REVIEW ARTICLE

Venous Thromboembolism Associated With Long-Term Use of Central Venous Catheters in Cancer Patients

By Melina Verso and Giancarlo Agnelli

Abstract: **Long-term central venous catheters (CVCs) have considerably improved the management of cancer patients because they facilitate chemotherapy, transfusions, parenteral nutrition, and blood sampling. However, the use of long-term CVCs, especially for chemotherapy, has been associated with the occurrence of upper-limb deep venous thrombosis (UL-DVT). The incidence of clinically overt UL-DVT related to CVCs has been reported to vary between 0.3% and 28.3%. The incidence of CVC-related UL-DVT screened by venography reportedly varies between 27% and 66%. The incidence of clinically overt pulmonary embolism (PE) in patients with CVC-related UL-DVT ranges from 15% to 25%, but an autopsy-proven PE rate of up to 50% has been reported. Vessel injury caused by the procedure of CVC insertion, venous stasis caused by the indwelling CVC, and cancer-related hypercoagulability are the main pathogenetic factors for CVC-related venous thromboembolism (VTE). Several studies have assessed the benefit of the prophylaxis of UL-DVT after CVC insertion in cancer patients. According to the results of these studies, prophylaxis with low molecular weight heparin or a low fixed dose of warfarin has been recently proposed. However, the limitations of the experimental design of the prophylactic studies do not allow definitive recommendations. The recommended therapy for UL-DVT associated with CVC is based on anticoagulant therapy with or without catheter removal. This review focuses on the epidemiology, pathogenesis, diagnosis, prevention, and treatment of VTE in cancer patients with long-term CVC.**

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IN THE last few years, several types of long-term central venous catheters (CVCs) have been introduced in clinical practice. The first long-term CVC was introduced in 1973 by Broviac for parenteral nutrition.[1] The Hickman catheter, a silastic, right atrial device, was the first permanent venous-access device used on a large scale for cancer chemotherapy.[2] In the early 1980s, totally implantable port systems were introduced in clinical practice,[3] followed, more recently, by peripherally implanted central catheters (PICCs).[4]

In cancer patients, the use of long-term CVCs facilitates chemotherapy, transfusions, parenteral nutrition, and blood sampling for laboratory testing. The ideal CVC should have the following features: ease of insertion, possibility of discontinuous long-term use, low infective risk, low back-bleeding risk, and low thrombogenicity. CVCs can be classified as partially or totally implantable (Table 1). The partially implanted CVCs are indicated for short-term daily in-hospital therapy, whereas the totally implanted CVCs are preferred for use with prolonged cyclic chemotherapy in outpatients. The site of insertion for a CVC is either the subclavian vein or the internal or external jugular vein. PICCs can be inserted in the cephalic, basilic, or brachial vein.[5]

To reduce the invasiveness of the insertion procedures, the majority of CVCs are positioned with fluoroscopic or ultrasonographic guidance. However, a surgical (cutdown approach)[6] or a bedside-blinded technique, on the basis of the anatomic-landmark method, is possible.

The use of long-term CVC is associated with complications that may occur early, during the insertion procedure, or later, during the catheter dwell. Among the early complications are catheter misplacement or breakage, pneumothorax and hemothorax, air embolism, and injury to adjacent anatomic structures.[7,8] The estimated rate of these complications ranges from 0.3% to 12%.[7] Among the late complications are catheter occlusion by catheter sleeve, local or systemic infection, and CVC-related deep venous thrombosis (DVT).

The catheter sleeve is an adherent coating of fibrin and collagen that envelopes the CVC, and is occurring in up to 47% of the patients.[9-11] The catheter sleeve is in itself a benign complication, but it interferes with the catheter function, facilitates the development of local infection and sepsis, and may lead to mural thrombosis.[12]

Catheter-related infection is observed in 2% to 43% of patients.[7] The risk of infection is particularly high in neutropenic patients or patients who have undergone transplantation.[13] Available data suggest that subclavian catheters are less likely to result in CVC-related infection than are internal jugular catheters, although the two approaches have not been compared in randomized trials.[14] The subcutaneous ports have a significantly

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Table 1. Classification of Central Venous Catheters

CVC Types	Main Components	Subtypes
Totally implantable CVCs (ports)	Reservoir or port	Open tip or closed tip
	Central line	Low profile or standard profile Single or double system
Partially implantable CVCs	Subcutaneous Dacron* cuff	Tunneled or nontunneled
	Central line	Single or multiple lumen(s) With or without valve Open tip or closed tip

Abbreviation: CVC, central venous catheter.
*E.I. du Pont de Nemours and Company, Wilmington, DE.

lower incidence of CVC removal for sepsis than the partially implantable catheters.[15] This lower rate of infection is presumably because of the protection of the CVC from contamination by skin bacteria. In two prospective, randomized trials, the use of antimicrobial-impregnated CVCs was associated with reduced rates of catheter colonization and CVC-related bloodstream infection, as compared with unimpregnated CVCs.[16,17] Thus, the choice of the subclavian site, the subcutaneous ports, and the antimicrobial-impregnated CVCs seem to minimize the risk of infectious complications.

