review

2008 SOR guidelines for the prevention and treatment of thrombosis associated with central venous catheters in patients with cancer: report from the working group

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Background: In view of the lack of recommendations on central venous catheter (CVC)-associated thrombosis in cancer patients, we established guidelines according to the well-standardized Standards, Options and Recommendations methodology.

Material and methods: A literature review (1990–2007) on CVC-associated thrombosis was carried out. The guidelines were developed on the basis of the corresponding levels of evidence derived from analysis of the 36 of 175 publications selected. They were then peer reviewed by 65 independent experts.

Results: For the prevention of CVC-associated thrombosis, the distal tip of the CVC should be placed at the junction between the superior cava vein and right atrium; anticoagulants are not recommended. Treatment of CVC-associated thrombosis should be based on the prolonged use of low-molecular weight heparins. Maintenance of the catheter is justified if it is mandatory, functional, in the right position, and not infected, with a favorable clinical evolution under close monitoring; anticoagulant treatment should then be continued as long as the catheter is present.

Conclusions: Several rigorous studies do not support the use of anticoagulants for the prevention of CVC-associated thrombosis. Treatment of CVC-associated thrombosis relies on the same principles as those applied in the treatment of established thrombosis in cancer patients.

Key words: cancer, catheter, clinical practice guidelines, heparin, thrombosis, vitamin K antagonists

introduction

Long-term central venous catheters (CVCs) are commonly used in patients with cancer. Their placement may be complicated by the occurrence 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. In recent reviews in cancer patients, the incidence of symptomatic and asymptomatic CVC-associated thrombosis ranged between 0% and 28% and between 12 and 66%, respectively [1–4]. CVC-associated thrombosis may result in pulmonary embolism in 10%–15% of patients and loss of 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].

So far, no international recommendations focusing specifically on both the prophylaxis and treatment of CVC-associated thrombosis in patients with cancer (including the role of placement techniques) have been published [6]. For this reason, but also in view of recent major publications on this topic, wide heterogeneities in clinical practices, and a likely increase in the incidence of catheter thrombosis (related to an increasing incidence of cancer and a greater use of CVC), a multidisciplinary working group was set up by the French National Federation of Cancer Centers (Fédération Nationale des Centres de Lutte Contre le Cancer) to develop national guidelines for this setting according to the well-standardized procedure of the Standards, Options and Recommendations

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(SOR). Initiated in 1993, the SOR program was set up to develop guidelines for the standardization of 'good clinical practice' throughout the various disciplines involved in cancer care [7–10]. Its methodology is based on a literature review and a critical appraisal by a multidisciplinary working group of experts [11]. It involves the cooperation of French regional cancer centers, both public and private practice sectors, scientific societies, and the French National Cancer Institute, which has led this program since May 2008.

materials and methods

literature review and analysis
A literature review of the studies published between January 1999 and January 2007 was carried out using the MEDLINE database and the following subject headings: cancer, thrombosis, and catheter. A prospective follow-up of the literature on this subject (meta-analyses and prospective studies only) was continued up to January 2008. National guidelines and several Evidence-Based Medicine sites were also consulted. The literature search was limited to publications in English or in French.

Meta-analyses, systematic reviews, randomized clinical trials, or nonrandomized 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.

We selected studies on adults and children with solid tumors or hematologic malignancies and a CVC with or without a history of thromboembolic events since the guidelines were established for both the prevention and treatment of CVC-associated thrombosis. We also analyzed publications on the role of catheter placement in CVC-associated thrombosis. We excluded studies concerning malfunctioning of catheters not related to thrombosis; these latter events are generally due to an intraluminal thrombus without mural involvement, the formation of a fibrin sleeve around the catheter, or compression of the catheter between the medial portion of the clavicle and the anterior face of the first rib (pinch-off syndrome). Likewise, we excluded studies concerning only patients with no cancer or patients with a cancer in remission for more than 5 years, a tumor-associated thrombosis, thrombocytopenia, or a catheter infection. Studies focusing on methods of diagnosing CVC-associated thrombosis were not analyzed.

For the prevention studies, the outcomes analyzed were signs and symptoms of thrombosis, asymptomatic or symptomatic thrombosis objectively confirmed (Doppler ultrasonography, contrast venography, or scanner), pulmonary embolism, or major bleeding. For the treatment studies, the outcomes analyzed were recurrence of thrombosis, pulmonary embolism, or major bleeding [12].

critical appraisal and data extraction
The quality of the studies was evaluated with a validated reading grid assessing their methods and clinical relevance [13]. Two reviewers (Lise Bosquet, Diana Kassab Chahmi) extracted the data in a double-blind manner. Any discrepancies between reviewers were resolved by consensus.

consensus development
Following the selection and critical appraisal of the articles, a first version of the guidelines was established based on the conclusions, the corresponding levels of evidence, and 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). In these guidelines, the recommendations were classified as Standards or Options (Table 2). The document was then peer reviewed in November 2007 by 65

