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ORIGINAL ARTICLE

International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer

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Summary. *Background:* Although long-term indwelling central venous catheters (CVCs) may lead to pulmonary embolism (PE) and loss of the CVC, there is lack of consensus on management of CVC-related thrombosis (CRT) in cancer patients and heterogeneity in clinical practices worldwide. *Objectives:* To establish common international Good

Clinical Practices Guidelines (GCPG) for the management of CRT in cancer patients. *Methods:* An international working group of experts was set up to develop GCPG according to an evidence-based medicine approach, using the GRADE system. *Results:* For the treatment of established CRT in cancer patients, we found no prospective randomized studies, two non-randomized prospective studies and one retrospective study examining the efficacy and safety of low-molecular-weight heparin (LMWH) plus vitamin K antagonists (VKAs). One retrospective study evaluated the benefit of CVC removal and two small retrospective studies were on thrombolytic drugs. For the treatment of symptomatic CRT, anticoagulant treatment (AC) is recommended for a minimum of 3 months; in this setting, LMWHs are suggested. VKAs can also be used, in the absence of direct comparisons of these two types of anticoagulants in this setting [Guidance]. The CVC can be kept in place if it is functional, well-positioned and non-infected and there is good resolution under close surveillance; whether the CVC is kept or removed, no standard approach in terms of AC duration has been established [Guidance]. For the prophylaxis of CRT in cancer patients, we found six randomized studies investigating the efficacy and safety of VKA vs. placebo or no treatment, one on the efficacy and safety of unfractionnated heparin, six on the value of LMWH, one double-blind randomized and one non randomized study on thrombolytic drugs and six meta-analyses of AC and CVC thromboprophylaxis. Type of catheter (open-ended like the Hickman® catheter vs. closed-ended catheter with a valve like the Groshong® catheter), its position (above, below or at the junction of the superior vena cava and the right atrium) and method of placement may influence the onset of CRT on the basis of six retrospective trials, four prospective non-randomized trials, three randomized trials and one meta-analysis. In light of these data: use of AC for routine prophylaxis of CRT is not recommended [1A]; a CVC should be inserted on the right side, in the jugular vein, and distal extremity of the CVC should be located at the junction of the superior vena cava and the right atrium [1A]. *Conclusion:* Dissemination and implementation of these international GCPG for the prevention and treatment of CRT in cancer patients at each national level is a major public health priority, needing worldwide collaboration.

Keywords: anticoagulant, cancer, catheter, clinical practice guidelines, GRADE system, thrombosis.

Introduction

Long-term central venous catheters (CVCs) are commonly used in patients with cancer, who require infusion chemotherapy and intravenous administration of supportive care treatments. However, the placement of a CVC may be complicated by the occurrence of thrombotic events. The reported incidence of CVC-associated thrombosis, defined as a mural thrombus extending from the catheter into the lumen of a vessel, and leading to partial or total catheter occlusion with or without clinical symptoms, varies widely between studies. In the review published by Klerk *et al.* [1], the incidence of symptomatic CVC-associated thrombosis ranged from 0 to 20% in cancer patients not receiving a prophylactic anticoagulant. Another review by Verso and Agnelli [2] reported an overall incidence of 4–5% (between 0 and 28% depending on the study) for symptomatic events and 30% (between 27 and 66%) for asymptomatic events detected by venography. In one prospective study of 444 consecutive cancer patients, 19 patients (4.3%) suffered a symptomatic CVC-related DVT at a median of 30 (range 6–162) days post-catheter placement, corresponding to an incidence of 0.3 per 1000 catheter-days (95% CI, 0.2–0.5) [3]. A prospective study of 2144 patients with peripherally inserted central venous catheters found a similar rate of thrombosis (3%) [4]. A number of factors may explain this variability, including differences in the definition of CVC-associated thrombosis, diagnostic procedures, study populations, CVC subtypes and CVC placement methods.