Venous thromboembolism (VTE) is one of the leading causes of death in cancer patients.[18] Patients with clinically overt cancer may develop VTE at any stage of their disease. This risk is significantly increased after cancer surgery and during chemotherapy. CVCs used for chemotherapy recently have been recognized as an additional risk factor for thrombosis in cancer patients. This review focuses on the epidemiology, pathogenesis, diagnosis, prevention, and treatment of VTE in cancer patients with long-term CVC. Epidemiologic studies, clinical trials, and case reports, identified through a MEDLINE search and a complementary manual search on reference lists of relevant articles, were reviewed.

EPIDEMIOLOGY OF CVC-RELATED VTE

The incidence of VTE associated with long-term CVC in cancer patients has been assessed in a number of studies. However, the careful definition of this incidence has been hampered by some inconsistencies among the studies. These include differences in study design and study population, lack of standardization of the technique of CVC insertion, inconsistency in the definition of the VTE events (the difficulty in distinguishing mural thrombosis from CVC occlusion by catheter sleeve), differences in the quality of patient surveillance, and different accuracy of the diagnostic tests used to confirm thrombosis.

The reported incidence of symptomatic catheter-related DVT in adult patients varies from 0.3% to 28.3% (Table 2).[19-66] Although the rate of symptomatic CVC-related DVT in pediatric patients has been reported to be as high as 12%,[39,47,61,67-69] the majority of studies report a much lower rate of 0% to 3.1%. The incidence of CVC-related DVT assessed by venography has been reported to vary from 27% to 66%[23,70-82] (Table 3). Most of the thrombi in these studies were asymptomatic.

The estimated incidence of CVC-related DVT has been found similar for subclavian and jugular access.[10,58,83] A recent study reported a high incidence of DVT, diagnosed by color-Doppler ultrasonography (US), after short-term catheterization of the right internal jugular vein with triple-lumen CVCs in patients undergoing cardiac surgery.[84]

De Cicco et al[80] prospectively evaluated the distribution of upper-limb (UL)-DVT in 127 cancer patients undergoing CVC insertion. Venography-documented UL-DVT was observed in 66% of the patients, with prevalent involvement of subclavian vein versus innominate or superior caval veins (97%, 60%, and 13%, respectively; $P < .001$). Balestrieri et al[78] assessed the features of the thrombi in cancer patients with long-term CVC. UL-DVT was shown at venography in 56% of the patients (32 of 57); in 81.2% of patients DVT was nonocclusive, whereas it was occlusive in the remaining patients. Similar venography features have been reported by Martin et al,[10] who found that 71.4% of the DVT were partially occlusive and 28.6% were completely occlusive DVT.

Thrombotic complications associated with the use of PICCs are less common but not infrequent: the symptomatic DVT rate ranges from 1% to 4%,[57,85] whereas the venographic DVT rate was reported to be 23%.[85] PICC lines are also associated with a high rate of clinically overt thrombophlebitis of the cephalic and basilic veins.[9,86,87] In a study by Cowl et al,[87] the complication-free delivery rate (DVT and/or superficial thrombophlebitis) was higher with CVC than with PICCs lines (67% *v* 46%; $P < .05$). In a recent study, Grove et al[57] showed in a multivariate analysis that the PICC diameter is a determinant for the thrombosis rate (0% for CVC < 3 French [F], 1% for 4 F, 6.6% for 5 F, and 9.8% for 6 F).

A number of studies compared the incidence of UL-DVT observed with different types of long-term CVC (mainly ports *v* partially implantable CVCs), but only a few studies were prospective[88,89] and randomized[36,60] trials. Indirect comparisons showed a lower incidence of CVC-related DVT in patients with subcutaneous ports versus partially implantable catheters.[36] Recently, Biffi et al[60] have compared venous ports connected to standard open-ended or to Groshong catheters in 302 cancer patients and showed a similar incidence of thromboembolic complications with the two access devices.

Pierce et al[90] assessed whether heparin bonding (HB)-CVCs reduce thrombotic and infective complications in critically ill children. The results of this prospective, randomized trial showed a significant reduction in terms of incidence of thrombotic and infective complications associated with the use of HB-CVCs (symptomatic DVT rate, 0% *v* 8%, $P = .006$; infection rate, 4% *v* 33%, $P < .0005$).

It has been suggested that during the first weeks after CVC insertion, cancer patients are at particularly high risk for UL-DVT.[91] De Cicco et al[80] reported a 64% and 98% incidence of thrombosis at day 8 and day 30 after CVC insertion, respectively. Luciani et al[92] reported a mean interval of 42.2 days between CVC insertion and detection of thrombosis.

In conclusion, although the epidemiology of CVC-associated VTE needs to be further refined, this complication seems to be an