Table 1. Definition of levels of evidence

Level	Definition
Level A	Based on one or several high-quality meta-analyses or on several high-quality randomized clinical trials with consistent results
Level B	Based on good quality evidence from randomized trials (B1) or prospective or retrospective studies (B2), with consistent results when considered together
Level C	Based on studies that are weak, with inconsistent results when considered together
Level D	Absence of any scientific data or only a series of cases available

Table 2. Classification of recommendations

Recommendations	Definition
Standards	Procedures or treatments considered to be the 'gold standard' by unanimous decision of the experts
Options	Procedures or treatments acknowledged to be appropriate by the experts; one of the options may be preferred by the experts

independent experts encompassing all the medical and surgical specialties involved in the management of patients with cancer [including oncologists (33%), anesthesiologists and surgeons (9%), and hematologists (5%)] according to the AGREE grid [11], and their comments were integrated in the final version in February 2008.

results

primary prevention of CVC-associated thrombosis in patients with cancer

literature search results. Out of 175 publications on CVC-associated thrombosis, 31 publications on the primary prevention of this event in patients with cancer were identified and used for developing these guidelines [14–44].

efficacy and safety of vitamin K antagonists. Five randomized studies [14–18] investigated the efficacy and safety of vitamin K antagonists (VKA) in the prevention of CVC-associated thrombosis in patients with cancer (Table 3). In four studies [14–17], warfarin was administered at the once-daily dose of 1 mg/day without laboratory monitoring. In two studies, warfarin was given in order to achieve an INR (international normalized ratio) between 1.3 and 1.9 [17] or 1.5 and 2 [18]. Only the oldest study found a significant effect of VKA, compared with no treatment, in preventing CVC-associated thrombosis; this effect was obtained without increasing the risk of major bleeding [14]. VKA were not significantly more effective than placebo or no treatment in the four other later studies [15–18]. Interestingly, the percentage of CVC-associated thrombosis was lower in patients in whom warfarin was administered with a target INR between 1.5 and 2.0 than in

Table 3. Vitamin K antagonists in the primary prevention of CVC-associated thrombosis in patients with cancer: randomized studies from 1990 to 2007

Reference; study date	Type of patients; type of catheter	No. of patients recruited	Treatment	Catheter flushing	Follow-up	End points	Results
Bern et al. [14]; not specified	Solid tumors and lymphoma; CVC in subclavian vein (Port-a-cath)	121 patients (82 patients analyzed)	A: warfarin (1 mg/day) for 90 days; B: no treatment	UFH (up to 500 U/week)	90 days	Asymptomatic CVC-associated DVT (venography)	A: 9.5% (9/42); B: 37.5% (15/40), $P < 0.001$
Heaton et al. [15]; not specified	Hematologic malignancies; CVC in subclavian vein (double-lumen CVC)	88 patients (102 CVC but 88 CVC analyzed)	A: warfarin (1 mg/day); B: no treatment	Hickman®: UFH (50 µg, 2×/day); Groshong®: saline	90 days	Symptomatic thrombosis (confirmed by venography)	A: 17.8% (8/45, with two CVC-associated DVT and six intraluminal thromboses); B: 11.6% (5/43, with one CVC-associated DVT and four intraluminal thromboses), P = NS
Couban et al. [16]; 1999–2002	Solid tumors (20%), hematologic malignancies (80%); CVC (tunneled and implanted)	255 patients; 255 CVC	A: warfarin (1 mg/day) for 8 weeks (median); B: placebo for 9 weeks (median)	Not specified	25 weeks (range 1–184 weeks)	1. Symptomatic, CVC-associated thrombosis during CVC life span (confirmed by US or venography) 2. Death 3. Major bleeding	1. A: 4.6% (6/130), B: 4.0% (5/125), P = NS 2. A: 17% (22/130), B: 17% (21/125), P = NS 3. A: 0% (0/130), B: 2% (3/125), P = NS
Young et al. [17]; not specified	Solid tumors (52% colorectal cancer), hematologic malignancies; CVC (location not specified)	1589 patients (90% analyzed)	A: warfarin (1 mg/day) for 8 weeks (median); B: warfarin (INR: 1.5–2.0); C: no treatment	Not specified	Not specified	1. Symptomatic, CVC-associated thrombosis (radiologically proven) 2. Major bleeding	1. A: 7%, B: 3%, A + B: 5%, C: 6%, A versus B: $P < 0.01$, A + B versus C: P = NS 2. A: 2%, B: 4%, A + B: 2%, C: 0.2%, A versus B: P = NS, A + B versus C: P = NS
Ruud et al. [18]; 2002–2003	Cancer (children); CVC in jugular vein	73 patients (62 patients analyzed)	A: warfarin (INR: 1.3–1.9); B: no treatment	Not specified	Not specified	1. Asymptomatic, CVC-associated jugular thrombosis (US at 1, 3, and 6 months) 2. Symptomatic DVT (CVC-associated thrombosis and PE) 3. Major bleeding	1. A: 48%, B: 36%, P = NS 2. A: one symptomatic DVT, B: one symptomatic DVT 3. A: two major bleeds, B: zero major bleed

CVC, central venous catheter; DVT, deep vein thrombosis; INR, international normalized ratio; NS, not significant; PE, pulmonary embolism; UFH, unfractionated heparin; US, ultrasonography; VKA, vitamin K antagonists.

patients with a fixed dose of warfarin (3% versus 7%, respectively, $P < 0.01$); however, this was obtained at the expense of a nonsignificant increase in major bleeding (4% versus 2%, respectively) [17].

