Editors: Robin Foà, Victor A. Hoffbrand
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CATHETER-RELATED THROMBOSIS IN HEMATOLOGIC PATIENTS

For many years central venous catheters (CVC) have been utilized to monitor hemodynamics and to deliver parenteral nutrition, blood products, pharmacological therapies or infusion fluids. Recently, CVC use has greatly increased with significant impact on the administration of chemotherapy, stem cell transplantation and other treatments to cancer patients. However, CVC use may be accompanied by a variety of side-effects, which increase with the duration of implantation. The most common catheter-related complications are thrombotic events and blood-stream infections. The true incidence of these complications is still uncertain and has changed over time due to CVC device improvement. More data are available in solid tumor than in oncohematologic patients. Recently, much attention has been paid to the issues of prevention and treatment of these complications. Some strategies have been proposed: fixed dose warfarin or low molecular weight heparins have been evaluated in some clinical trials of thromboprophylaxis in this condition. However, more studies are still needed to address this issue. This review will focus on CVC use and complications in oncohematologic patients.

Introduction

Today the vast majority of hospitalized patients with hematologic malignancy undergo the insertion of a CVC. These devices importantly contribute to make easy and safe the delivery of chemotherapy, parenteral nutrition and blood components, and facilitate blood sampling and vital signs monitoring (1). Central catheters have therefore become essential to the care of patients undergoing high dose chemotherapy and/or HSC transplantation or apheresis to harvest HSC. However, even though the presence of a long-term venous access greatly increases patient comfort and enhances therapeutic options, CVC may induce or enhance complications, either thrombotic or infectious. The optimal approach to prevent and treat these complications is still matter of debate (2). This is an important issue, as cancer patients with CVC are more prone to develop thrombotic complications compared to non-cancer patients with CVC, but they are also exposed to a greater hemorrhagic risk.
Finally, while there is quite a large number of reports about CVC use in ICU or in solid cancer patients, few studies specifically deal with onco-hematologic patients, who are characterized by severe and long-lasting neutropenia and thrombocytopenia (3 5).
In this review, we will attempt to summarize the most recent concepts on the use of CVC, particularly in hematologic patients, giving also an overview of current information on the epidemiology, prophylaxis and treatment of CVC-related CR-thrombotic complications.

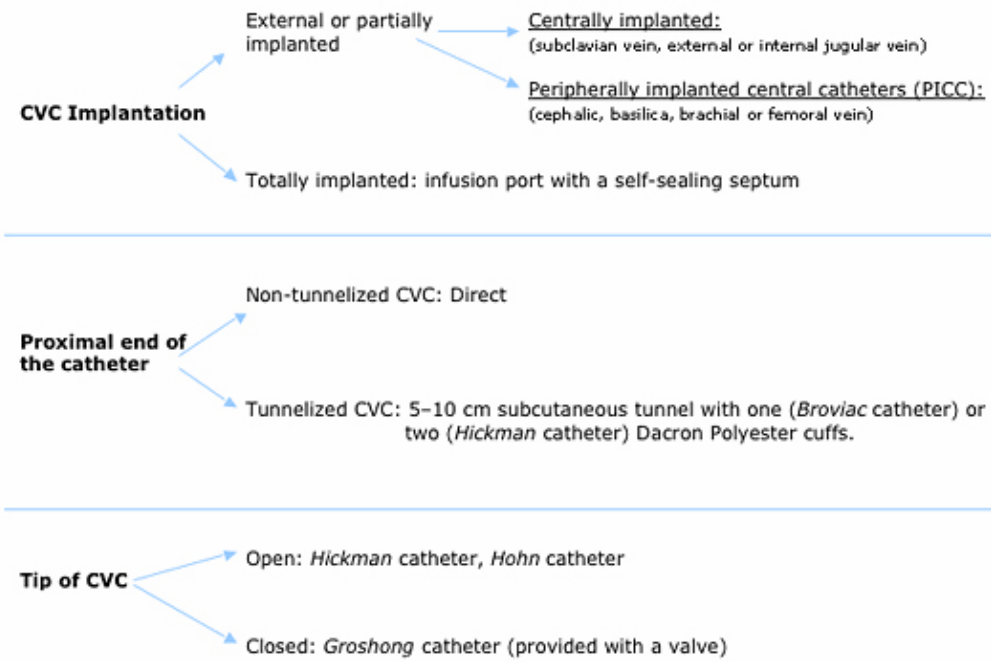
Types of CVC

The first type of long-term CVC was introduced in clinical practice by Broviac about thirty years ago (6). Since then, a number of changes of the catheter material itself as well as variations in the insertion modalities have been made. These modifications (Table 1) have been realized in order to increase catheter biocompatibility, duration and ease of insertion, to improve patient comfort and cosmesis and to reduce thrombogenicity of intravenous lines as well as the risk of local or systemic infections.

Table 1 - Catheter modifications in the recent years	
Type of modification	**Aim**
Material (Silicone, Polyurethane vs. Polyvinyl chloride, Polyethylene)	Increase biocompatibility and duration of CVC. Reduce thrombotic risk
Lumens (Multiple vs. Single)	Allow contemporary administration of multiple drugs/fluids
Implantation (Total, i.e. Port systems vs. Partial, i.e. External CVC)	Adapt the CVC choice to the planned duration of use. Reduce infectious risk. Increase patient comfort. Allow discontinuous long-term use
Site of insertion (Peripheral vs. Central)	Allow CVC insertion in patients lacking suitable central access
Tip (Closed vs. Open)	Reduce infectious risk
Distal end (With valve vs. Without valve)	Reduce infectious risk
Proximal end (Subcutaneous tunnel vs. Untunneled; Double cuff vs. Single cuff)	Reduce infectious risk. Avoid catheter dislodgement
Antiseptic/Antibacterial Coating or Impregnation	Reduce infectious risk
Heparin Bonding	Reduce thrombotic and infectious risk

The various types of catheters are summarized in Table 2. CVC are inserted into a central or peripheral vein and the tip is positioned in the superior vena cava or right atrium. According to the site of insertion, CVC can be classified as Centrally Implanted (i.e. insertion in the subclavian vein or in the external or internal jugular vein) or PICC (i.e. insertion in the cephalic, basilica, brachial or femoral vein) (7, 8). The proximal end of the catheter may be exteriorized directly (Non-Tunnelized CVC) or by a 5- to 10-cm subcutaneous tunnel (Tunnelized CVC) with one (e.g. Broviac catheter) or (e.g. Hickman catheter) two Dacron polyester cuffs. The tip of CVC may be open (e.g. Hickman catheter, Hohn catheter) or closed and the catheter provided of a valve (e.g. Groshong catheter). All these catheters are collectively called External or Partially Implanted CVC.

