
   Values and preferences: subcutaneous injections.

5 Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic lung cancer treated with chemotherapy and having a low bleeding risk [Grade 2B].
   Values and preferences: subcutaneous injections.
6 In patients treated with IMiDs combined with steroids and/or chemotherapy (doxorubicin), VTE prophylaxis is recommended; in this setting, VKA at low or therapeutic doses, LMWH at prophylactic doses and low-dose aspirin have shown similar effects with regard to preventing VTE; however, the efficacy of these regimens remains unclear [Grade 2C].
   Values and preferences: subcutaneous injections.

Special situations

Treatment of established VTE in patients with a brain tumor. Four non-randomized studies reporting the use of anticoagulant agents for the treatment of established VTE in patients with a brain tumor were identified [55,57,117,118]; one was prospective and three were retrospective (Table S26 of supporting information). Overall, few patients were included in these studies (between 11 and 51) and their characteristics were heterogeneous. Anticoagulant treatment varied between studies: UFH + VKA, tinzaparin alone, or vena cava filter insertion. Under anticoagulation, the rates of VTE recurrence and bleeding events varied between 0% and 12% and 0% and 17.4% (intracerebral bleeding, 0–7%), respectively. In the two studies assessing the value of vena cava filters in a total of 52 patients, the rate of VTE recurrence was about 40% [55,57].

Prophylaxis of VTE in cancer patients undergoing neurosurgery. We identified eight prospective randomized studies [94,119–125], of which four were double-blind [122–125] (Table S27 of Supporting Information). In these studies, the majority of patients underwent neurosurgery for a brain tumor. In addition, two meta-analyses of studies evaluating therapeutic measures to prevent VTE in a mixed neurosurgical population were available [95,126] (Table S28 of Supporting Information).

Overall, compared with placebo or no treatment, LMWH and UFH reduced the risk of postoperative VTE by 50% without an excess of major bleeding but with a 2-fold higher rate of minor bleeding. LMWH and UFH (5000 IUSC/12 h) were associated with the same rates of VTE and bleeding events. The reduction in VTE rate with ECD was about 60% compared with no prophylaxis, GCS + IPC having the same efficacy as GCS alone. LMWHs were shown to be superior to ECD, with a reduction in VTE rate from 40% to 20%, an increase in minor bleeding (RR: 2), and no increase in intracranial bleeding or major bleeding. After surgery for brain or spinal tumors, adding LMWH to an intermittent compression device increased the risk of minor bleeding but not that of major or intracranial bleeding.

Other special situations. For the treatment and prophylaxis of VTE in cancer patients with thrombocytopenia or renal insufficiency, or in pregnant women with cancer, the literature search retrieved no study. For thrombocytopenia or renal insufficiency, we used the thresholds generally constituting exclusion criteria in clinical trials as a basis for discussion to reach consensus.

Recommendations.

1 A brain tumor *per se* is not a contraindication for anticoagulation for established VTE [Grade 2C].
Values and preferences: based on individual clinical assessment.

2 For the treatment of established VTE in cancer patients with a brain tumor we prefer LMWH [Best clinical practice, based on evidence of very low quality and a balance between desirable and undesirable effects to be assessed individually (high bleeding risk)].
Values and preferences: this opinion reflects the views of the panel group.

3 We recommend the use of LMWH or UFH commenced postoperatively for the prevention of VTE in cancer patients undergoing neurosurgery [Grade 1A].
Values and preferences: subcutaneous injections.

4 In the presence of severe renal failure (creatinine clearance < 30 mL min^{-1}) we suggest using UFH followed by early VKA (possible from day 1) or LMWH adjusted to anti-Xa level for the treatment of established VTE [Best clinical practice, in the absence of data and an unknown balance between desirable and undesirable effects].

5 In patients with severe renal failure (creatinine clearance < 30 mL min^{-1}), an ECD may be applied, and pharmacological prophylaxis may be considered on a case-by-case basis; in patients with severe renal failure (creatinine clearance < 30 mL min^{-1}), UFH can be used on a case-by-case basis [Best clinical practice, in the absence of data and a balance between desirable and undesirable effects depending on the level of VTE risk].

6 In cancer patients with thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is > 50 G L^{-1} and there is no evidence of bleeding; for patients with a platelet count below 50 G L^{-1}, decisions on treatment and dosage should be made on a case-by-case basis with the utmost caution [Best clinical practice, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk vs. VTE risk].

7 In cancer patients with mild thrombocytopenia, platelet count > 80 G L^{-1}, pharmacological prophylaxis may be used; if the platelet count is below 80 G L^{-1}, pharmacological prophylaxis may only be considered on a case-by-case basis and careful monitoring is recommended [Best clinical practice, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk vs. VTE risk].