CVC-associated thrombosis therefore represents a major problem in contemporary oncology practice. It may notably lead to pulmonary embolism in 10–15% of patients and loss of the central venous access in 10% of patients [2]. From an economic perspective, it also accounts for a significant increase in direct treatment-related and management costs [5]. Several national and international guidelines for the prevention and treatment of VTE in cancer patients have been published recently [6–15]. However, so far, only one guideline has specifically addressed the issue of prophylaxis and treatment of CVC-associated thrombosis [12]. For this reason, plus in view of recent major publications on this topic, the wide diversity of clinical practices and the likely increase in the incidence of catheter thrombosis (related to the increasing incidence of cancer and a greater use of CVCs), 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. This working group developed harmonized guidelines for this setting, 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 concerning the prevention and treatment of catheter-related thrombosis (CRT) 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 HB) as well as two nurses.

Literature review and analysis

A literature search for all studies published in French or English between January 1996 and January 2011 was performed using the MEDLINE® and several other databases (e.g. EMBASE, CCTR, etc.) and the following subject headings: cancer, catheter, venous thromboembolism and anticoagulant drugs. A prospective follow-up of the literature was continued up to June 2011. Members of previous guideline working groups and authors of meta-analyses added references not found by the literature search, and data previously extracted [7–9,16]. National guidelines and several sites of evidence-based medicine were also consulted.

Meta-analyses, systematic reviews, randomized clinical trials, or non-randomized prospective or retrospective studies in the absence of randomized clinical trials, were included in the analysis. Editorials, letters to the editor, case reports, publications without an abstract, press releases and animal studies were excluded. Abstracts were included only if a full paper had been accepted in a peer-reviewed medical journal. The literature search was limited to publications in English or French.

The included studies concerned the prophylaxis and treatment of central catheter-related thrombosis in cancer patients. Studies in non-cancer patients with CVC, patients with a peripheral intravenous or dialysis catheter or patients with a history of cancer in remission for more than 5 years were not considered.

The main study outcomes were rates of proven CRT, extension of CRT, pulmonary embolism (PE) associated with CRT, major and minor bleeding, thrombocytopenia and death. Studies evaluating only the outcomes of catheter obstruction without vessel wall thrombosis, deep-vein thrombosis (DVT) of the lower limbs, PE unrelated to CRT and superficial-vein thrombosis, were not analyzed. 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 [17,18]. 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 working group members.

Consensus development

For each question, the results of the literature analysis were summarized and discussed by the 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 [19,20]. The level of evidence (Table 1) depended on the study design as well as on study limitations, inconsistency, indirectness, imprecision and publication bias [19,20]. 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) [19,20]. 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 encompassing all medical and surgical specialties involved in the management of patients with cancer, and three 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 appreciation of the document by a quantitative and qualitative evaluation. Discrepancies in

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

opinion between the reviewers and the members of the working group were resolved by consensus during a final meeting.

Results

Treatment of established catheter-related thrombosis

The literature search retrieved no prospective randomized study evaluating treatments for established CRT, and no study evaluating new oral anticoagulant agents in this setting.

Low-molecular-weight heparin (LMWH) + vitamin K antagonist (VKA) Only two non-randomized prospective studies [21,22] and one retrospective study [23] examined the efficacy and safety of LMWH + VKA in the treatment of CVC-associated thrombosis (Table S1). The study by Savage *et al.* [21] was performed in 46 outpatients with confirmed upper extremity DVT, of whom 34 (74%) had cancer and 16 (35%) had a CVC. Dalteparin (200 IU kg^{-1} once daily) was administered subcutaneously for a minimum of 5 days. Warfarin was usually initiated on the first day of anticoagulant therapy with a target INR of 2.0–3.0. Six of the 46 patients (13%) received dalteparin only for 10–90 days. Patients were followed for 12 weeks after diagnosis. Recurrence of DVT, confirmed by ultrasonography or venography, was reported in one patient (2.2%). No patient developed pulmonary embolism. Major bleeding occurred in one patient. In the second non-randomized prospective study in 74 patients with solid tumor and confirmed symptomatic CVC-associated VTE, of whom 30% had received mini-dose warfarin prophylaxis (1 mg day^{-1}), treatment consisted of dalteparin 200 IU kg^{-1} once daily administered subcutaneously for a minimum of 5 days followed by warfarin initiated on the first day with a target INR of 2.0–3.0 [22]. Patients were followed-up for 3 months. The primary outcome (catheter removal) occurred in 32 (43%) patients. In addition, CRT recurrence occurred in three (4.7%) patients and major bleeding was reported in seven patients (10.9%), one episode being fatal. In the retrospective study of 899 CVCs inserted in 498 patients, 39 patients experienced CRT, of whom 30 received heparin and nine warfarin for 3 months [23]. No PE, recurrent DVT or bleeding events were reported.