Table 2 - Catheters classification



In 1982 Niederhuber et al. implanted Port Systems under the skin of the chest wall, to substitute external catheters in cancer patients. These Totally Implanted CVC consist of an infusion port with a self-sealing septum, easily reached by percutaneous needle puncture, and of a catheter for the parenteral delivery of drugs, fluids and blood components (9). The integral skin barrier between the device and the external environment significantly decreases the risk of contamination, with a negligible impact on patient s everyday activities. However, chest port insertion may be troublesome in patients with anatomic alterations of central veins or chest wall, as well as in those with severe thrombocytopenia, with a risk of complications such as pneumothorax or bleeding, respectively (10). Peripheral Ports, totally implantable in the arm or leg, eliminate the risk of pneumothorax as a procedural complication (11).
Due to all these technical improvements, hematologists can utilize today a CVC array flexible enough to cope with the different needs they meet in clinical practice. Short-term in-hospital therapy can be delivered through partially implanted CVC, whereas totally implanted ports systems and tunnelled devices are useful for long-term intermittent therapy (e.g. cyclic chemotherapy) in day-hospital or even at home (1, 5, 12, 13).
Available data indicate that in United States, more than 5 million CVC/year are implanted as a short-term or long-term venous access (14). According to the 1-day prevalence survey of CVC by the Prevention Epicenter Program of the CDC, 29% of the adult inpatients have a CVC. Of them 59.3% were ICU and 23.7% were non-ICU patients. The majority of catheters were centrally inserted into the subclavian (55%) or jugular (22%) veins, whereas arm (15%) and femoral (6%) sites were less frequent (15).
The prevalence of CVC use appears far higher among hematologic patients compared to other cancer patients. According to a questionnaire survey proposed by MASCC, more than 50% patients with hematologic malignancies had a CVC, compared to only 20% of patients with solid tumors (16).

CR thrombotic complications

Central catheter use is associated to significant morbidity and occasional mortality. Adverse events that are both harmful to patients and costly are reported in more than 15% of patients who receive these catheters. CR-complications include bleeding at the insertion site, pneumothorax, catheter dislodgement, extravasation of infusate, catheter malfunction, tip thrombosis or embolization, PICC-related peripheral thrombophlebitis, CR-central deep vein thrombosis and both local and systemic CR-infections.
In spite of the efforts that have been made to minimize endothelium trauma following catheter implantation, to improve catheter biocompatibility and to prevent thrombotic events in patients bearing a CVC, the frequency of CR-DVT remains a problem with the potential for the development of life-threatening complications such as pulmonary embolism (PE) (1).
The estimated incidence ranges from 5 to 19% for mechanical complications, from 2 to 26% for thrombotic complications and from 5 to 26% for infectious complications (17). Mechanical complications such as catheter dislodgement or rupture have been reported to occur frequently (4.5 events/1000 CVC-days) and to be the main cause of premature loss of Broviac/Hickman catheter in pediatric patients with hematologic and oncologic diseases (18).
[dict: CR]-complications may arise early, during the implantation, or later, during the catheter stay into the vein. The early

complications include catheter misplacement, arterial puncture, air embolism and damage of the nearby anatomic structures with consequent hemo-, chylo- or pneumothorax, local hematomas or hemorrages. They are reported in 0.3 to 12% of patients (19 22). Late adverse events include catheter breakage and both thrombotic and infectious complications (17, 23 28). The rate of late complications can vary widely among different patient populations in which catheters are inserted. For instance, infection rate can be as high as 4.3 per 1000 catheter days in children with cancer (26) and as low as 0.14 per 1000 catheter days in those with hemophilia (29).

The accurate definition of the incidence of the various CVC-associated complications has been difficult due to much differences between the different studies principally due to the lack of standardization of the implantation techniques, the procedures for maintenance and nursing of catheters, the diagnostic tests utilized for the definition of thrombotic events such as DVT, and PE and, finally the study designs.

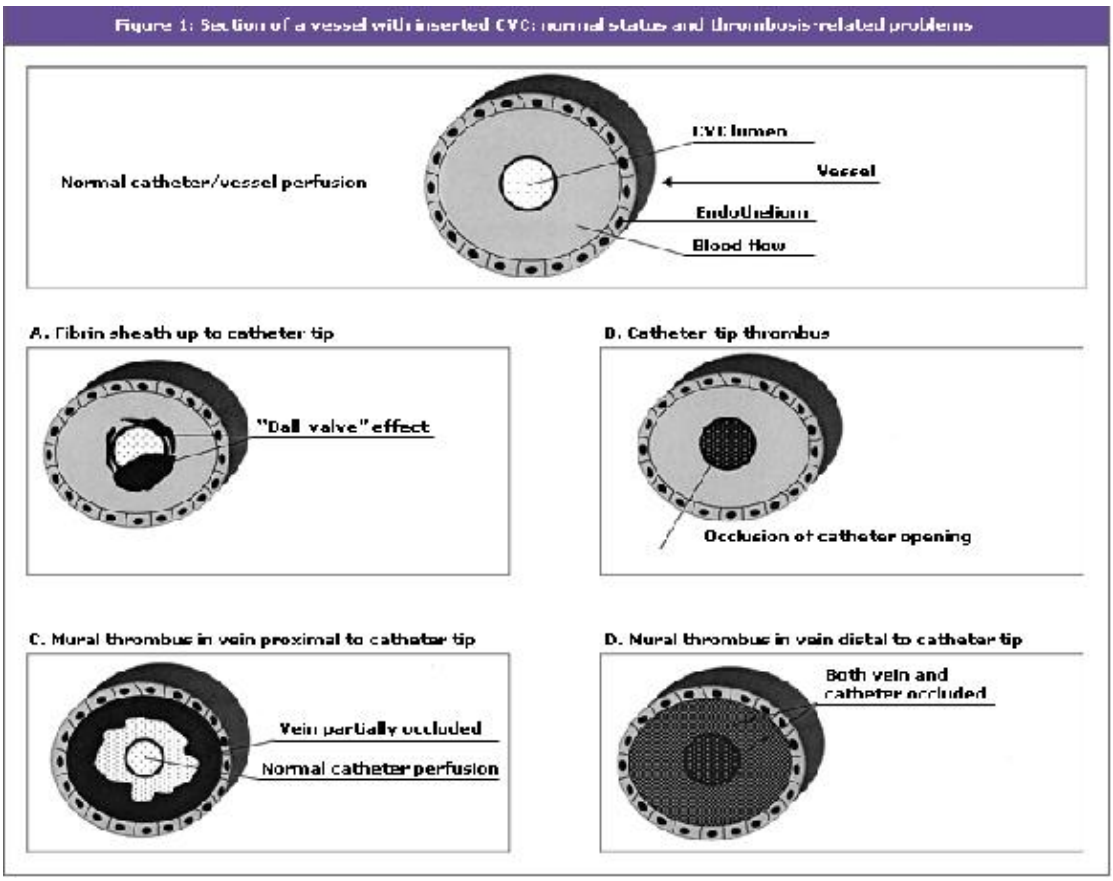
Pathogenesis

The pathogenesis of CR-thrombotic complications depends on multiple factors, acting during the time of the catheter intravascular life. Early acting factors are closely linked to the trauma of the CVC insertion procedure and the related loss of vessel integrity, whereas catheter chemical structure, size and technique of implantation, catheter tip position, and catheter infection probably are the main late acting factors, besides patient characteristics.