Five meta-analyses evaluated the efficacy and safety of VKA in the prevention of CVC-associated thrombosis [19–23] (Table 4). 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 versus placebo or no treatment. However, in one meta-analysis [21], fixed low doses of VKA were more effective than placebo in preventing both asymptomatic and symptomatic CVC-associated thrombosis [relative risk = 0.37 (95% confidence interval 0.26–0.52), $P < 0.001$). Of note, this meta-analysis was not specific to cancer patients. Furthermore, these meta-analyses included a number of nonrandomized studies.

In view of the known interaction between VKA and 5-fluorouracil (5-FU), two retrospective studies (in 95 and 72 patients, respectively) [24, 25] and one noncomparative prospective study (in 247 patients with gastrointestinal cancer) [26] analyzed the effect of warfarin (1 mg/day) in cancer patients with a CVC receiving this cytotoxic drug. All showed an INR increase >1.5 in 5-FU-treated patients; depending on the study, this increase was reported in 33%–50% of patients. In one study [24], the INR was >3.0 in 19% of patients. Major hemorrhages were reported in 3.2%–8% of patients, 90% of these occurring in patients with a high INR.

In conclusion, the incidence of CVC-associated thrombosis in patients with cancer depended on the study. In the most recent studies, the rate of thrombosis was comparable with or without a prophylactic anticoagulant drug (∼5% with regard to symptomatic thromboses) (level of evidence: A). Fixed low doses of VKA (1 mg/day) with an INR <1.5 were not effective in preventing venous thrombosis associated with a superior vena cava catheter in patients with cancer (level of evidence: B1). Published data showed that the combination of low-dose VKA with 5-FU may be harmful (INR increase with consequent bleeding risk) (level of evidence: B2).

efficacy and safety of unfractionated heparin. Only one randomized study evaluated the efficacy and safety of unfractionated heparin (UFH) in the prevention of CVC-associated thrombosis in 108 patients with hematologic diseases (including 34 with non-malignant diseases) [27]. Patients (aged from 4 to 60 years) were randomly assigned to receive either UFH (100 U/kg/day, $n = 65$) or saline ($n = 63$) by continuous i.v. infusion. The CVC were externalized, nontunneled, 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, respectively, in the heparin and control groups ($P = 0.18$).

Due to the limited number of patients and their clinical specificity (bone marrow transplantation), it was not possible to conclude on the efficacy and safety of UFH in the primary prevention of CVC-associated thrombosis in patients with cancer (level of evidence: nonevaluable).

efficacy and safety of low-molecular weight heparins. Six randomized studies assessing the value of low-molecular weight heparins (LMWH) in the prevention of CVC-associated thrombosis were analyzed (Table 5) [28–33]. Subcutaneous dalteparin (2500 or 5000 IU/day) was used in three studies, nadroparin (2850 IU/day) in two studies, and enoxaparin (40 mg/day) in one study.

In five studies, the comparator was either placebo [29, 30, 33] or no treatment [28, 32]. In these last two studies [28, 32], LMWH were significantly more effective in preventing asymptomatic CVC-associated thrombosis than no treatment. However, the beneficial preventive effect of LMWH, in terms of either asymptomatic or symptomatic thromboses, was not demonstrated in the three large placebo-controlled studies [30, 31, 33]. In no study was LMWH administration associated with a significant increase in the risk of bleeding. Overall, the various meta-analyses confirmed these results (Table 4). Of note, a meta-analysis combining seven studies comparing VKA, UFH, or LMWH versus placebo or no treatment in cancer patients with CVC showed that the risk of symptomatic deep vein thrombosis was significantly reduced by 44% in the group of anticoagulated patients [relative risk = 0.56 (95% confidence interval 0.34–0.92)]; there was no significant difference in the incidence of major bleeding between the two groups [22].

LMWH (dalteparin and nadroparin) were compared with fixed low-dose VKA in two studies [29, 32]. Neither study showed a statistically significant difference between the two classes of drugs in either hemorrhagic safety or efficacy. However, a meta-analysis of these two studies showed that LMWH were less effective than VKA in preventing both asymptomatic and symptomatic CVC-associated deep vein thrombosis [relative risk = 1.88 (95% confidence interval 1.28–2.75)].

In conclusion, on the basis of five concordant randomized trials of good methodological quality in patients with cancer, LMWH did not show any benefit in preventing symptomatic thromboses of the superior cava veins; however, they did not increase the bleeding risk (level of evidence: A) [21].

efficacy and safety of thrombolytic drugs. Only one nonrandomized prospective study investigated the efficacy and safety of thrombolytic drugs in the prevention of CVC-associated thrombosis [34]. This study evaluated the effect of urokinase (10 000 IU in each catheter lumen for 4 h once a week) in 15 children (16 CVC) with malignant disease; the results were compared with those obtained in a historical series of 15 children (19 CVC) without thromboprophylaxis. On systematic ultrasonography, the rate of asymptomatic thrombosis was significantly lower in the urokinase group (44%, 7 of 16 cases) than in the control group (82%, 9 of 11 cases) ($P = 0.047$). No hemorrhagic complications were reported.