CVC removal One retrospective study evaluated the benefit of CVC removal in patients with CRT [24] (Table S1). In this study in 319 cancer patients, 112 (35%) exhibited CRT on radionuclide venography. Various therapeutic interventions, including anticoagulation with heparin or warfarin, or both, CVC removal, or a combination of these interventions, were performed. Altogether, the catheter was removed in 52% of these patients. Only four patients failed to show resolution of their presenting symptoms; in these cases, the CVC was removed. No patient experienced PE.

No reliable data on the optimal timing between CVC withdrawal and initiation of anticoagulant therapy, or on the optimal duration of anticoagulant treatment after catheter removal, were found.

Thrombolytic therapy The value of thrombolytic drugs in the treatment of CVC-associated thrombosis was assessed in two retrospective studies [25,26], each including few patients (Table S2).

The first study concerned 18 cancer patients receiving high-dose chemotherapy who developed CRT [26]. These patients were treated with urokinase (75 000–150 000 U h^{-1} for 24–96 h) infused into a vein of the ipsilateral upper extremity. Partial or complete resolution of clinical signs and symptoms was reported in all patients. A partial radiographic response was recorded for nine patients (50%). Recurrent CVC thrombosis was reported in 22% (4/18) of patients. Major bleeding was observed in four patients and minor bleeding in three.

The second study comprised a retrospective comparison of the efficacy of various thrombolytic drugs vs. LMWH in 57 patients with CRT [25]. Thirty-two patients received systemic treatment with a thrombolytic drug: streptokinase ($n = 16$), urokinase ($n = 5$), tissue plasminogen activator ($n = 4$) or a combination of streptokinase and urokinase ($n = 7$), followed by enoxaparin for 3 weeks, then VKA. Restoration of flow (as assessed by systematic Doppler ultrasonography) was observed in 16 patients (50%). No serious side-effects were seen. By comparison, in 25 patients treated with therapeutic doses of enoxaparin for 3 weeks followed by warfarin, restoration of flow was observed in only one patient (5%, $P = 0.009$ vs. thrombolytic drugs).

Discussion Our systematic review of studies evaluating the treatment of CVC-associated thrombosis found two non-randomized prospective studies of anticoagulation [21,22], one retrospective study of CVC removal [24], two retrospective studies of localized or systemic thrombolysis [25,26] and one retrospective study investigating a variable treatment approach (thrombolysis, CVC removal or anticoagulation) [23]. Although both the studies on anticoagulation and the two studies on thrombolysis found evidence of a favorable treatment response, the level of evidence was very poor. Thus, we conclude that there is insufficient evidence in cancer patients with CRT to support the use of LMWH + VKA or long-term LMWH, the withdrawal of a non-infected, functioning, well-positioned CVC, or thrombolytic therapy *via* the catheter, or systemic thrombolysis. On the basis of good-quality studies showing concordant results concerning the efficacy and safety of LMWH in the treatment of DVT of the lower limbs or PE in patients with cancer [27], the experts recommend that the use of LMWH alone, for a minimum of 3 months, should be considered for the treatment of CRT, depending on the clinical status of the patient.

The experts do not recommend catheter removal if all the following conditions are met: (i) the distal catheter tip is in the right position (at the junction between the superior vena cava and the right atrium), (ii) the catheter is functional (good blood reflux), (iii) the catheter is mandatory or vital for the patient, and (iv) there is no fever or any sign or symptom of infected thrombophlebitis. In contrast, catheter removal is warranted if there is a prime risk factor for thrombosis (catheter too short, misplaced, etc.). There are no reliable data permitting

determination of the optimal timing between CVC withdrawal and initiation of anticoagulant therapy, or of the optimal duration of anticoagulant treatment after catheter removal.