Endothelial injury due to catheter insertion and the reduced venous flow rate caused by the intravascular device are the main mechanical causes favoring vessel thrombosis in patients with CVC. Acute endothelial injury immediately follows the insertion procedure and is associated with endothelial cell and platelet activation. The intermittent rubbing of the indwelling catheter against the vessel wall determines a chronic endothelial injury.

In patients with solid tumor or hematologic malignancy, the cancer itself (cancer-related hypercoagulability) or the related treatments (i.e. chemotherapy, surgery, stem cell transplantation, total parenteral nutrition, long-term estro-progestinic therapy in female patients with childbearing potential) represent additional potential pathogenetic mechanisms. The role of congenital or acquired thrombophylic abnormalities needs to be further elucidated.

CR-thrombi can develop in different ways. Figure 1 summarizes the most common types of thrombosis (5, 30). The catheter sleeve is an adherent sheath of fibrin that forms on the outer surface and envelopes the indwelling catheter. This thin pericatheter thrombus evolves, within two weeks from implantation, into a collagen sheath (31, 32). Sleeve thrombi are quite common, occurring in up to 47% of patients and, although benign in itself, may lead to catheter malfunction (inability to infuse or to withdraw blood due to a ball-valve effect at the catheter tip level), complete occlusion of the catheter tip or even mural thrombosis. Sleeve thrombi can eventually serve as a reservoir for bacterial overgrowth (33).



Complete or partial blockage of catheter function may also origin from intraluminal thrombi: their presence requires locking or flushing of the catheter with thrombolytic agents to restore its patency (34). Sleeve or intraluminal thrombus formation may precede or cause the third and more concerning complication, which is DVT, i.e. the development of occlusion of large veins such as superior vena cava, subclavian vein or axyllary vein (2).
Superficial thrombophlebites, involving the arm veins, represent a fourth type of thrombotic CR-adverse event that may be observed in patients bearing PICC or midline cathethers. Patients with CR-thrombotic complications may have a number of signs and symptoms, including pain, oedema, skin discoloration and the development of superficial collateral circulation. However, frequently, DVT may go totally unnoticed.
DVT of the upper or lower extremities may in turn predispose patients to potentially lethal complications such as PE or post-thrombotic syndrome (35).
In onco-hematologic patients carrying CVC, both silent and clinically evident VTE complicates the management of the disease and may significantly worsen the prognosis. In fact, VTE is one of the leading causes of death in cancer patients (19). CVC insertion, besides the cancer itself, cancer surgery and chemotherapy, represents a risk factor for thrombotic events. An exact quantification of this risk may help to define the best strategies to prevent VTE in cancer.

Catheter use possibly leads to thrombotic complications ranging from localized, asymptomatic phenomena up to clinically overt deep vein thrombosis.

Epidemiology

The rate of CR-thrombosis in cancer patients has been estimated in numerous prospective and retrospective cohort studies (36 62). Because long-term catheters are located deeply in the mediastinum, DVT may long be clinically asymptomatic. Therefore the CR-DVT incidence reported in the literature varies according to the test used for detecting the endpoint: when venography was performed as a programmed surveillance tool, the DVT rate is greater than when utilized only as a confirmation symptoms of clinically suspected DVT. The estimated frequency of upper limb DVT further decreases when either ultrasonography or impedance plethysmography are used, or when the diagnosis of DVT is merely based on clinical symptoms.
In fact, the reported rate of clinically manifest CR-DVT in adult patients ranges from as low as 0.3% up to 28.3% (3) (or from 0.02 to 0.92 events per 1000 device life days) (1). Differently, it raises up to 27% to 66% when surveillance venography is utilized to detect DVT. Most thrombi detected in imaging studies, particularly by venography, were totally asymptomatic (2, 28, 36, 63 66).
In patients with hematologic diseases, a cumulative incidence of clinically overt thrombosis of about 12% (2.2 events per 1000 catheter days) has recently been reported (61, 67, 68), whereas consistent estimates for subclinical thrombosis are scant. In the study by van Rooden et al. one hundred and five patients affected by hematologic malignancies were enrolled prospectively to assess the validity of Doppler-ultrasonography to predict for CR-thrombosis (clinically overt or asymptomatic) (67).
Among paediatric patients, the rate of clinically overt CR-DVT appears to be lower, the reported incidence ranging from 0 to 12% (43, 59, 69, 70). However, now radiographic evidence exists that as many as 50% of children with cancer, bearing a CVC, develop thrombosis of large veins, that are in a great majority asymptomatic. Most thrombi, detected in cancer patients by venography, are not only clinically silent but also non-occlusive. Indeed, in two recent studies, the estimated percentage of non-occlusive DVT in cancer patients was 81.2% and 71.4%, respectively (65, 71).
The true impact of partial obstructions on catheter life and functioning as well as on patient morbidity and mortality is uncertain. However, the silent course of non-occlusive CR-thrombosis may progress to sudden overt clinical signs of PE. In a recent meta-analysis, aimed to evaluate the role of thrombosis prophylaxis in patients with CVC, a systematic review of prospective trials including three different patient populations, i.e. patients receiving PN, patients with cancer, and critically ill patients in the ICU, have been performed. Given the very restricted inclusion criteria, only eleven out of thirty-five studies of patients with hematologic or other malignancies, were analyzed. The recorded incidence of thromboses was largely different. Indeed it was 0 to 20%, when only symptomatic thrombosis were taken into account, but raised to 27 to 90% when thrombosis was investigated by imaging technique. Furthermore, the majority of trials included small cohorts of patients and very few studies addressed patients with hematologic malignancies (10).
Cortelezzi et al. evaluated the rate of thrombotic complications in a cohort of 126 patients with hematologic malignancies, in whom a total of 207 CVC were implanted. In this study, clinically symptomatic thrombotic complications developed in 15.5% of CVC (7.9 events/1000 catheter days). The incidence was significantly higher in patients with peripherally inserted PICC than in those with centrally inserted CVC ($p<0.0001$), the PICC showing a 4.1-fold increased risk of developing DVT, a 14.8-fold risk of superficial thrombophlebitis, and a 2.6-fold risk of catheter malfunction, as compared to centrally inserted CVC (4).
Patients carrying a CVC are particularly prone to develop thrombo-embolic complications during the first weeks after catheter insertion (4). This is suggested by several observations: Luciani et al. reported a mean interval of 42.2 days between CVC implantation and appearance of signs of thrombosis (72), whereas De Cicco et al. found that over a half of DVT were detectable within 8 days after catheter insertion (66). In patients with hematologic malignancies, the median number of days between CVC insertion and clinical detection of thrombosis was 17d in the study by Van Rooden et al. (67). About three fourths of thromboses were diagnosed within the third week after CVC implantation, confirming that this is an early complication also in hematologic patients (67). The incidence of clinically detectable PE, as a complication of CR-upper limb-DVT, is reported to vary from 15 to 25%, but PE incidence was 50% at necroscopy (1). On the other hand, in both the prospective studies of patients with upper-limb DVT in which PE diagnosis was made by objective testing, the incidence of PE was 36 and 17%, respectively (64, 73).