In view of the limited number of patients, it was not possible to conclude on the efficacy and safety of thrombolytic drugs in the primary prevention of CVC-associated thrombosis in patients with cancer (level of evidence: nonevaluable).

influence of type, position, and method of insertion of the catheter. A number of factors may influence the occurrence of thrombosis in patients with CVC, including the type of catheter (open-ended, such as the Hickman® catheter, versus

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Table 4. Anticoagulant drugs in the primary prevention of CVC-associated thrombosis: meta-analyses from 1990 to 2007

Reference	Number of studies analyzed; period of study selection	No. of patients; treatment	Thrombosis	Other outcomes
Carrier et al. [19]	Seven studies; 1950–2007	2131 patients; VKA (warfarin 1 mg) or LMWH	Symptomatic CVC-related thrombosis (defined as upper extremity DVT or CVC occlusion); VKA versus control: RR (95% CI) = 0.82 (0.46–1.47); LMWH versus control: RR (95% CI) = 0.43 (0.12–1.56); VKA or LMWH versus control: RR (95% CI) = 0.71 (0.42–1.20)	–
Rawson and Newburn-Cook [20]	Four studies; 1966–2007	1236 patients; VKA (warfarin 1 mg or INR > 1.5)	CVC-related thrombosis (symptomatic and asymptomatic); VKA versus control: risk difference (95% CI) = 2.0% (−9.0% to +5.0%]	–
Kirkpatrick et al. [21]	15 studies (10 studies on only cancer patients); 1964–2006	1714 patients; VKA (fixed low dose) or LMWH	CVC-related DVT (symptomatic and asymptomatic); VKA versus control: RR (95% CI) = 0.37 (0.26–0.52), P < 0.001; LMWH versus control: RR (95% CI) = 0.72 (0.57–0.90), P = 0.045; LMWH versus VKA: RR (95% CI) = 1.88 (1.28–2.75) CVC-related DVT (symptomatic); VKA versus control: RR (95% CI) = 0.60 (0.30–1.20); LMWH versus control: RR (95% CI) = 0.69 (0.30–1.59)	Major bleeding: VKA versus control: RR (95% CI) = 0.24 (0.03–2.13); LMWH versus control: RR (95% CI) = 0.66 (0.12–3.68)
Akl et al. [22]	Nine studies; from 1966	852 patients for asymptomatic DVT and 1859 patients for symptomatic DVT; VKA or heparin (UFH or LMWH)	Asymptomatic DVT: VKA versus control: RR (95% CI) = 0.56 (0.10–2.99); LMWH versus control: RR (95% CI) = 0.84 (0.52–1.36); Heparin versus control: RR (95% CI) = 0.82 (0.51–1.32); VKA or heparin versus control: RR (95% CI) = 0.82 (0.73–1.68) Symptomatic DVT: VKA versus control: RR (95% CI) = 0.62 (0.30–1.27); LMWH versus control: RR [95% CI] = 0.49 [0.17-1.39] - Heparin *vs* control: RR (95% CI) = 0.43 (0.18–1.06); VKA or heparin versus control: RR (95% CI) = 0.56 (0.34–0.92); P < 0.05	Major bleeding: Heparin versus control: RR (95% CI) = 0.68 (0.10–4.78); VKA or heparin versus control: RR (95% CI) = 1.83 (0.34–9.87) Death: LMWH versus control: RR (95% CI) = 0.73 (0.39–1.36); heparin versus control: RR (95% CI) = 0.74 (0.40–1.36); VKA or heparin versus control: RR (95% CI) = 0.74 (0.40–1.36)
Chaukiyal et al. [23]	Eight studies; 1966–2006	1428 patients; VKA (warfarin 1 mg) or heparin (UFH or LMWH)	CVC-related thrombosis (symptomatic and asymptomatic): VKA versus control: RR (95% CI) = 0.75 (0.24–2.35); Heparin versus control: RR (95% CI) = 0.46 (0.18–1.20); P = 0.06; VKA or heparin versus control: RR (95% CI) = 0.59 (0.31–1.13); P = 0.11; VKA versus LMWH: RR (95% CI) = 1.71 (0.56–5.26)	Major bleeding: VKA versus control: RR (95% CI) = 0.14 (0.01–2.63); heparin versus *s* control: RR (95% CI) = 0.41 (0.05–3.30); VKA or heparin versus control: RR (95% CI) = 0.44 (0.12–1.67)

CI, confidence interval; CVC, central venous catheter; DVT, deep vein thrombosis; INR, international normalized ratio; LMWH, low-molecular weight heparins; RR, relative risk; UFH, unfractionated heparin; VKA: vitamin K antagonists.