Published data demonstrated the feasibility of thrombolytic therapy in cancer patients, including those treated with intensive chemotherapy. The experts therefore proposed that, based on these data, the administration of thrombolytic drugs for the treatment of CRT may be considered only in specific circumstances, when the thrombotic risk is greater than the risk associated with the use of these drugs. In particular, thrombolytic treatment may be justified in the event of superior vena cava thrombosis associated with recent, poorly tolerated vena cava syndrome objectively confirmed (at least on a thoracic CT scan and/or by opacification of the superior vena cava) or if maintenance of a CVC is imperative.

The bases for these recommendations are: (i) CRT represents a triggered episode of VTE related to the CVC and the thrombophilia associated with the underlying cancer and its treatment; (ii) the risk of recurrence is high, as long as the CVC remains in place, so treatment should continue until the CVC is removed; (iii) most cancer patients will need another form of central venous access after CVC removal, and insertion of another CVC will probably place them at high risk of recurrent CVC-related VTE; (iv) it is likely that the underlying activation of coagulation associated with this triggered event will abate over a time course similar to that of other triggered VTEs (i.e. those related to surgery or trauma), so at least 3 months of anticoagulation should be sufficient; (v) once the CVC has been removed and at least 3 months of anticoagulation have been completed, patients with CVC-related VTE should be at low risk for recurrent VTE, as their thrombotic event required the presence of a CVC as a local trigger; (vi) two prospective studies (although of limited quality) suggested the efficacy of primary anticoagulation in the treatment of CVC-related VTE [21,22]; (vii) CVC removal is associated with the theoretical concern of thromboembolism on catheter withdrawal; and (viii) thrombolytic therapy may be superior to anticoagulation as regards thrombus dissolution and vessel patency, but will is also likely to be associated with a greater risk of bleeding complications [28].

In conclusion, randomized studies investigating the treatment of CVC-related VTE are clearly warranted to improve the evidence basis for the treatment of this common complication of cancer therapy.

Recommendations

1 For the treatment of symptomatic CRT in cancer patients, anticoagulant treatment is recommended for a minimum of 3 months; in this setting, LMWHs are suggested. Oral VKA can also be used, in the absence of direct comparisons of these two types of anticoagulants in this setting [Best clinical practice].'

2 The CVC can be kept in place if it is functional, well-positioned and non-infected with good resolution of symptoms under close surveillance; whether the CVC is kept or removed, no standard approach in terms of duration of anticoagulation is established [Best clinical practice].

Values and preferences: subcutaneous self-injections if an LMWH is used.

Prophylaxis of catheter-related thrombosis

VKA Six randomized studies [29–34] investigated the efficacy and safety of VKA vs. placebo or no treatment in the prevention of CRT in patients with cancer (Tables S3 and S4). In five studies [29–31,33,34], warfarin was administered at the once-daily dose of 1 mg day^{-1} without laboratory monitoring. In two studies, the dose of warfarin was adjusted to achieve an INR (international normalized ratio) between 1.3 and 1.9 [32], or between 1.5 and 2 [33]. Warfarin was started at various times relative to CVC insertion: 3 days before CVC insertion in three studies [29,33,34], on the day of CVC insertion in two studies [31,32], and 72 h after CVC insertion in one study [30]. The first of the six studies found a significant effect of VKA, compared with no treatment, in preventing any CRT (9.5% vs. 37.5%) and symptomatic CRT (9.5% vs. 32.5%); this effect was obtained without any increase in the risk of major bleeding [29]. VKAs were not significantly more effective than placebo or no treatment in four of the subsequent studies [30–33]. In one of these studies, the incidence of symptomatic CRT was lower in patients in whom warfarin was administered with a target INR between 1.5 and 2.0 than in patients receiving a fixed dose of warfarin (2.7% vs. 7.2%, respectively, $P = 0.002$); however, this benefit was obtained at the expense of an increase in major bleeding (3.4% vs. 1.5%, respectively; $P = 0.04$) [33]. Finally, in the sixth study warfarin was more effective than no treatment in preventing non-occlusive and asymptomatic CRT with no increase in bleeding risk [34]; however, the rate of occlusive CRT did not differ between the two groups.