Clinical features

Signs and symptoms of clinically overt CR-DVT include shoulder girdle, neck or jaw pain, headache, skin discoloration and/or erythema, oedema ranging from slight arm swelling to full-blown superior vena cava syndrome with venous congestion and the development of collateral circulation vessels on the chest wall. However, the clinical course of CR-DVT is often silent. According to De Cicco et al., only 6% of patients with venographic evidence of DVT are symptomatic (66). Both an apparently aspecific sign, such as aspiration difficulty from the catheter, or a dramatic clinical picture, such as PE, may be the presenting hallmark of DVT in a significant percentage of patients. Upper-limb DVT may more frequently run a silent clinical course than lower limb DVT, given the wider possibility to develop a collateral circulation in the upper extremity. Asymptomatic DVT may be suspected in the presence of catheter malfunction, mainly a difficulty in blood withdrawal due to ball-valve effect generated by a sleeve thrombus on the catheter tip. A positive relationship between this ball-valve effect and the development of mural thrombosis in cancer patients is suggested by Tolar et al. (74). In this prospective study significantly more CR-DVT occurred in patients with catheter showing a ball-valve effect, than in patients without aspiration difficulty (20 out of 30 vs. 65 out of 191; p=0.01). Further, blood aspiration difficulty was documented in almost the three fourths of patients who later developed DVT.

A difficult blood aspiration from CVC may be a sign of asymptomatic DVT.

Risk factors

A number of factors have been shown to influence the risk of CR-thrombosis, including catheter characteristics and biocompatibility, catheter insertion techniques, patient characteristics and treatment, and associated infection.

There is no substantial difference in thrombotic risk between the different types of external catheters (i.e Hickman, Broviac, Groshong) (1, 46), whereas totally implantable ports carry a lower rate of thrombosis compared to partially implantable devices (3, 26). A lower incidence of upper limb DVT with chest ports (0.3 14%) versus peripherally placed ports (4.5 26%) and external catheters (7 20%) has been reported (1, 46, 75). Cancer patients with venous ports connected to open-end or closed-end valved CVC have an analogous incidence of CR-thrombotic complications (58).

The thrombogenic potential of PICC lines is substantial. The reported rate of PICC-related DVT appears lower as compared with centrally inserted CVC (76, 77). However, PICC are definitely associated with a consistent rate of symptomatic upper limb thrombophlebitis (4, 31, 78, 79), and the complication-free delivery rate (i.e. the percentage of catheter life free of both thrombophlebitis and DVT) is significantly in favor of centrally inserted vs peripherally inserted catheters (79).

Both the CVC size and lumens number (i.e. single-lumen vs. multi-lumen) have been reported to increase the likelihood of CR-thrombotic events. This particularly applies to children with large indwelling catheters and rather small veins (5).

Large-bore peripheral lines have been shown to be significantly more thrombogenic than smaller lines by Grove et al., with a reported incidence of thrombosis of 0%, 1%, 6.6% and 9.8% for PICC with a diameter <3F, 4F, 5F and 6 F, respectively (76). Similar results were obtained by Eastridge et al. who showed that 12F triple-lumen Hickman catheters were associated to a higher number of thrombotic complications than the 10F double-lumen (20.1 vs. 6.9%; p<0.05) (46). However, recently, the effect of the number of lumens on CR-complications has been questioned (80), and it has been suggested that the choice of either a single-lumen or a multi-lumen should not be influenced by this concept (17).

Catheter rigidity and roughness may directly impact on endothelial integrity; in addition a rough surface may favor both the coagulation process and the deposition and anchoring of a bacterial biofilm. Catheters made of more biocompatible material, such as silicone and polyurethane appear less thrombogenic than polyvinyl or polyethylene CVC (81).

The site and the side (left versus right) of device insertion (59, 82, 83), the number of vein punctures as well as the location of the catheter tip (distal vs. not distal to the junction of the superior vena cava and the right atrium) are all insertion technique-associated variables that may modify catheter thrombogenicity. A correct positioning of the catheter tip dramatically reduces the risk of DVT when compared to a peripherally misplaced catheter tip (i.e. located into axillary or subclavian-innominate veins), while the location of the distal end of the device is an independent risk factor for the development of CR-thrombosis (50, 72, 84 86). Possibly due to the different length of left-sided and right-sided innominate veins and to anatomic diversity of the subclavian-innominate angles, left-sided inserted CVC are associated with an enhanced thrombotic risk (66, 82 84). Non-subclavian cannulation is associated with a significantly higher thrombotic risk than catheter insertion into the subclavian vein. This has been demonstrated comparing the incidence of CR-thrombosis after catheter positioning at the subclavian level with that at both femoral (1.9 vs. 21.5%; p<.001) (87) and internal jugular levels (88).

Skilled implantation technique and the improvement in the imaging assistance during catheter insertion in cancer patients result in a reduced risk not only of immediate mechanical complications, such as catheter misplacement or injury of adjacent anatomic structures, but also of secondary thrombotic events (3, 19, 40, 89).

Correct positioning of the catheter significantly reduces the risk of CR-DVT.