Table 5. Low-molecular weight heparins in the primary prevention of CVC-associated thrombosis in patients with cancer: randomized studies from 1990 to 2007

Reference; study date	Type of patients; type of catheter	No. of patients	Treatment	Catheter flushing	Follow-up	End points	Results
Monreal et al. [28]; 1993–1995	Solid tumors; CVC (Port-a-cath)	32 patients; (29 patients analyzed)	A: dalteparin (2500 IU/day); B: no treatment	Heparinized saline (10 ml, once a week)	90 days	1. Asymptomatic CVC-associated DVT (venography) 2. Major bleeding	1. A: 6.2% (1/16), B: 61.5% (8/13), $P = 0.002$ 2. A: one patient, B: zero patient
Mismetti et al. [29]; 1998–2000	Solid tumors; CVC (totally implantable port-system CVC) in subclavian (95%) or jugular vein	59 patients (45 patients analyzed)	A: nadroparin (2850 IU/day) for 90 days; B: warfarin (1 mg/day) for 90 days	Saline (10 ml) and heparinized saline (500 U, 5 ml)	6 months	1. Asymptomatic and symptomatic CVC-associated DVT (venography) at 90 days 2. All VTE events at 90 days 3. All VTE events at 6 months 4. Major bleeding	1. A: 28.6% (6/21), B: 16.7% (4/24), $P = $ NS 2. A: 31.8%, B: 16.7%, $P = $ NS 3. A: 36.4%, B: 16.7%, $P = $ NS 4. A: one patient, B: zero patient
Verso et al. [30]; 2000–2003	Solid tumors (54% of gastrointestinal cancer), hematologic malignancies (9%); CVC (polyurethane or silicone) in subclavian (89%) or other vein	385 patients (310 patients analyzed)	A: enoxaparin (40 mg/day) for 6 weeks; B: placebo for 6 weeks	Not specified	3 months	1. Composite of asymptomatic or symptomatic upper limb DVT (venography) or symptomatic PE 2. Major bleeding 3. Death	1. A: 14.1% (22/155), B: 18.0% (28/155), $P = $ NS 2. A: 0, B: 0 3. A: 2.6% (5/191), B: 1.0% (1/194)
Karthaus et al. [31]; 1999–2001	Solid tumors (90%), hematologic malignancies; CVC	439 patients (425 patients analyzed)	A: dalteparin (5000 IU/day) for 16 weeks; B: placebo for 16 weeks	UFH (500 U) in saline solution during CVC use	16 weeks	1. Symptomatic CVC-associated DVT (venography, US, CT scan) 2. Asymptomatic CVC-associated DVT (venography, US) 3. Bleeding events	1. A: 3.7% (11/294), B: 3.4% (5/145), $P = $ NS 2. A: 3.4% (10/294), B: 4.1% (6/145), $P = $ NS 3. A: 17.5% (50/285), B: 15.0% (21/140), $P = $ NS
DeCicco et al. [32]; not specified	Cancer; CVC	450 patients (348 patients analyzed)	A: acenocoumarin (1 mg/day) initiated 3 days before CVC insertion and continued for 8 days after CVC insertion; B: dalteparin (5000 IU/day) for 8 days after CVC insertion; C: no treatment	Not specified	Not specified	1. Asymptomatic CVC-associated DVT (venography) 2. PE 3. Major bleeding	1. A: 21.9%, B: 40%, C: 55.3%; A versus B: $P = 0.003$; A versus C: $P < 0.001$; B versus C: $P < 0.02$ 2. No PE 3. No major bleeding
Niers et al. [33]; not specified	Hematologic malignancies; CVC (chemotherapy and stem-cell transplantation)	113 patients (87 patients analyzed)	A: nadroparin (2850 IU/day) for 3 weeks; B: placebo for 3 weeks	Not specified	3 weeks	1. Asymptomatic CVC-associated DVT (venography) 2. Major bleeding	1. A: 17% (7/41), B: 9% (4/46), $P = 0.49$ 2. A: 0, B: 0

CVC, central venous catheter; DVT, deep-vein thrombosis; NS, not significant; PE, pulmonary embolism; UFH, unfractionated heparin; US, ultrasonography; VTE, venous thromboembolism.

closed-ended catheter with a valve, such as the Groshong® catheter), its position (above, below, or at the junction of the superior cava vein and the right atrium), and the method of placement. The analysis of the role of these factors in CVC-associated thrombosis was based on two randomized studies, five nonrandomized prospective studies, and four retrospective series (Tables 6– 8) [35–44].

Closed-ended or valved catheters were compared with open-ended or nonvalved catheters in two randomized studies (Table 6) [35, 36]. None of these studies showed any significant difference between the two study groups in terms of symptomatic thrombosis.

The influence of the position of the catheter tip on CVC-associated thrombosis was assessed in six nonrandomized studies: in four of these studies [38, 41, 43, 44], a higher rate of thrombosis was observed when the CVC tip was located above the junction between the superior cava vein and the right atrium. Three studies also reported that a left-sided insertion of CVC significantly increased the risk of thrombotic complications [39, 42, 43]. Other risk factors for symptomatic thrombosis were femoral position of the CVC, a duration of placement >25 min [39], and more than one CVC placement attempt [40].