Six meta-analyses evaluated the efficacy and safety of VKA in the prevention of CVC-associated thrombosis [35–40] (Table S5). None showed that VKA (either at a fixed low dose or with a target INR between 1.5 and 2.0) exerted a beneficial effect on the occurrence of symptomatic thromboses vs. placebo or no treatment. In one meta-analysis [38], fixed low doses of VKA were more effective than placebo in preventing both asymptomatic and symptomatic CRT (relative risk, 0.37; 95% CI, 0.26–0.52; $P < 0.001$) but not symptomatic CRT alone (relative risk, 0.60; 95% CI, 0.30–1.20). Of note, this meta-analysis was not specific to cancer patients. Furthermore, these meta-analyses included a number of non-randomized studies.

Unfractionated heparin (UFH) Only one randomized study evaluated the efficacy and safety of UFH in the prevention of CRT in 108 patients with hematologic diseases (patients undergoing bone marrow transplantation, including 34 with non-malignant diseases) [41] (Table S4). Patients (aged from 4 to 60 years) were randomly assigned to receive either UFH (100 U kg day^{-1}, $n = 65$) or saline ($n = 63$) by continuous intravenous infusion. The CVC were externalized, non-tunneled, double-lumen catheters. CVC-related

asymptomatic thrombosis occurred in 1.5% of the patients treated with heparin and 12.6% of the control patients ($P = 0.03$). Severe bleeding was reported in two and three patients in the heparin and control groups ($P = 0.18$), respectively. In conclusion, continuous intravenous infusion of UFH may decrease the incidence of symptomatic and asymptomatic CRT as diagnosed by ultrasonography in bone marrow transplant recipients (adults and children).

LMWH Six randomized studies assessing the value of LMWH in the prevention of CVC-associated thrombosis were analyzed [34,42–46] (Table S4). Subcutaneous dalteparin (2500 or 5000 IU day^{-1}) was used in three studies, nadroparin (2850 IU day^{-1}) in two studies and enoxaparin (40 mg day^{-1}) in one study. In five studies, the comparator was either placebo [44–46] or no treatment [34,42]. In the last two studies [34,42], LMWHs were significantly more effective than no treatment in preventing asymptomatic CRT. In the Decicco study, however, the rate of occlusive CRT did not differ between the LMWH and no treatment groups [34]. In addition, the beneficial effect of LMWH, in terms of preventing either asymptomatic or symptomatic thromboses, was not demonstrated in the three placebo-controlled studies [44–46]. In no study was LMWH administration associated with a significant increase in the risk of bleeding compared with placebo or no treatment. Overall, meta-analyses confirmed these findings, showing a trend towards better efficacy of LMWH compared with placebo or no treatment in preventing symptomatic and/or asymptomatic CRT [35,36,38,39] (Table S5). Of note, a meta-analysis combining seven studies comparing VKA, UFH or LMWH vs. placebo or no treatment in cancer patients with CVC showed a significant 44% reduction in the risk of symptomatic DVT in the group of anticoagulated patients (RR, 0.56; 95% CI, 0.34–0.92); there was no significant difference in the incidence of major bleeding between the two groups [36].

LMWHs (dalteparin and nadroparin) were compared with fixed low-dose VKA in two studies [34,43]. Neither study showed a statistically significant difference in safety between the two classes of drugs with respect to bleeding. In one study, nadroparin and warfarin showed similar efficacy in preventing asymptomatic and symptomatic CRT, although a trend was seen in favor of warfarin [43]. In the other study acenocoumarol was more effective than dalteparin in preventing non-occlusive and asymptomatic CRT events, but the rate of occlusive CRT did not differ between the two groups [34].

In conclusion, on the basis of six randomized trials of good methodological quality in patients with cancer, LMWH did not increase the bleeding risk, but also did not show any benefit in preventing symptomatic thromboses.

Thrombolytics One non-randomized prospective study [47] and one double-blind randomized study [48] investigated the efficacy and safety of thrombolytic drugs in the prevention of CRT (Table S6). The first study evaluated the effect of urokinase (10 000 IU infused in each catheter lumen for 4 h once a week) in 15 children with malignant disease (16 CVC); the results were compared with those obtained in a historical series of 15 children (19 CVC) who received no thromboprophylaxis [47]. On systematic ultrasonography (or magnetic resonance imaging if symptoms were present), the rate of CRT was significantly lower in the urokinase group (44%, 7/16 cases) than in the control group (82%, 9/11 cases) ($P = 0.047$). No bleeding complications were reported. In the second study, 160 cancer patients were randomized to receive either urokinase (5000 IU over 4 h once a week) or placebo [48]. The rate of CVC-related infection (primary outcome) did not differ between the two groups. Symptomatic confirmed CRT occurred in 1.2% of urokinase-treated patients and 6.4% of placebo-treated patients (RR placebo vs. urokinase, 2.22; 95% CI, 0.65–7.76).