Table 2. Incidence of Clinically Overt CVC-Related DVT in Cancer Patients

Author	Year	Study Design	Population	No. of CVCs	CVC-Related DVT (%)
Blackett[19]	1978	Prospective	Adults	178	4.5
Di Costanzo[20]	1980	Prospective	Adults	250	4.4
Padberg[21]	1981	Retrospective	Adults	175	4.8
Smith[22]	1983	Retrospective	Adults	2800	0.3
Lokich[23]	1983	Prospective and retrospective	Adults	53	28.3
Wagman[24]	1984	Prospective	Adults	55	10.0
Soto-Velasco[25]	1984	Retrospective	Adults	1611	0.7
Raaf[26]	1985	Prospective	Adults	826	0.7
Lokich[27]	1985	Retrospective	Adults	92	16.3
Stanislav[28]	1987	Retrospective	Adults	115	7.8
Cassidy[29]	1987	Prospective	Adults	416	2.6
Moss[30]	1989	Prospective	Adults	190	3.7
Wenke[31]	1990	Prospective	Adults	82	3.6
Jansen[32]	1990	Prospective	Adults	123	4.1
Haire[33]	1990	Prospective	Adults	162	12.9
Mertz[34]	1990	Prospective	Children*	52	1.9
Rau[35]	1991	Prospective	Adults	78	3.2
Mueller[36]	1992	Prospective	Adults	92	6.0
Gould[37]	1993	Prospective	Adults	255	14.5
Torromade[38]	1993	Prospective	Adults	234	10.0
Wesenberg[39]	1993	Prospective	Children	77	0
Soh[40]	1993	Prospective	Adults	22	5.0
Anderson[41]	1995	Prospective	Adults	168	17.0
Eastridge[42]	1995	Prospective	Adults	322	10.0
Horne[43]	1995	Prospective	Adults	50	21.0
Loughran[44]	1995	Retrospective	Adults	322	0.3
Laurenzi[45]	1996	Retrospective	Adults	223	3.0
Cunningham[46]	1996	Prospective	Adults	18	26.0
Kock[13]	1996	Retrospective	Adults	1500	2.5
Dobois[47]	1997	Prospective	Children	285	0.3
Nightingale[48]	1997	Prospective	Adults	949	4.7
McBride[49]	1997	Prospective	Adults	253	3.5
Meisenberg[50]	1997	Retrospective	Adults	177	4.8
Wilimas[51]	1998	Prospective	Children	23	12.0
Martin[10]	1999	Prospective	Adults†	60	11.6
O'Neill[52]	1999	Retrospective	Adults	110	9.0
Lyon[53]	1999	Retrospective	Adults	409	2.2
Knofler[54]	1999	Prospective	Children	77	14.0
Schwarz[55]	2000	Prospective	Adults	923	3.1
Lagro[56]	2000	Prospective	Adults	390	6.9
Grove[57]	2000	Prospective	Adults	813	4.5
Trerotola[58]	2000	Retrospective	Adults	774	16.0
Hartkamp[59]	2000	Prospective	Adults	126	7.3
Povoski[6]	2001	Prospective	Adults	100	5.0
Biffi[60]	2001	Prospective	Adults	304	6.6
Molinari[61]	2001	Retrospective	Children	362	2.2
Coccaro[62]	2001	Prospective	Adults	98	2.1
Chemaly[63]	2002	Retrospective	Adults	2063	2.5
Fijnheer[64]	2002	Prospective	Adults	277	4.7
Harter[65]	2002	Prospective	Adults	233	1.5
Kuriakose[66]	2002	Prospective	Adults	422	7.1

Abbreviations: CVC, central venous catheter; DVT, deep venous thrombosis.
*Critically ill children.
†Intensive care unit patients.

emerging clinical problem. There is no conclusive evidence that a particular type of CVC is more or less thrombogenic than others. Most of the thrombi are nonocclusive. The analysis of the time course of CVC-associated VTE indicates that the first 6 weeks after CVC insertion present the highest risk of thromboembolic complications.

PATHOGENESIS OF CVC-RELATED DVT

The pathogenesis of UL-DVT in patients with CVC is probably multifactorial. Vessel injury caused by the procedure of CVC insertion, venous stasis caused by indwelling CVC, and cancer-related hypercoagulability contribute to the development of UL-DVT.

Table 3. Incidence of Venographic CVC-Related DVT in Cancer Patients

Author	Year	Study Design	Population	No. of CVCs	CVC-Related DVT (%)
Stoney[70]	1976	Prospective	Adults	203	31.0
Ladefoged[71]	1978	Retrospective	Adults	48	27.1
Burt[72]	1981	Prospective	Adults	21	33.3
Valerio[73]	1981	Prospective	Adults	22	27.3
Brismar[74]	1982	Prospective	Adults	53	35.8
Bozetti[75]	1983	Prospective	Adults	52	28.8
Lokich[23]	1983	Prospective and retrospective	Adults	53	41.5
Pottecher[76]	1984	Prospective	Adults	52	38.5
Bern[77]	1990*	Retrospective, controlled	Adults	42	37.5
Balestrieri[78]	1995	Prospective	Adults	57	56.0
Monreal[79]	1996*	Retrospective, controlled	Adults	29	62.0
De Cicco[80]	1997	Prospective	Adults	127	66.0
Martin[10]	1999	Prospective	Adults‡	60	58.3
Glaser[81]	2001	Prospective	Children	24	50.0
Frank[82]	2000†	Retrospective	Adults	319	35.1

NOTE. Most thrombi in these studies were asymptomatic.
Abbreviations: CVC, central venous catheter; DVT, deep venous thrombosis.
*In the control group.
†Radionuclide venography.
‡Intensive care unit patients.

The loss of vessel integrity caused by the procedure of CVC insertion determines changes in the endothelial cells with production of procoagulant factors and activation of platelets and blood coagulation. These events could cause, usually within 24 hours from CVC insertion, the formation of a fresh thrombus, which is reversible in the large majority of patients. In some patients, the persistence of the CVC stimulus determines the formation of collagen that induces the stabilization of the thrombus.[11] Over the long term, the indwelling CVC determines the development of intimal hyperplasia. This is probably caused by chronic intermittent injury to the vein wall resulting from knocking and rubbing movements of the catheter against the wall.[93]

A number of risk factors have been hypothesized for the development of CVC-related DVT, such as CVC biocompatibility (ie, chemical structure, rigidity, diameter, surface structure, and presence of additive agents), number of lumens, catheter tip position, side of insertion, CVC insertion techniques, previous CVC insertions and catheter-related complications (mainly CVC malfunction or infections), and high platelet count (Table 4).