In conclusion, the concordant data of these studies highlighted the lower thrombogenicity of some placement characteristics of CVC, i.e. (i) distal tip at the junction of the superior cava vein and the right atrium (level of evidence: B2) and (ii) whenever possible, right-sided insertion (level of evidence: B2). Conversely, various placement characteristics increase the risk of CVC-associated thrombosis, i.e. (i) number of attempts (more than two) and duration of placement (level of evidence: D) and (ii) placement of the CVC in a femoral vein (level of evidence: D).

treatment of CVC-associated thrombosis in patients with cancer

literature search results. Out of 175 publications on CVC-associated thrombosis, five publications on the curative treatment of CVC-associated thrombosis in patients with cancer were identified and used for developing these guidelines [45–49].

efficacy and safety of LMWH. Only one nonrandomized prospective study examined the efficacy and safety of LMWH in the treatment of CVC-associated thrombosis [45]. In this study, 46 outpatients (34 with a cancer and 16 with a CVC) with confirmed upper extremity deep vein thrombosis were treated with dalteparin (200 IU/kg once daily for a minimum of 5 days) followed by warfarin (target INR: 2.0–3.0); at 12 weeks, there was one recurrence of deep vein thrombosis confirmed by Doppler ultrasonography or venography and one major bleeding.

Based on the published data (only one low-quality study), it was not possible to conclude on the efficacy and safety of short-term LMWH followed by VKA in the curative treatment of CVC-associated thrombosis in patients with cancer (level of evidence: nonevaluable).

However, the experts proposed that, on the basis of good quality studies showing concordant results concerning the efficacy and safety of LMWH given for 3–6 months in the treatment of deep vein thrombosis of lower limbs or pulmonary

Table 6. Influence of type, position, and method of insertion of catheter in the primary prevention of CVC-associated thrombosis: randomized studies from 1990 to 2007

Reference; study date	Type of study; type of patients	No. of patients recruited	Treatment	Catheter flushing	Follow-up	End points	Results
Biffi et al. [35]; 1997–1998	Randomized study; solid tumors	304 patients (302 CVC)	A: 8.0-F, silastic Groshong® CVC; B: 9.6-F, silastic, open-ended CVC	Saline (20 ml), then heparinized saline after each CVC use (5 ml at 50 U/ml)	237 days	1. Asymptomatic and asymptomatic DVT in internal jugular or subclavian vein (venography) 2. CVC removal 3. Clinically relevant bleeding	1. A: 3.9% (6/152), B: 7.3% (11/150), P = NS 2. A: 2.7% (4/152), B: 3.3% (5/150) 3. No clinically relevant bleeding
Carlo et al. [36]; not specified	Randomized study; solid tumors	73 patients	A: valved port; B: nonvalved port	A: saline (10 ml); B: heparinized saline (10 ml)	180 days or until CVC removal	Symptomatic thrombosis of internal jugular vein	A: 2.7% (1/37), B: 2.8% (1/36), P = NS

CVC, central-venous catheter; DVT, deep vein thrombosis; NS, not significant.

Table 7. Influence of type, position, and method of insertion of catheter in the primary prevention of CVC-associated thrombosis: prospective studies from 1990 to 2007

Reference; study date	Type of study; type of patients	No. of patients recruited	Treatment	Catheter flushing	Follow-up	End points	Results
Nightingale et al. [37]; 1993–1994	Nonrandomized prospective comparative study; gastrointestinal cancer; tunneled CVC in right subclavian (727), left subclavian (81), right femoral (two) or jugular (one) vein	949 patients; (832 patients analyzed)	Warfarin (1 mg/day)	Heparinized saline	Not specified	1. Thrombotic complications leading to CVC removal 2. Predictive factor for CVC removal (multivariate analysis)	1. 4.7% (38/817); if distal CVC tip in SVC: 3.5% (20/569); if distal CVC tip in right atrium: 2.5%, (4/160), $P = $ NS 2. CVC in SVC: HR ([95% CI] = 2.57)
Luciani et al. [38]; 1995–1998	Nonrandomized prospective comparative study; oropharyngeal tract cancer; totally implantable CVC	145 patients (113 CVC)	Not specified	Saline (10 ml), then heparinized saline (5 ml at 50 U/ml)	>3 years	Asymptomatic and symptomatic CVC-associated DVT (Doppler US)	11.7% (17/145), 76% of which were asymptomatic 1. If distal CVC tip in the SVC or at the junction between SVC and right atrium: 6% (5/87); if distal CVC tip above the junction between SVC and right atrium: 46% (12/26), $P < 0.001$ 2. Left-sided CVC: 65% (11/17); right-sided CVC: 35% (6/17), $P = $ NS
Morazin et al. [39]; 1995–1999	Nonrandomized prospective comparative study; solid tumors (50% breast cancer); tunneled CVC (silicone)	5447 CVC	Not specified	Not specified	Up to CVC removal	Predictive factors for symptomatic CVC-associated DVT (venography, Doppler US, contrast computed tomography) (multivariate analysis)	2.5% (135/5447) 1. Left subclavian vein + jugular vein versus right subclavian vein: RR = 2.6, $P < 0.001$ 2. Femoral vein versus right subclavian vein: RR = 6.5, $P < 0.001$ 3. Placement duration >25 min versus ≤25 min: RR = 1.52, $P = 0.02$