The risk of thrombosis differs among the patient populations, as the underlying disease may affect the risk of thrombosis. This is the case of malignancy (90). In patients with cancer risk is further enhanced by anti-tumor treatments, including surgery, high-dose chemotherapy or HSC transplantation (67). However Brown et al. did not observe significant differences in the rate of CR-thrombotic complications between different chemotherapeutic modalities, i.e. short-term or continuous intravenous chemotherapy, and in-hospital vs. out-of-hospital cancer therapy (91). Patients undergoing bone marrow harvesting develop a hypercoagulability state (23). Indeed, plasma levels of coagulation activation markers (prothrombin fragments, thrombin-antithrombin complexes, fibrinopeptde A and fibrin monomers) are shown to increase after bone marrow harvesting and

Hickman catheter insertion in autologous bone marrow transplanted patients with malignant lymphoma (92).
The influence of one or more of the following patient characteristics and type of infused therapy is also suggested, i.e.: platelet count at the time of catheter insertion, inherited thrombophilia, and nature of the substance administered (fluid replacement vs total parenteral nutrition). Chemotherapy may directly damage the vascular endothelium and the hyperosmolarity of PN can also alter the vessel wall (23, 75, 92). Conversely, chemotherapy may lower the platelet number, thus also favoring a bleeding tendency.
Enhanced thrombotic risk has been documented in childhood acute lymphoblastic leukemia (1, 59, 93), in association with Levo-asparaginase induction therapy. This agent decreases the protein synthesis leading to an acquired deficiency of antithrombotic factors, such as antithrombin III, protein C and protein S (94). The use of GM-colony stimulating factor or of Interleukin 2 has also been associated to high incidence of catheter occlusions (95, 96).

Some pharmacological agents increase the risk of CR-thrombosis.

In spite a substantial number of studies and anecdotal reports available in the literature, the exact role of inherited or acquired coagulation abnormalities in patients with cancer or hematologic malignancies bearing a CVC is still controversial (28, 56, 59, 61, 97 101). It has been suggested that Factor V Leiden gene mutation may be a consistent thrombotic risk factor in acute lymphoid leukemia patients and in stem cell transplanted patients with CVC (61, 99).
Undoubtedly infection is one of the leading complications of CVC (3, 17, 19). CR-BSI cause an increase in hospital stay of about 20 days, with an estimated additional cost of more than 3,000 euros/case (102). Seventy per cent of all in-hospital BSI occur in patients with CVC, with a reported mortality rate of about 20%. In one third (6.7%) of these cases, death can be directly attributable to CR-septicemia (103).
There is a broad variation in the reported frequency of CR-infectious complications in cancer patients, both in terms of incidence (from less than 1% to 25%) and in terms of incidence density (from 0.21 to 30.2 complications per 1000 CVC-days) (103). These variations depend on the kind of indwelling device, the population investigated and the microbiological diagnostic techniques. The frequency of CR-BSI rises with the length of CVC intravascular life. The use of subcutaneous ports, subclavian insertion site and antimicrobial-impregnated catheters consistently reduces the risk of infectious complications (17, 104 106).

Risk of bloodstream infections increases with the time of catheter intravascular life.

Other reported risk factors for CR-BSI are increased patient age and/or low performance status, number of CVC manipulations, administration of TPN, severity and duration of neutropenia, diagnosis of hematologic malignancy or solid tumor and stem cell transplantation (3, 103). The overall incidence of CR-BSI in patients with acute leukemia was very low in the study by Karthaus et al. (107). In this prospective trial, only 1.9 proven CR-BSI were documented per 1000 CVC-days. However, the number of proven CR-BSI was much higher (5.2 events per 1000 CVC-days) in another recent report in patients with hematologic malignancies (4).
The relationship between catheter infection and thrombosis is bi-directional, as the two processes may influence each other in several ways (33, 88, 108). The fibrin and fibronectin network of the catheter sleeve is an ideal docking site for the adherence of bacteria, particularly staphylococci, on the catheter surface and catheter colonization (33). These slime-producer adherent bacteria may subsequently generate coagulase enzymes that exert a pro-thrombotic activity. Finally, the embolization of an infected thrombus can lead to both thromboembolic and septicemic complications. It is therefore expected that a clinical correlation exists between these two CR-complications, i.e infection and thrombosis (1). Albeit in a small cohort of patients, a significantly higher (23% vs 1%; $p<0.01$) incidence of septicaemia was found among patients with necroscopic evidence of mural on catheterized veins, in comparison to patients without CR-thrombosis (33).
Protocols aimed to decrease the incidence of CR-BSI through the prevention of both extra-luminal and endo-luminal contamination of catheter (i.e. aseptic catheter insertion and hub handling, use of tunnelling catheters, totally implantable ports, and antimicrobial-bonded catheters) may possibly lead to a parallel reduction of CR-thrombotic rate. Conversely, an effective anti-thrombotic prophylaxis might contribute to reduce the rate of catheter colonization and CR-infection.

Diagnosis

[dict: CVC] malfunction and/or occlusion, superficial thrombophlebitis, DVT of the upper limb and PE can be the consequence of a thrombus related to the CVC presence. As reported before, most of these thrombotic events are asymptomatic.
Malfunction of a CVC causes persistent pain during infusion or impossibility for sampling and/or infusion (ball-valve effect at the catheter tip level). When this malfunction/occlusion occurs after at least 24-hour adequate CVC function, is not reversible after at least two flushings with saline, and other possible causes (i.e. kinking or rupture) are excluded, it is attributable to thrombosis. Color-Doppler ultrasound may be useful to locate thrombi in the catheter vein: however, the sensitivity is not satisfactory and a negative finding cannot rule out the thrombotic origin of malfunction/occlusion.
Superficial thrombophlebitis due to CVC is evidenced by one or more of the followings: induration or erythema, warmth, pain or tenderness along the course of the catheter vein. The diagnosis is made on the basis of clinical signs and symptoms: instrumental tools (color-Doppler ultrasound, contrast venography) may be useful in excluding a coexisting DVT.

CR-DVT of the upper limb

Signs and symptoms of clinically overt CR-DVT, such as shoulder girdle, neck or jaw pain, headache, skin discoloration and/or