Borow et al[94] demonstrated that both silicone and polyurethane CVCs are less thrombogenic compared with polyvinylchloride and polyethylene CVCs. Eastridge et al[42] showed a significantly higher incidence of thrombotic complications in patients with triple-lumen catheters than with dual-lumen catheters (20.1% in 12 F triple-lumen Hickman CVC *v* 6.9% in 10 F double-lumen Hickman CVC; $P < .05$).

The position of the catheter tip emerged as an independent risk factor for the development of thrombotic complications.[95] It is recommended that the tip of a long-term CVC be located at the junction of the superior caval vein and the right atrium.[96] Luciani et al[92] have recently demonstrated that a correct positioning of the distal catheter tip is associated with a significantly lower rate of CVC-related UL-DVT. In particular, only five (6%) of 87 patients with a correctly positioned CVC tip developed thrombosis, compared with 12 (46%) of 26 patients with a misplaced catheter tip ($P < .001$). In a randomized study, catheter tip location in the superior caval vein was compared with location in the axillary and subclavian-innominate veins, demonstrating an increased risk of thrombosis with peripheral (compared with central) tip location (60% *v* 21%; $P < .05$).[97] The correlation between the CVC tip position and the incidence of thrombosis was confirmed by Puel et al,[95] who found that eight of 10 patients with thrombosis had the catheter located in the innominate vein. In a prospective study of 949 patients with gastrointestinal malignancy, the risk of CVC removal for catheter tips located in the superior caval vein was 2.6 times that of catheter

Table 4. Risk Factors for Development of CVC-Related DVT

CVC Features	Patient Features
Chemical structure[94]	High platelet count[33]
Catheter diameter[57]	Cancer-related activation of coagulation cascade[109]
Numbers of lumens[42]	CVC-related activation of coagulation cascade[108]
Catheter tip positions[48,57,92,95,96,97]	Chemotherapy-related activation of coagulation cascade[110]
Side of insertion[37,80,95,100]	Thrombophilic molecular abnormalities[64,81,112-114]
Insertion techniques[32,35,49,101-104]	
Previous CVC insertion[105]	
CVC-related infections[12,106-107]	

Abbreviations: CVC, central venous catheter; DVT, deep venous thrombosis.

tips located in the right atrium ($P = .003$).[48] Alternatively, cardiac complications such as cardiac tamponade[98] and severe arrhythmias[99] have been reported when the catheter tip was located in the right atrium.

It has also been reported that the left-sided insertion of the CVC leads to an increased risk of thrombotic complications[37,80,95,100]. In the study by De Cicco et al,[80] the rate of CVC-related DVT was higher in the left arm than in the right arm (87.5% *v* 62%, respectively; $P < .01$). This could be due to the anatomic difference between the venous systems of the ULs.

The insertion technique and the radiologic or surgical approach can influence the rate of thrombotic complications both in adult[32,35,49,101,102] and pediatric[103] cancer patients. In a prospective, comparative study, the ultrasonographic-assisted cannulation, compared with the external landmark-guided technique, reduced the rate of thrombotic complications in patients with a CVC in the internal jugular vein.[104]

Previous CVC insertion is to be considered a risk factor for UL-DVT. Approximately 40% of patients with a history of previous long-term CVC were found to have evidence of thrombosis in one or more central veins at duplex scanning.[105]

Catheter infection may contribute to the pathogenesis of thromboembolic complications.[12,106,107] Microscopic examination revealed that the catheter sleeve, which is rich in fibrin and fibronectin, could promote the adherence on the catheter of bacteria (mainly *Staphylococcus aureus* and *S epidermidis*) and mycetes (mainly *Candida albicans*).[12] These microorganisms are able to produce a coagulase enzyme that enhances the thrombogenic process. The postmortem evidence of mural thrombosis on catheterized veins was correlated with premortem microbiologic data.[12] A correlation between mural thrombi and colonization of catheters or sepsis was observed: sepsis was found in seven of 31 patients with mural thrombi versus none of 41 patients without postmortem evidence of mural thrombi ($P < .01$).

More than 80% of indwelling CVCs are associated with measurable thrombin activity at the time of removal.[108] The catheter-related thrombin activity suggests that physiologic anticoagulant mechanisms are unable to inactivate surface-bound thrombin because it is relatively resistant to inhibition by antithrombin III.

A high platelet count at the time of catheter insertion seems to be correlated with the rate of thrombotic complications in cancer patients. Haire et al[33] reported a lower risk of CVC-related DVT in cancer patients with a low platelet count.

The abnormalities of blood coagulation associated with adenocarcinomas and the type and intensity of chemotherapy can be considered contributing factors for venous thromboembolic events.[109] Brown et al[110] found no differences in thrombotic complications for patients receiving different regimens of chemotherapy (push or bolus *v* infusional regimens) and home-based versus hospital-based chemotherapy administration.