Influence of type, position and method of insertion of the catheter Several factors may influence the occurrence of thrombosis in patients with CVC, including the type of catheter (open-ended, such as the Hickman® catheter, vs. closed-ended catheter with a valve, such as the Groshong® catheter), its position (above, below or at the junction of the superior vena cava and the right atrium) and the method of placement. The role of these factors in CRT was analyzed on the basis of six retrospective studies [49–54], four prospective non-randomized trials [3,55–57] (Table S7), three randomized trials [58–60] and one meta-analysis [61] (Table S8).

Closed-ended or valved catheters were compared with open-ended or non-valved catheters in two randomized studies [58,59]. Neither of these studies showed any significant difference between the two study groups in terms of CRT. The influence of the position of the catheter tip on CVC-associated thrombosis was assessed in six non-randomized studies [49–52,55–57]: in five of these studies [49,51,52,55,56], a higher rate of thrombosis was observed when the CVC tip was located above the junction between the superior vena cava and the right atrium. Three studies also reported that a left-sided insertion of CVC significantly increased the risk of thrombotic complications [50,51,53]. Other risk factors for symptomatic thrombosis were femoral vein placement of the CVC, a duration of placement exceeding 25 min [53], more than one CVC placement attempt, previous CVC insertion, CVC blockage [3], use of a triple (vs. double) lumen CVC [49], and external (vs. internal) CVC [54]. A meta-analysis of 5636 adult cancer patients fitted with a CVC enrolled in randomized controlled trials showed that, in terms of risk factors for CRT during catheter insertion, implanted ports were better than external catheters, and implantation in the jugular vein was better than implantation in the subclavian vein. This meta-analysis also confirmed that the rate of thrombosis was higher when the CVC tip was located above the junction between the superior vena cava and the right atrium [61]. Finally, one prospective randomized study showed that Doppler US guidance of CVC insertion did not confer any advantage [60].

Discussion CVC-related thrombosis is an important cause of morbidity in cancer patients [3,36]. Consequently, many investigators have attempted to identify an effective CVC-DVT prophylaxis regimen. An open, randomized study by Bern and colleagues suggested that low-dose warfarin (1 mg daily) could significantly reduce the incidence of CVC-DVT in cancer patients (37.5% vs. 9.5%) [29]. However, several subsequent randomized clinical trials failed to demonstrate any protective effect with fixed low-dose warfarin [30–33]. In the WARP study, a large multicenter open-label study comparing no warfarin, fixed-dose warfarin (1 mg daily) and adjusted-dose warfarin (INR 1.5–2.0), Young and colleagues demonstrated that adjusted-dose warfarin was associated with a significant reduction in CRT (13/473, 2.7% vs. 34/471, 7.2%; OR = 0.38; 95% CI, 0.20–0.71; $P = 0.002$), but also with a trend towards more major bleeding events (16/473, 3.4% vs. 7/471, 1.5%; $P = 0.04$), when compared with fixed-dose warfarin [33]. Randomized, controlled trials of LMWH showed similar results. A small, open-label randomized study conducted by Monreal *et al*. [42] demonstrated that dalteparin 2500 IU once daily significantly reduced CVC-DVT compared with no treatment (1/16, 6.2% vs. 8/13, 61.5%; $P = 0.002$). However, subsequent larger randomized trials evaluating prophylactic regimens of dalteparin, nadroparin and enoxaparin were unable to demonstrate reductions in CVC-DVT [34,44–46]. A small, open-label study of continuous infusion UFH (100 IU kg day^{-1}) performed in adult and pediatric bone marrow transplant patients showed a significant reduction in CVC-DVT (1/65, 1.5% vs. 8/63, 12.6%; $P = 0.03$) [41]. However, this regimen has not been replicated, perhaps because it is rather cumbersome and labor-intensive to administer.