Table 7. (Continued)

Reference; study date	Type of study; type of patients	No. of patients recruited	Treatment	Catheter flushing	Follow-up	End points	Results
Lee et al. [40]; 2002–2003	Nonrandomized prospective comparative study; solid tumors (66%); hematologic malignancies (34%); all types of CVC in the upper limb vasculature	444 patients (555 CVC)	Not specified	Implanted ports: heparinized saline (100 U/ml); other CVC: saline	Up to CVC removal + 4 weeks or up to 52 weeks after CVC insertion	Predictive factors for symptomatic CVC-associated DVT (US, venography, contrast computed tomography, or magnetic resonance imaging) (multivariate analysis)	1. >1 insertion attempts: OR (95% CI) = 5.5 (1.2–24.6), $P = 0.03$ 2. Previous CVC insertion: OR (95% CI) = 3.8 (1.4–10.4), $P = 0.01$ 3. CVC blockage: OR (95% CI) = 14.7 (5.5–40), $P < 0.001$

CI, confidence interval; CVC, central venous catheter; DVT, deep vein thrombosis; HR, hazard ratio; NS, not significant; OR, odds ratio; RR, relative risk; SVC, superior vena cava; US, ultrasonography.

embolism in patients with cancer [50], the prolonged use of LMWH alone may be considered for the treatment of CVC-associated thrombosis, depending on the clinical status of the patient. By analogy with the management of patients with venous thromboembolism and renal insufficiency [51], the experts recommended that in the event of severe renal impairment, the treatment should be based on the use of UFH, rapidly followed (possibly as early as the first day) by VKA.

efficacy and safety of thrombolytic drugs. The value of thrombolytic drugs in the treatment of CVC-associated thrombosis was assessed in two nonrandomized prospective studies [46, 47] and one retrospective study [48], each with a limited number of patients. In the first, small study, only four adults and one child with cancer and CVC-associated thrombosis were treated with a continuous infusion of both recombinant tissue-type plasminogen activator (0.5 mg/kg per 24 h, preceded by a 5-mg bolus injection in adult patients or a 2-mg bolus injection in the child) and UFH for 4.5–7.9 days [46]. The treatment was effective in resolving large vessel obstruction without bleeding in three out of five patients. Partial lysis of the thrombus and moderately severe hemorrhage were observed in the other two patients.

The second study concerned 18 cancer patients receiving high-dose chemotherapy who developed CVC-associated thrombosis [47]. These patients were treated with urokinase (750 00–150 000 U/h for 24–96 h) infused into a vein of the ipsilateral upper limb. A partial or complete resolution of clinical signs and symptoms was reported in all patients. A partial radiographic response was found in nine patients (50%). Major bleeding was observed in four patients.

The third study was a retrospective comparison of the efficacy of various thrombolytic drugs versus LMWH in 57 patients with CVC-associated thrombosis [48]. Thirty-two patients received a thrombolytic drug, streptokinase ($n = 16$), urokinase ($n = 5$), tissue plasminogen activator ($n = 4$), or a combination of streptokinase and urokinase ($n = 7$), via a systematic route. Repermeabilization (as assessed by systematic Doppler ultrasonography) was observed in 16 patients (50%). No serious side-effects were observed. By comparison, in 25 patients treated with curative doses of enoxaparin for 3 weeks followed by warfarin, repermeabilization was observed in only one patient (5%, $P = 0.009$ versus thrombolytic drugs).

In conclusion, it was not possible to conclude on the efficacy and safety of thrombolytic drugs, administered either systemically or locally. Published data have shown the feasibility of their administration, including in patients treated with intensive chemotherapy (level of evidence: D).

Thus, the experts proposed that, based on published data, the administration of thrombolytic drugs for the treatment of CVC-associated thrombosis may only be considered in specific circumstances, in which the thrombotic risk is superior to the risk associated with the use of these drugs, i.e. in the event of superior vena cava thrombosis associated with recent, poorly tolerated, vena cava syndrome objectively confirmed (at least on a thoracic computed tomography scan and/or opacification of the superior vena cava), or imperative maintenance of a CVC.

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Table 8. Influence of type, position, and method of insertion of catheter in the primary prevention of CVC-associated thrombosis: retrospective studies from 1990 to 2007