Finally, the prevalence of thrombophilic molecular abnormalities in cancer patients with CVC-related DVT is controversial.[54,64,81,111-114] De Cicco et al[111] suggested that a reduced level of antithrombin III is a risk factor for CVC-related DVT. Riordan et al[112] reported a low prevalence of factor V Leiden gene mutation in cancer patients with CVC-related DVT (7% of patients had a heterozygous mutation). Wermes et al[113] found a DVT in 67% of patients with acute lymphoblastic leukemia and genetic mutation (factor V G1691A, prothrombin G20210A, and homozygous methyl tetrahydrofolate reductase variant) as compared with 21% of patients without genetic mutation. Similarly, Fijnheer et al[64] reported a CVC-related DVT in 54% of patients with heterozygous factor V Leiden, who received CVC for bone marrow transplantation. The authors concluded that the genetic mutations seem to be an additional risk factor for the development of DVT in cancer patients.

In conclusion, the pathogenesis of UL-DVT in patients with CVC is probably multifactorial. Early thromboembolic events are essentially related to the loss of vessel integrity caused by CVC placement. Late thromboembolic events are probably related to CVC features, insertion technique, catheter tip position, and occurrence of catheter infection. The role of thrombophilic molecular abnormalities is less clear.

CLINICAL ASPECTS OF CVC-RELATED DVT

The majority of patients with CVC-related DVT is asymptomatic or have nonspecific symptoms. De Cicco et al[80] reported that only 6% of patients with CVC-related DVT, screened by venography, were symptomatic. CVC-related DVT is more frequently asymptomatic than UL-DVT not associated with CVC, probably because thrombosis is less acute and less commonly occlusive.[115] The clinical presentation of UL-DVT includes arm swelling, erythema, pain, distal paresthesias, neck swelling, headache, and congestion of subcutaneous collateral veins. Shoulder pain was reported as a peculiar symptom in CVC patients.[48]

CVC malfunctioning may be the first clinical manifestation of an otherwise asymptomatic CVC-related DVT. A history of CVC malfunction, mainly aspiration difficulty (Ball-valve effect), was reported in 70% of patients who developed venous thromboembolic complications.[37,116] In a prospective study, it was found that cancer patients with Ball-valve effect were more likely to develop subsequent CVC-related DVT in comparison with patients without this effect (20 of 30, compared with 65 of 191; $P = .01$).[116] This suggests a correlation between the formation of the catheter sleeve and the development of mural venous thrombosis.

In addition to being a complication of established CVC-related DVT, pulmonary embolism (PE) may be the first clinical manifestation of this disease.

In conclusion, the nonocclusive nature of CVC-associated thrombi helps explain the apparent discrepancy between the incidence of symptomatic events and that of thrombosis screened by venography. Given the silent nature of CVC-associated thrombi, it is not surprising that in a remarkable proportion of patients, PE is the first clinical manifestation of the disease. A history of CVC malfunction is not uncommon in patients with CVC-related DVT.

DIAGNOSIS OF UL-DVT IN CVC PATIENTS

Contrast venography is considered the gold standard in detecting UL-DVT, particularly in patients with CVC. However,

this method is not applicable for diagnosis or surveillance as a routine procedure because of its invasiveness, cost, and use of contrast medium. Consequently, contrast venography is reserved for clinical trials and difficult diagnostic situations.

In the case of clinical suspicion of CVC-related DVT, compressive US, especially with Doppler and color imaging, currently is used to confirm the diagnosis. The main criteria of color-Doppler US are visualization of mural thrombi or incompressibility of the veins, absence of spontaneous flow or presence of turbulent blood flow, absence of transmission of cardiac pulsatility or respiratory phasicity, and visualization of increased venous collaterals.

A recent systematic review of the literature[117] regarding individual studies on the diagnosis of suspected UL-DVT, including 170 patients, 96 of whom had CVC, has reported a sensitivity of duplex US ranging from 56% to 100% and a specificity ranging from 94% to 100%. However, no prospective study evaluated the safety of withholding anticoagulant therapy without additional testing in patients with negative US.

The accuracy of color-Doppler US for the diagnosis of UL-DVT essentially has been evaluated in patients with clinical suspicion of UL-DVT, whereas only limited data are available in patients with CVC both with and without symptoms. In patients with clinical suspicion of UL-DVT an accuracy rate ranging from 82% to 95% has been reported for color-Doppler US, using venography as the gold standard.[118-122]

Koksoy et al[123] reported data regarding the diagnostic value of color-Doppler US, compared with venography, in CVC-related DVT. The authors reported a sensitivity of 94% and a specificity of 96% of color-Doppler US for the CVC-related DVT.

The sensitivity of US is related to the location of venous thrombosis; US is reliable for the detection of UL-DVT in the jugular, and axillary and subclavian veins (with a sensitivity of 95% for axillo-subclavian vein and of 100% for jugular vein) but is less reliable for UL-DVT in the innominate and superior caval veins (with a sensitivity of approximately 5%).[124]

Recently, Male et al[125] reported the results of a comparison between venography and US for the diagnosis of asymptomatic UL-DVT in 66 children with acute leukemia. The authors concluded that US is insensitive for UL-DVT but may be more sensitive than venography for DVT in the jugular veins. A combination of US and venography for the screening of the asymptomatic UL- DVT is recommended. Haire et al[126] compared the sensitivity of duplex US with venography in 32 asymptomatic patients with the CVC inserted in the subclavian vein. Only three of 11 CVC-related DVTs detected at venography were identified by duplex US. The authors concluded that duplex US in insensitive for asymptomatic subclavian vein thrombosis.