erythema, and oedema are not sensitive or specific for DVT. In addition, the clinical course of CR-DVT is often silent.
Contrast venography is still considered the gold standard in detecting upper limb DVT in patients with CVC. However, this tool is not frequently used in common practice because of its invasiveness, cost, and use of contrast medium. Furthermore, patients with hematologic malignancies have frequently severe neutropenia with high risk of infection and there is concern about moving them from a protected environment (i.e. sterile rooms) to other departments, such as radiology. As a consequence, the use of contrast venography is often confined to clinical trials (in which it is utilized to obtain a blinded evaluation by an external panel of experts) and to difficult diagnostic situations.
In the case of clinical suspicion of CR- DVT, the non invasive method of compressive ultrasound, especially with Doppler and color imaging, is currently used to confirm the diagnosis. The main criteria of color-Doppler ultrasound 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 (109) on the accuracy of the diagnosis of suspected upper limb DVT in 170 patients (96 of whom had CVC) reported a sensitivity of duplex ultrasound ranging from 56% to 100% and specificity ranging from 94% to 100%. The accuracy of color-Doppler ultrasound for the diagnosis of upper limb DVT has been evaluated in patients with clinical suspicion of DVT, whereas only limited data are available in patients with CVC without symptoms.
In case of clinical suspicion of upper limb DVT, an accuracy rate ranging from 82% to 95% has been reported for color-Doppler ultrasound, using venography as the gold standard (74, 109 112). Koksoy et al. (90) reported on the diagnostic value of color-Doppler ultrasound compared to venography, in CR-DVT; a sensitivity of 94% and a specificity of 96% were found. The sensitivity of ultrasound depends on the location of venous thrombosis. Ultrasound techniques are reliable for the detection of DVT in the jugular, axillary and subclavian veins (with a sensitivity of 95% for axillo-subclavian vein and of 100% for jugular vein) but are less reliable for DVT in the innominate and superior caval veins (with a sensitivity of approximately 5%). Recently, Male et al. (113) compared venography and ultrasound for the diagnosis of asymptomatic DVT in 66 children with acute leukemia. The Authors concluded that ultrasound is insensitive for upper-limb DVT, but may be more sensitive than venography for DVT in the jugular veins. They recommended a combination of ultrasound and venography for the screening of the asymptomatic upper limb DVT. However, a similar protocol is not easily feasible and accepted by clinicians. Taking into account the true incidence of clinically relevant thrombotic complications in hematologic patients with CVC, as it appears from recent reports (4, 114), an aggressive diagnostic approach such as a screening of asymptomatic patients is probably not justified. The low sensitivity of Doppler ultrasound for asymptomatic subclavian thrombosis is confirmed by the study of Haire et al. (115), who compared the sensitivity of duplex ultrasound with venography in 32 asymptomatic patients with the CVC inserted in the subclavian vein. Only 3 out of 11 CR-DVT detected at venography were identified by duplex ultrasound. It is likely that the reduced sensitivity of ultrasound for upper limb DVT, as compared with DVT of the lower limbs, is due to the difficulty in exploring the compressibility of the proximal vein segments of the upper limbs. This could be likely the case of CR-DVT, which is frequently located in the more proximal segments.
Impedance plethysmography is not an acceptable and validated diagnostic tool in patients with suspected CR-DVT of the upper limbs, due to its very low sensitivity and specificity. The presence of CVC itself in the vein can alter venous tone and flow, decreasing the accuracy of this test. Further, impedance plethysmography does not allow a direct visualization of the thrombus and today has been abandoned also for the diagnosis of DVT of the lower limbs. More recently, magnetic resonance venography and spiral computed tomography have been used in the diagnosis of suspected CR-DVT (116 118). The promising results of these tools in the diagnosis of upper limb DVT are to be confirmed by additional studies. However, due to the increased availability of the instrument and the velocity of the test, spiral computed tomography (which is also reliable for the diagnosis of PE) is gaining consent among clinicians.
Laboratory tests such as D-dimer have not been validated in the diagnosis of CR-DVT in hematologic patients. In many outpatients with a clinical suspicion of DVT or PE, values of D-dimer below pre-defined cut-off levels proved to reliably rule out thrombosis (119).
However, the underlying disease and the presence of the CVC make it unlikely the utility of D-dimer as a diagnostic test in this setting of patients.
In conclusion, in the case of clinical suspicion of CR-DVT, compressive US should be used as a first-step choice to confirm or rule out the diagnosis. Patients with positive ultrasound should be considered having DVT and treated accordingly. Patients with negative ultrasound but persisting symptoms should undergo serial testing or venography before the diagnosis of upper limb DVT is ruled out. Spiral CT scan is probably the more promising tool for the near future.

If a CR-DVT is suspected, a Color-Doppler ultrasound test should be performed, followed, in case of negativity, by venography.

Prophylaxis

Due to its frequency, the potential harms (DVT of the upper limbs, PE, fatal PE) and the silent nature of the disease, primary prophylaxis of CR-thrombotic complications has been suggested and studied by many Authors. Table 3 summarizes the main studies conducted in patients with cancer (63, 64, 120 125). Fewer data are available in patients with hematologic malignancies.

Table 3 - Clinical trials of prophylaxis of CVC-related venous thromboembolism in patients with cancer							
Author, year	**Study design***	**N°of pts**	**Prophylactic regimens**	**Duration**	**Endpoint assessment**	**CVC-DVT %**	**P value**
Bern (63), 1990	P,O,C	82	Warfarin 1 mg no treatment	90 days	mandatory venography	9.5 37.5	<0.001
Monreal (64), 1996	P, O, C	29	Dalteparin 2500 U no treatment	90 days	mandatory venography	6 62	0.002
Boraks (120), 1998	O, with historic control	223	Warfarin 1 mg no treatment	variable	symptomatic events	5 13	0.03
PROTEKT (121), 2001	R,O,C	188 children	Reviparin 30-50 U/Kg standard care	30+14 days	mandatory venography	14.1 12.5	0.82
Reichardt (122), 2002	R,D-B, C	439	Dalteparin 5000 U Placebo	16 weeks	symptomatic events	3.7 3.4	0.9
Mismetti (127), 2003	R,D-B	57	Nadroparin 2850 U Warfarin 1 mg	90 days	mandatory venography	28.6 16.7	0.48

**P: prospective, O: open-label, R: randomized, C:controlled, D-B: double-blind trial*

Before analysing in more details these studies, it is necessary to make some preliminary remarks. The question if mandatory venography is a more reliable endpoint than clinically overt thrombotic events is still a matter of debate. Venography is an accurate tool to assess DVT: however, it may be considered a surrogate endpoint, since the real goal of prophylaxis is to prevent clinically relevant thrombotic events and not venographic events. This consideration is valid for many studies on primary prophylaxis of VTE (i.e. in surgical patients), but it is even more relevant in hematologic patients with CVC, since there is no convincing evidence that venographic thrombotic events (which are very frequent) are strongly correlated with severe clinical consequences. Based on this observation, it is not surprising that studies aimed at showing a reduction in the incidence of clinically overt CR-VTE need larger sample size than studies using mandatory venography.

Another remark is that the true incidence of complications seems to be decreased in the more recent studies, if compared with previous studies. The use of newer, less thrombogenic devices and the higher skill in technical positioning may possibly explain this finding.