Reference; study date	Type of study; type of patients	No. of patients recruited	Treatment	Catheter flushing	Follow-up	End points	Results
Eastridge and Lefor [41]; 1989–1992	Nonrandomized retrospective comparative study; solid tumors (51%); hematologic malignancies (49%); tunneled CVC (65%); implantable CVC (35%)	274 patients (332 CVC)	Not specified	Heparinized saline (3 ml/day at 100 U/ml)	Not specified	Predictive factors for symptomatic CVC-associated DVT (venography or clinical follow-up)	1. Position of CVC tip: above third dorsal vertebra = 78% of patients with CVC-associated thrombosis (versus 37% if below third dorsal vertebra), $P < 0.05$ 2. Triple lumen CVC = 21% (10/48); double lumen CVC = 7% (11/160), $P < 0.05$ 3. Implantable CVC = 6% (7/113); tunneled CVC = 10% (21/209), $P = $ NS
Craft et al. [42]; not specified	Nonrandomized retrospective comparative study; solid tumors (48%); hematologic malignancies (41%); tunneled CVC (Hickman®)	122 patients (120 patients analyzed); 153 CVC (150 CVC analyzed)	Not specified	Heparinized saline	55 days (range 1–650)	Predictive factors for symptomatic CVC-associated DVT (venography)	1. Position of CVC tip: junction right atrium SVC or lower third of SVC: 8.2%%; upper third of SVC: 7.5%, $P = $ NS 2. Side of CVC: right sided: 5%; left sided: 19%, RR (95% CI) = 4.4 (1.2–16), $P = 0.04$
Cadman et al. [43]; 1996–2001	Randomly sampled retrospective study; solid tumors (69%); hematologic malignancies (31%); tunneled CVC	334 patients (448 CVC)	Not specified	Not specified	72 days (range 1–720)	Predictive factors for symptomatic CVC-associated DVT (venography, Doppler US)	9% (30/334) 1. Position of CVC tip: right atrium: 0%; lower third of SVC: 2.6%; middle third of SVC: 5.3%; upper third of SVC: 41.7%, $P < 0.005$ 2. Side of CVC placement: right sided: 6.8%; left sided: 25.6%, $P < 0.001$
Caers et al. [44]; 1993–1998	Nonrandomized retrospective comparative study; solid tumors (84%); hematologic malignancies (13%)	437 patients (448 CVC)	Not specified	Saline (10 ml), then heparinized saline (5 ml at 100 U/ml)	–	Predictive factors for symptomatic CVC-associated DVT (venography, Doppler US) (multivariate analysis)	8.5% (37/437) 1. CVC tip in the brachiocephalic vein: OR (95% CI) = 64.7 (7.6–553.8) 2. CVC tip in the cranial part of the SVC: OR (95% CI) = 17.4 (2.0–148.8)

CI, confidence interval; CVC, central venous catheter; DVT, deep vein thrombosis; NS, not significant; OR, odds ratio; RR, relative risk; SVC, superior vena cava; US, ultrasonography.

evaluation of catheter removal. One retrospective study evaluated the benefit of CVC removal in patients with CVC-associated thrombosis [49]. In this study, in 319 cancer patients, 112 (35%) exhibited CVC-associated thrombosis on radionuclide venography. Various therapeutic interventions, including anticoagulation with heparin or warfarin or both; line removal or replacement; or a combination thereof, were carried out. Overall, the catheter was removed in 52% of these patients. Only four patients did not show resolution of their presenting symptoms; they were treated by line replacement. No patient experienced pulmonary embolism.

In conclusion, the published data are insufficient (only one retrospective study with methodological biases) to conclude on the value of catheter removal. In the event of catheter removal, no data were reported on the optimal interval between removal and initiation of anticoagulant treatment (level of evidence: nonevaluable).

The experts did 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 on the optimal duration of anticoagulant treatment after catheter removal.

conclusion

Based on the literature review and the well-argued judgment of experts, the 2008 SOR guidelines for the prevention and treatment of CVC-associated thrombosis in patients with cancer are as follows.

primary prevention of CVC-associated thrombosis in patients with cancer

standards.
1 The distal tip of CVC should be placed at the junction between the superior vena cava and the right atrium.
2 The primary prevention of CVC-associated thrombosis with anticoagulant drugs is not recommended in patients with cancer.

options.
1 Right-sided insertion and placement of the CVC in a specialized unit should be favored.

treatment of CVC-associated thrombosis in patients with cancer

standards.
1 The treatment of CVC-associated thrombosis should be based on the prolonged use of LMWH.
2 In the event of severe renal impairment, the treatment should be based on the use of UFH, rapidly followed (possibly as early as the first day) by VKA.

3 Maintenance of the catheter is justified in the event that the catheter is mandatory, functional, in the right position, and not infected, with a favorable clinical evolution under close monitoring. In this case, an anticoagulant treatment should be maintained as long as the catheter is present.
4 In the event of catheter removal, there is no standard approach in terms of the interval between removal and initiation of anticoagulant treatment.

options.
1 If it is necessary to place a new catheter, the status of the superior vena cava network should be evaluated by a scan or Doppler ultrasonography.
2 In the event of refusal or impossibility of a prolonged treatment with LMWH, short-term use of LMWH followed by VKA may be proposed.
3 Thrombolytic drugs may be considered in specialized units in the event of poor clinical tolerance (vena cava syndrome) and in the absence of any contraindications.
4 There are no reliable data on the optimal duration of anticoagulant treatment after catheter removal.

Of note, for all recommendations classified as 'Options', further research is warranted. Moreover, none of these recommendations applies to patients with tumor-associated thrombosis or to patients with catheters that are malfunctioning for reasons other than thrombosis (fibrin sleeve, pinch-off, intraluminal thrombus), infected catheters, or femoral catheters.

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