The reduced sensitivity of US for UL-DVT, as compared with DVT of the lower limbs, probably is due to the difficulty in exploring the compressibility of the proximal vein segments of the ULs. This could be the case particularly for CVC-related UL- DVT, which is frequently located in the more proximal segments.

Because of the low sensitivity, upper-extremity impedance plethysmography is not an acceptable diagnostic method in patients with suspected CVC-related DVT.[127] The low sensitivity of impedance plethysmography to UL-DVT probably results from the abundant collateral circulation that appears consequently to vein obstruction. Furthermore, the presence of CVC in the vein alone can alter venous tone and flow, probably through the release of endothelial products secreted in response to physical stimulation by the CVC.

Recently, magnetic resonance venography and spiral computed tomography have been used both in the preinsertion evaluation of the central chest veins[128,129] and in the diagnosis of suspected CVC-related DVT.[130-132] The promising results of magnetic resonance imaging and spiral computed tomography in the diagnosis of UL-DVT should be confirmed in additional studies using venography as a reference standard.

In conclusion, in the case of clinical suspicion of DVT-related DVT, compressive US should be used to confirm or rule out the diagnosis. Patients with positive US should be treated with anticoagulant therapy; patients with negative US should undergo serial testing or venography before the diagnosis of UL-DVT is ruled out.

Table 5. Incidence of PE in Cancer Patients With CVC-Related DVT

Author	Year	Study Design	Population	No. of CVCs	PE (%)
Monreal[137]	1991	Prospective	Adults	20	25.0
Monreal[138]	1994	Prospective	Adults	86	15.1
Kooni[139]	1997	Prospective	Adults	41	17.0
Massicotte[140]	1998	Retrospective	Children	244	15.9

Abbreviations: PE, pulmonary embolism; CVC, central venous catheter; DVT, deep venous thrombosis.

COMPLICATIONS OF UL-DVT

Although early reports emphasize the rarity of PE associated with UL-DVT, the incidence of clinically overt PE is estimated at 12%.[121,133,134] This incidence seems higher in cancer patients with CVC-related DVT, ranging from 15% to 25%[135-140] (Table 5). The studies evaluating the incidence of PE in cancer patients with CVC-related DVT are of small size. In two studies,[137,138] PE was symptomatic in 25% and 30%, respectively, of the patients with lung-scan–proven PE.

Patients with a CVC for total parenteral nutrition present a high incidence of PE as the first clinical manifestation of VTE.[141] Autopsy-proven PE is also common in children with CVC for chemotherapy.[142] Monreal et al[138] found that 15.4% (two of 13) of CVC patients with PE died because of recurrent, massive PE despite adequate heparin therapy. Cancer patients with DVT are at high risk for developing DVT recurrence.[143,144]

Postphlebitic syndrome, caused by outflow obstruction and valvular injury, is a long-term complication of UL-DVT characterized by chronic limb edema, pain, cyanosis, functional impairment of the limb, and skin ulcerations. Prandoni et al[121] observed a postphlebitic syndrome in 14.8% of the patients with UL-DVT. This syndrome could cause further discomfort in cancer patients affected by damage of the superficial veins of the ULs caused by chemotherapy. However, long-term disability seems to occur less frequently in patients with CVC-related DVT compared with patients with UL-DVT that is not associated with CVC.[133]

Table 6. Clinical Trial of VTE Prophylaxis in Cancer Patients With CVC

Author	Year	Study Design	No. of Patients	Prophylactic Regimens	Duration	End Point Assessment	CVC-DVT (%)	*P*
Bern[77]	1990	P, O, C	82	Warfarin 1 mg	90 days	Mandatory venography	9.5	< .001
				No treatment			37.5	
Monreal[79]	1996	P, O, C	29	Dalteparin 2,500 U	90 days	Mandatory venography	6	.002
				No treatment			62	
Boraks[145]	1998	O, with historic control	223	Warfarin 1 mg	Variable	Symptomatic events	5	.03
				No treatment			13	
Protekt[146]	2001	R, O, C	188 children	Reviparin 30-50 U/kg	30 + 14 days	Mandatory venography	14.1	.82
				Standard care			12.5	
Reitchard[147]	2002	R, D-B, C	439	Dalteparin 5,000 U	16 weeks	Symptomatic events	3.7	.9
				Placebo			3.4	
Mismetti[151]	2003	R, D-B	57	Nadroparin 2,850 U	90 days	Mandatory venography	28.6	.48
				Warfarin 1 mg			16.7	

Abbreviations: VTE, venous thromboembolism; CVC, central venous catheter; DVT, deep venous thrombosis; P, prospective; O, open-label; C, controlled; R, randomized; D-B, double-blind.

In conclusion, PE is associated with CVC-related UL-DVT. However, the incidence of symptomatic PE is unclear. The incidence of postphlebitic syndrome after CVC-related UL-DVT is also unclear.

PROPHYLAXIS OF UL-VTE IN CANCER PATIENTS WITH CVC

Several studies[77,79,145-149,151] have been performed on the prophylaxis of UL-DVT after CVC insertion in cancer patients (Table 6).

Bern et al[77] evaluated the efficacy and safety of a low, fixed dose of warfarin. In this open prospective study, 42 patients were randomly assigned to receive 1 mg of warfarin, beginning 3 days before CVC insertion and continuing for 90 days. Forty patients did not receive warfarin and served as control patients. In the warfarin group, four patients (9.5%) had venography-confirmed UL-DVT, compared with 15 patients (37.5%) in the nonwarfarin group ($P < .01$). It was concluded that a low, fixed dose of warfarin could prevent CVC-related DVT.