Heparin, LMWH and oral anticoagulants (mainly warfarin) have been tested for thromboprophylaxis in patients with CVC. Bern et al. (63) evaluated the efficacy and safety of warfarin, administered at fixed dose of 1 mg/day, in an open prospective study. Forty-two patients were randomized to receive warfarin and forty patients to the control arm (no treatment). Warfarin was started 3 days before CVC insertion and was continued for 90 days. In the warfarin group, four patients (9.5%) had venography-confirmed upper limb DVT, compared with 15 patients (37.5%) in the control group. The results are consistent with Authors conclusions that this regimen is effective in the prophylaxis of CR-DVT. Monreal et al. (64) tested a LMWH (dalteparin) in an open prospective study. The Authors found that dalteparin 2,500 U once daily for 90 days is effective and safe in the prophylaxis of upper limb DVT in this setting. In this study, nine of 29 patients (31%) developed symptomatic upper limb DVT confirmed by venography: one of 16 (6%) in the dalteparin group and eight of 13 (62%) in the untreated control group. A study by Boraks et al. (120) in hematologic malignancies tested the efficacy and safety of warfarin prophylaxis in 108 patients with CVC. In this open label study, warfarin was used at a fixed low dose of 1 mg/day during the period of CVC dwell. The incidence of CR-DVT, in treated patients was compared with that observed in a historical population with similar characteristics. Venography or ultrasounds were used to confirm the clinical suspicion of CR-DVT, which was observed in 5% of patients treated with warfarin and in 13% of the historical controls.

The PROTEKT study (121) was an open-label, randomized controlled trial on the prevention of CR-thrombotic complications with a LMWH (reviparin) in children with leukemia. The dose of reviparin was 30 U/kg/day for patients younger than 3 months and 50

U/kg/day for patients older than 3 months. The efficacy endpoint was DVT detected by venography performed at day 30. The study was prematurely terminated because of the slow patient enrolment and the high rate of adverse events. As a matter of fact, VTE rate of 14.1% was reported in the reviparin group as compared with 12.5% in the control group. Many reasons could have affected the results of this study, for example the disease itself (leukemia) and its treatment, and the poorly known responsiveness of children to antithrombotic prophylaxis, which may have caused the choice of ineffective prophylactic doses. A recent randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of dalteparin in preventing CR-complications in solid tumor patients (122). The endpoint of this study was clinically overt CR-thrombotic complications (DVT, PE and CVC obstruction requiring CVC removal). Patients were randomly assigned to receive 5,000 U/day of dalteparin or placebo for 16 weeks. No advantage in terms of reduction of CR-thrombotic complications was found in the dalteparin group as compared to placebo (3.7 vs. 3.4%). The overall rate of VTE was low and this finding could be explained by the use of a clinical endpoint rather than a venography endpoint, as already discussed. Lagro et al. (123) found nadroparin to be ineffective in the prevention of CR-DVT in bone marrow transplant recipients. Heaton et al. (124) performed a randomised, open label study with low-dose warfarin, 1 mg/day, or placebo in 88 patients. The endpoint of the study was symptomatic, venography-confirmed CR-DVT in patients with hematologic malignancies. The Authors found no significant difference in the incidence of CR-thrombotic events and no significant variation in catheter survival in patients treated with warfarin. The same dosage of warfarin was used by Couban et al. (125) in a randomized, double-blind, placebo controlled study on the prevention of symptomatic CR-DVT in 255 patients with cancer. Clinically overt VTE occurred in 4% of patients in the placebo group and in 4.6% of patients in the warfarin group. No difference in the incidence of major or minor bleedings in the two groups was found. A recent meta-analysis (126) of randomized controlled trials in CVC patients showed a benefit of heparin in the prevention of VTE 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). An open, prospective, randomized venography trial (127) compared the efficacy and safety of the LMWH nadroparin with low-dose warfarin in 57 cancer patients with long-term CVC for chemotherapy. Warfarin (1 mg/day) and nadroparin at a fixed daily dose of 2,850 U/day were given for 90 days. Six out of 21 patients in the nadroparin group (28.6%) and four out of 24 patients in the warfarin group (16.7%) had venography-confirmed CR-DVT at 90 days. Safety was similar in both treatments and the Authors concluded for a substantial equivalence of the two treatments.

It is noteworthy that on the basis of the available data, mainly those by Bern (63) and Monreal (64), the Sixth Consensus Conference of the American College of Chest Physicians (128) recommended prophylaxis with LMWH or 1 mg/day fixed-dose warfarin in cancer patients with CVC. However, as reported above, most of the available studies are open, small in size, and with different endpoints (venography-detected DVT or clinically overt thrombosis). In addition, major hemorrhagic complications are not fully described in these studies, which are of paramount importance in patients with hematologic malignancies. Indeed, thrombocytopenia is very frequent in these patients. It may increase the risk of bleeding and contraindicate the use of anticoagulant drugs, although some reports suggest that thrombocytopenia might decrease the risk of thrombosis. Unfortunately, severely thrombocytopenic patients were excluded in most available studies. Perusal of the published studies does not allow a firm conclusion on the risk/benefit ratio of a pharmacological prophylaxis of CR-VTE in hematologic patients.

Larger, prospective studies on the incidence and the clinical relevance of CR-thromboembolic complications, and on the risk of hemorrhage related to the use of anticoagulant drugs in hematologic patients are required. A recent prospective, observational study in 8 Italian Hematology Departments enrolled 412 patients (458 CVC) with hematologic malignancies (114). Clinical events registered up-to 3 months of follow-up were: CR-DVT and PE (strumentally proven), CR-superficial thrombophlebitis, CVC-occlusion / malfunction of thrombotic origin, major cardiovascular events, bleeding, infections and death. CR-thrombotic complications were significantly more frequent in patients with platelet counts > 50,000 x 10^6/L (17.4%). However, the incidence of clinically relevant CR-thrombotic events was not negligible even in patients with more severe thrombocytopenia (10.2%). Since the use or not of thromboprophylaxis was left to the investigator (about 14% of patients received LMWH), no conclusion about the efficacy of prophylaxis can be drawn by this study. However, no increase in bleeding was observed in thrombocytopenic patients receiving anticoagulants, so that pharmacological prophylaxis of CR-DVT does not appear to increase clinically relevant bleeding in these patients.

Treatment

There is scanty literature on the treatment of CR-upper limb DVT in patients with hematologic malignancies. A few data are reported in patients with solid tumors. As a consequence, the treatment of CR-thromboembolic complications is not thoroughly standardized.

The management of thrombotic events may differ in the various clinical settings and depends on the clinical presentation.

CR-DVT of the upper limbs

The main goals of treatment of CR-DVT are to reduce mortality and morbidity from the acute event and minimize late complications. It is always necessary to objectively confirm DVT. In agreement with the common management of DVT, anticoagulant therapy is likely to be the treatment of choice. Accordingly, treatment is started with intravenous unfractionated heparin (adjusted in order to keep the activated partial thromboplastin time between 1.5 and 2.5 times the basal values) or subcutaneous LMWH (about 160-200 IU/kg/day) for 5 to 7 days, and continued with oral anticoagulation with warfarin, started on the first day, with target INR of 2.5 (therapeutic range: INR 2.0-3.0).