Six meta-analyses of anticoagulant CVC thromboprophylaxis have been performed [35–40]. Carrier *et al*. and Kirkpatrick *et al*. did not note any reduction in symptomatic CVC-associated DVT [35,38], while Akl *et al*. found a 44% relative risk reduction in symptomatic CVC-DVT episodes when the results of all anticoagulant modalities were combined [40]. Kirkpatrick *et al*. [38] reported that VKA and LMWH were associated with a 63% and 28% relative risk reduction, respectively, in all CVC-DVTs (asymptomatic plus symptomatic), but these results were not confirmed by Chaukiyal *et al*., [39], possibly due to differences in study inclusion criteria. No study demonstrated the superiority of any antithrombotic regimen over another (e.g. VKA vs. LMWH). No differences in major bleeding or mortality between control patients and patients receiving anticoagulants were noted.

Two studies tested thrombolytic agents for the prevention of CVC-DVT [47,48]. In a small study in 30 pediatric oncology patients, Kalmanti *et al*. [47] found that 10 000 units of urokinase administered once weekly reduced the rate of CVC thrombosis from 81% (9/11) to 44% (7/16). No bleeding was noted. In contrast, van Rooden *et al*. [48] found no difference in symptomatic CRT, catheter-related and non-catheter-associated infections and premature catheter removal with 5000 units of urokinase administered three times weekly compared with placebo.

In conclusion, we consider that there is no evidence to support the routine use of LMWH, the routine use of low-dose VKA (warfarin 1 mg daily), the routine use of VKA to maintain an INR between 1.5 and 2, the use of continuous IV UFH or the use of fibrinolytics to prevent symptomatic CRT in comparison to no prophylaxis. It is acknowledged, however, that VKA may be used in certain circumstances when the risk of symptomatic CRT is considered to be very high, according to the treating physician's judgment.

Retrospective and prospective observational studies, as well as randomized controlled trials [58,59] and one meta-analysis [61], suggest that catheter insertion site (left > right, femoral > subclavian > jugular vein) and catheter tip location (superior vena cava > right atrium) can influence the risk of CVC-DVT. Previous CVC implantation and more than one insertion attempt were also found to be risk factors for CVC-DVT in one study [3]. Implanted ports may carry a lower thrombosis risk than peripheral indwelling central catheters or external CVCs [54]. In contrast, ultrasound-guided placement has not been shown to decrease the risk of CVC-DVT [60].

In summary, the existing literature does not support the use of routine thromboprophylaxis for CVC in cancer patients. The results of the WARP trial [33] suggest that more intensive anticoagulant regimens such as dose-adjusted warfarin may be promising, but more research is warranted to identify convenient, effective and safe regimens for CVC thromboprophylaxis, including those based on new oral anticoagulant agents. Catheter location can influence the risk of CVC-DVT, so low-risk locations should be preferred.

Recommendations

1 Use of anticoagulation for routine prophylaxis of CRT is not recommended [Grade 1A].
Values and preferences: bleeding risk with anticoagulants.

2 Catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium [Grade 1A].

Addendum

DF and HB coordinated the working group. PD and MB evaluated the quality of the studies in a double-blind manner using GRADE appraisal grids. All authors participated in the working group, and performed data extraction, data entry in evidence tables, analysis of the data, issue of recommendations and writing of a comprehensive report. PD elaborated the first draft of the manuscript. The manuscript was reviewed by DF, HRB and HB, who provided comments at the various stages of its development.

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Disclosure of conflict of interest

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. Treatment of catheter-related thrombosis: LMWH + VKA and catheter removal.

Table S2. Treatment of established catheter-related thrombosis: thrombolytics.

Table S3. Randomized studies: VKA in the prevention of catheter-related thrombosis (CRT).

Table S4. Randomized studies: heparins in the prevention of catheter-related thrombosis (CRT).

Table S5. Meta-analysis: anticoagulation (VKA, UFH and LMWH) in the prevention of catheter-related thrombosis (CRT).

Table S6. Fibrinolytics in the prophylaxis of catheter-related thrombosis (CRT).

Table S7. Influence of type, position and method of insertion of catheter in the primary prevention of CVC-associated thrombosis: non-randomized prospective trials and retrospective studies.

Table S8. Influence of type, position and method of insertion of catheter in the primary prevention of CVC-associated thrombosis: meta-analysis and prospective randomized trials.

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