Monreal et al,[79] in an open prospective study, found that dalteparin, 2,500 U once daily for 90 days, is effective and safe in the prophylaxis of UL-DVT in patients with CVC. In this study, nine of 29 patients (31%) developed UL-DVT confirmed by venography: one of 16 (6%) in the dalteparin group and eight of 13 (62%) in the untreated control group.

Boraks et al[145] reported an open study on the efficacy and safety of warfarin prophylaxis in 108 patients with CVC. In this study, patients with hematologic malignancies received 1 mg of warfarin during the period of CVC dwell. The incidence of CVC-related DVT in treated patients was compared with that observed in a historical population with similar characteristics. Venography or US was used to confirm the clinical suspicion of CVC-related DVT. The reported rate of CVC-related DVT was 5% in the study patients and 13% in the historical controls ($P = .03$). The uncontrolled nature of this study is a major limitation for the evaluation of the intervention tested in the trial.

The PROTEKT study[146] was an open-label, randomized controlled trial on the prevention of CVC related thrombotic complications with reviparin-sodium in children affected by leukemia. The dose of reviparin was 30 U/kg/d for patients younger than 3 months and 50 U/kg/d for patients older than 3 months. The efficacy end point was DVT detected by venography performed at day 30 (+ 14 days, or earlier in case of CVC removal and symptomatic VTE confirmed by objective testing). The study was prematurely closed after the inclusion of 188 patients because of the slow patient accrual and the high rate of adverse events. A VTE rate of 14.1% (11 of 78 patients) was reported in the reviparin-sodium group as compared with 12.5% (10 of 80 patients) in the control group. The negative results observed in this study could be explained by the low responsiveness of children to antithrombotic prophylaxis, the high frequency of patients with leukemia in the study, or the use of ineffective prophylactic doses.

More recently, a randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of dalteparin in preventing catheter-related complications in cancer patients.[147] In this study, the end point was represented by clinically overt catheter-related complications including thrombotic events requiring anticoagulant or thrombolytic therapy, clinically overt PE, and CVC obstruction requiring CVC removal. Patients were randomly assigned in a 2-to-1 fashion to receive 5.000 U of dalteparin or placebo for 16 weeks starting within 5 days from CVC insertion. The results of this study did not show a benefit in terms of reduction of CVC-related complications in the dalteparin group as compared with placebo (3.7% *v* 3.4%; $P = .9$). The low rate of venous thromboembolic events observed in this study could be explained by the use of a clinical end point rather than a venography end point. Studies aimed at showing a reduction in the incidence of venous thromboembolic events with this experimental design would certainly require a larger sample size or a study population at particularly high risk for thrombosis.

Lagro et al[56] found nadroparin to be ineffective in the prevention of CVC-related DVT in bone marrow transplant recipients. In an open study on prophylaxis of CVC-related DVT in patients with hematologic malignancies, Heaton et al[148] randomly assigned 45 patients to low-dose warfarin, 1 mg/d and 43 patients to no treatment. Venography was used to confirm the clinical suspicion of CVC-related DVT. No significant difference in the incidence of catheter thrombosis or DVT and no significant variation in catheter survival were found between the study and control groups. This finding is not surprising, given the

reduced sample size of the study. More recently, Couban et al[149] reported the results of a randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of low-dose warfarin (1 mg/d) in the prevention of symptomatic CVC-associated DVT in 255 patients with cancer. A clinically overt thromboembolic event occurred in five of 125 (4%) patients in the placebo group and in six of 130 (4.6%) patients in the warfarin group. There was no difference in the incidence of major or minor bleedings in the two groups. In a large number of patients (191 of 255 [75%]) the treatment was interrupted because of thrombocytopenia. The authors concluded that low-dose warfarin did not reduce the incidence of symptomatic CVC-related DVT in patients with cancer.

A meta-analysis[150] of randomized controlled trials in CVC patients showed a benefit of heparin in the prevention of venous thromboembolic complications (relative risk, 0.43; 95% CI, 0.23 to 0.78) and of catheter colonization (relative risk, 0.18; 95% CI, 0.06 to 0.60).

The efficacy and safety of the low molecular weight heparin (LMWH) nadroparin and low-dose warfarin were compared in an open, prospective, randomized venography trial in 57 cancer patients with long-term CVC for chemotherapy.[151] Warfarin was given at the fixed daily dose of 1 mg, and nadroparin was injected at a fixed daily dose of 2,850 U for 90 days. Six of 21 patients in the nadroparin group (28.6%) and four of 24 patients in the warfarin group (16.7%) had venography-confirmed CVC-related DVT at 90 days ($P = .48$). Safety was similar in both treatments. The authors concluded that prophylactic doses of warfarin and nadroparin had comparable benefit-to-risk ratios in the prevention of CVC-related DVT in cancer patients.