8 In pregnant cancer patients, standard treatment for established VTE and standard prophylaxis should be implemented [Best clinical practice, in the absence of data and based on the contraindication of VKA during pregnancy].

Addendum

DF and HRB conceived and coordinated all the processes and the working group. PD and MB evaluated the quality of the studies in a double-blind manner using GRADE appraisal grids and provided the first draft of the supplemental tables. All authors participated in the working group, and contributed to data extraction and analysis, issue of recommendations and writing of a comprehensive technical report [Treatment of Venous Thromboembolism in Patients with Cancer. Copyright © 1093790 (OPIC 28/02/2012)], which served as the basis for the present manuscript. DF, PD, MB, HB, HRB and all the co-authors contributed to the elaboration of the guidelines. DF and PD elaborated the first draft of the manuscript, which was reviewed by HB and HRB.

Acknowledgements

Amsterdam, the Netherlands; M. Kruip, Erasmus University Medical Center, Rotterdam, the Netherlands; J-P. Laroche, Avignon, France; C. Le Hello, CHU Hôpital Côte de Nacre, Caen, France; A. Lee, BC Cancer Agency, Vancouver, Canada; A. Long, CHU Robert Debré, Reims, France; L. Mazzolai Duchosal, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; H-M. Otten, Slotervaart Hospital, Amsterdam, the Netherlands; K. Paraskevi, Laiko Hospital, Athènes, Greece; P. Perez-Segura, Hospital Clínico San Carlos, Madrid, Spain; G. Pernod, CHU de Grenoble, Grenoble, France; S. Rhodes, Great Western Hospitals NHS Foundation Trust, Swindon, United Kingdom; M. Righini, Hôpital Cantonal Genève, Genève, Switzerland; M-A. Sevestre, CHU d'Amiens, Amiens,France; A. Schrivastava, Vellore, India; H. Srtricker, Hôpital La Carità, Locarno, Switzerland; Z. Tazi, CHU Ibn Sina, Rabat, Morocco; L.M. Teixeira, Hôpital Saint-Antoine, Paris, France; A.J. Trujillo, Hospital General Santa María del Rosell, Cartagena, Murcia, Spain; L. Vidal de Verneix, Paris, France; S. Villiers, Hôpital Saint-Louis, Paris, France.

Disclosure of Conflict of Interests

Declarations of conflicts of interest have been provided to the editors.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Evidence-based medicine websites search.

Table S2. Treatment of VTE in cancer patients with vitamin K antagonists – retrospective studies.

Table S3. Treatment of VTE in cancer patients with vitamin K antagonists – prospective studies.

Table S4. Treatment of VTE in cancer patients with vitamin K antagonists – control arms of prospective randomized studies.

Table S5. LMWH in the initial treatment of venous thromboembolism – meta-analyses in the general population including cancer patients.

Table S6. Other studies on the treatment of VTE in cancer patients.

Table S7. Thrombolytic therapy.

Table S8. Vena cava filters.

Table S9. Prospective cohorts and randomized trials – long-term use of low-molecular-weight heparins.

Table S10. Meta-analyses.

Table S11. Other studies: idraparinux and duration of anticoagulation.

Table S12. Retrospective study – treatment of VTE recurrence.

Table S13. Randomized controlled trials – LMWH or UFH vs. placebo or no treatment and LMWH vs. UFH.

Table S14. Meta-analyses: LMWH or UFH vs. placebo or no treatment and LMWH vs. UFH.

Table S15. Randomized controlled trials – comparison of drugs and dose of LMWH.

Table S16. Randomized controlled trials – duration of prophylaxis.

Table S17. Extended prophylaxis meta-analysis.

Table S18. Randomized controlled trials: external compression device with intermittent compression device (ICD).

Table S19. Meta-analysis of studies in neurosurgical cancer patients: external compression device.

Table S20. Thromboprophylaxis with UFH vs. LMWH: randomized trials in general medical patients including cancer patients.

Table S21. Thromboprophylaxis with LMWH or fondaparinux: randomized double-blind trials in general medical patients including cancer patients.

Table S22. Prospective studies of primary prophylaxis of VTE in children with acute lymphocytic leukemia (ALL) treated with L-asparaginase.

Table S23. Ambulatory patients treated with chemotherapy.

Table S24. Studies of prophylaxis in patients with myeloma treated with thalidomide or lenalidomide.

Table S25. Meta-analysis: patients with myeloma treated with thalidomide or lenalidomide.

Table S26. Treatment of established VTE in patients with a brain tumor.

Table S27. VTE prophylaxis in cancer patients undergoing neurosurgery.

Table S28. Meta-analyses: VTE prophylaxis in neurosurgical cancer patients.

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