On the basis of the results of the studies of Bern et al[77] and Monreal et al,[79] the American College of Chest Physicians[18] recommends prophylaxis with LMWH or low-dose warfarin in cancer patients with CVCs. However, the analysis of the studies on the pharmacologic prophylaxis of thrombosis in cancer patients with CVC does not allow a firm conclusion on the clinical value of this approach. Most of the studies were open and of reduced sample size. Furthermore, the study end point varied—venography-detected DVT in some studies and clinically overt thrombosis in others. No double-blind venography-based studies were performed. In addition, major hemorrhagic complications were not fully described in these studies. This is not without importance, given that bleeding is a major concern regarding the administration of anticoagulants in cancer patients because they are often prone to developing thrombocytopenia during chemotherapy.[152]

In conclusion, additional studies using appropriate research methodology are needed to define the efficacy and safety of pharmacologic prophylaxis in this clinical setting. In view of this, a randomized, double-blind, placebo-controlled trial is ongoing to evaluate the efficacy and safety of enoxaparin, administered subcutaneously, at the dose of 40 mg/d for 42 days, for the prophylaxis of CVC-related DVT in approximately 400 cancer patients. The primary end point of the study is the incidence of UL-DVT, as detected by mandatory venography (CVC limb) at 6 weeks or earlier in the case of clinical suspicion of DVT, compulsory catheter removal, and/or symptomatic PE.

TREATMENT OF UL-VTE IN CANCER PATIENTS

Although CVC-related DVT complicates the management of cancer patients, the treatment of this condition has not yet been thoroughly standardized and critically analyzed. The standard management differs in the various clinical settings and depends on the clinical presentation, CVC malfunction, risk of bleeding, and other clinical considerations. The general objectives of treatment of CVC-related DVT are to reduce mortality and morbidity from the acute event and to minimize late complications.[82]

When UL-DVT is confirmed, anticoagulant therapy seems to be the treatment of choice, but there is no consensus on the optimal management of patients with CVC-related DVT because no prospective, comparative studies have been performed. At present, most patients receive anticoagulation according to current guidelines for lower-limb DVT. According to the current practice, treatment is started with adjusted-dose unfractionated heparin or LMWH for 5 to 7 days and continued with oral anticoagulation with warfarin.[18] If oral anticoagulation is contraindicated, patients usually receive long-term treatment with LMWH.[153,154] The use of LMWH has been evaluated in the treatment of Hickman-related thrombosis in five patients with thrombocytopenia who were undergoing bone marrow transplantation.[155] All patients were treated with the LMWH enoxaparin and recovered without hemorrhagic complications.

A recent prospective cohort study evaluated the administration of the LMWH dalteparin (200 anti-Factor Xa U/kg) in the treatment of 46 outpatients with UL-DVT.[156] The results of this study suggest the safety and efficacy of dalteparin in this clinical setting with the potential cost saving of outpatient treatment.

More aggressive therapeutic options for CVC-related DVT include systemic thrombolysis and thrombectomy. A number of studies of thrombolytic therapy in CVC-related DVT have been carried out,[157-163] but not one was a randomized study comparing thrombolysis to heparin treatment in patients with venographically confirmed UL-DVT. It is unclear whether thrombolytic therapy could reduce symptoms of VTE or prevent line or systemic infection and CVC malfunction.

In the presence of UL-DVT, the removal of the CVC is controversial and left to the discretion of the attending physician. The decision to remove the CVC depends on clinical symptoms, CVC function, the need to administer additional chemotherapy, and platelet count. The insertion of another CVC, generally on the contralateral UL, is associated with considerable morbidity and cost. The efficacy of CVC removal on the long-term outcome is unknown.

The optimal duration of anticoagulation treatment for CVC-related DVT in cancer patients is unknown. We recommend that cancer patients experiencing a VTE episode receive anticoagulation for at least 6 months or indefinitely, as long as cancer is active.

The superior caval vein filter has been used in patients who have UL-DVT and contraindications to anticoagulant therapy. In 41 patients with UL-DVT reported by Spence et al,[164] the

superior caval vein filter prevented PE and superior vena cava syndrome without complications, such as filter migration, dislodgment, or fracture. Ascher et al,[165] confirmed these findings in 72 patients with UL-DVT who received the Greenfield filter.

The conventional therapy for a blocked CVC resulting from catheter tip occlusion or catheter sleeve occlusion is local thrombolytic therapy with a low dose of single or repeated bolus of urokinase, streptokinase, or tissue plasminogen activator. Thrombolytic therapy restores catheter patency in most patients with well-positioned CVC.[166,167]

In conclusion, treatment of CVC-related VTE requires a 5- to 7-day course of adjusted-dose unfractionated heparin or LMWH followed by oral anticoagulants, or long-term LMWH if these are contraindicated. The optimal duration of oral anticoagulation treatment for CVC-related DVT is unknown, but patients with active cancer should be treated for at least 6 months or indefinitely. Thrombolysis is rarely required. The need for CVC removal in patients with CVC-related DVT remains controversial.

In summary: UL-DVT has recently emerged as a significant clinical problem. Until 10 to 15 years ago, UL-DVT represented about 2% of all DVT of the limbs,[168,169] whereas this disease now represents approximately 8% to 10% of total DVT of the limbs. Long-term CVCs represent a major cause of UL-DVT, especially in cancer patients.

CVC-related DVT in cancer patients complicates the management of the disease,[7] contributing to the morbidity and mortality of cancer patients. Recognition of risk factors associated with CVC-related DVT may help to reduce the rate of this complication. However, this objective is more likely to be achieved by pharmacologic prophylaxis during long-term CVC dwell. Ongoing studies will probably define the optimal prophylactic regimen in cancer patients undergoing CVC insertion for chemotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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