A recent prospective study evaluated the administration of a LMWH (dalteparin, 200 IU/kg/d) in the treatment of 46 outpatients with upper limb DVT (129), suggesting the safety and efficacy of outpatient treatment, which is cost saving and improves patients quality of life. If oral anticoagulation is contraindicated or not easily feasible (for example, for the interactions with chemotherapy), patients usually receive long-term treatment with LMWH. A prolonged treatment with LMWH at a reduced dosage (about 75% of the initial dose) showed a significant advantage over the conventional treatment with oral anticoagulants in patients with cancer and DVT of the lower limbs (130). The use of a LMWH (enoxaparin) has been evaluated in the treatment of CR-thrombosis in five patients with Hickman catheter and thrombocytopenia undergoing bone marrow transplantation (131). The treatment was effective and no severe hemorrhagic complications were recorded.

In summary, even if there is no consensus on the optimal management of patients with CR-DVT, at present most patients receive anticoagulation according to current guidelines for lower limb DVT. However, thrombocytopenia may be a major concern, and the management of patients with platelet counts below 50,000 x 10^6/L is still uncertain and left to individual evaluation of the risk/benefit ratio.
More aggressive therapeutic options for CR-DVT have been attempted by systemic thrombolysis and thrombectomy. Some studies of thrombolytic therapy in CR-DVT have been published (132 138). However, none of these studies compared thrombolysis to heparin treatment. It is unclear whether thrombolytic therapy could reduce symptoms of VTE or prevent line or systemic infection and CVC malfunction. Taking into account the high risk of bleeding in patients with hematologic malignancies and the current practice in patients with DVT, systemic thrombolysis should be limited to patients with severe PE, in the absence of absolute contraindications.
A debated matter is the removal of CVC in the presence of upper limb DVT. To date, there is no consensus on this matter and the removal of the CVC is left to the discretion of the attending physician who has to take into account the clinical symptoms, CVC function, the need to administer additional chemotherapy, and the platelet count. The efficacy of CVC removal on the long-term outcome is unknown. Our personal practice is not to remove the CVC in the acute phase of DVT, if its removal is not mandatory for severe infective complications. We treat DVT with heparin/LMWH and continue on using the CVC, if still working, until it is needed.
The optimal duration of anticoagulation treatment for CR-DVT in patients with hematologic malignancies is unknown. We usually prescribe anticoagulation (with LMWH or warfarin) until the CVC is dwelling and, if not contraindicated, for at least three months from DVT onset.
Some reports suggest the use of superior vena cava filters in patients who have upper limb DVT and absolute contraindications to anticoagulant therapy (139, 140).

CVC occlusion or malfunction of thrombotic origin

CVC tip occlusion or catheter sleeve occlusions are conventionally treated by local thrombolytic therapy with a low dose of single or repeated bolus of urokinase, streptokinase, or tissue plasminogen activator. This treatment is very effective in restoring CVC patency if the catheter is well positioned (141, 142). Recombinant tissue plasminogen activator has also been used. A dose as low as 2 mg in 2 mL was described as effective in pediatric patients (143). In patients with platelet count < 50,000 x 10^6/L is our practice to attempt local thrombolysis using total doses of urokinase equal or inferior to 10,000 U in single or repeated bolus injections. However, a lower dose of 2,000 U in single bolus injection may also be effective (144).
In summary, treatment of patients with CR-VTE is similar to that of thromboembolic events in patients without CVC. A 5- to 7- day course of unfractionated heparin or LMWH, followed by oral anticoagulants, is recommended in absence of contraindications in patients with DVT and/or PE. However, the frailty of hematologic patients (mainly due to severe thrombocytopenia) should be carefully considered in the choice of treatment. If oral anticoagulants are contraindicated or difficult to manage (for example for interactions with chemotherapy), LMWH seems to be a valid alternative. After four weeks of full therapeutic dose (about 200/U/kg/day as single or double subcutaneous injections) a reduced dose of about 150 U/kg/day can be administered. Renal impairment should be excluded, since it increases low molecular weigh heparin half-life and may cause over-dosage and bleeding. Also platelet count should be monitored during treatment. The optimal duration of anticoagulant treatment after CR-DVT is unknown, but at least 3 month of anticoagulation should be delivered in case of major thrombotic events. Systemic thrombolysis is seldom required in patients with CR-DVT and should be discoraged due to the high risk of bleeding. Local thrombolysis, with low doses of urokinase or recombinant tissue plasminogen activator, should be considered to restore CVC patency in occlusion/malfuncion of thrombotic origin. CVC removal has to be evaluated in each patient, but should preferably be postponed at least one month after the onset of DVT.

The use of LMWH seems to be a promising tool for the treatment of CR-thrombosis.

References

1) Bona RD Thrombotic complications of central venous catheters in cancer patients. Semin Thromb Hemost, 25: 147-155, 1999.
2) Franck DA, Meuse J, Hirsch D et al. The treatment and outcome of cancer patients with thromboses on central venous catheters. J Thromb Thrombolysis, 10: 271-75, 2000.
3) Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol, 21: 3665-3675, 2003.
4) Cortelezzi A, Fracchiolla NS, Maisonneuve P, et al. Central venous catheter-related complications in patients with hematological malignancies: a retrospective analysis of risk factors and prophylactic measures. Leukemia & Lymphoma, 44: 1495-1501, 2003.
5) Journeycake JM, Buchanan GR. Thrombotic complications of central venous catheters in children. Curr Opin Hematol, 10: 369-74, 2003.
6) Broviac JW,Cole JJ, Halvorsen S et al. A silicone rubber atrial catheter for prolonged parenteral alimentation. Surg Gynecol Obstet, 36: 602-05, 1973.
7) Hickman RO, Buckner CD, Clift RA. A modified right atrial catheter for access to the venous system in marrow transplant recipient. Surg Gynecol Obstet, 148: 871-75, 1979.
8) Larn S, Scannell R, Roessler D et al. Peripherally inserted central catheters in an acute-care hospital. Arch Intern Med 154: 1833-37, 1994.
9) Niederhuber JE, Ensminger W, Gyves JW et al. Totally implanted venous and arterial access system to replace external catheter in cancer treatment. Surgery, 92: 706-12, 1982.
10) Johansson E, Bjorkholm M, Bjorvell H et al. Totally implantable subcutaneous port systems versus central venous catheter placed before induction chemotherapy in patients with acute leukemia. A randomized study. Support Care Cancer, 12: 99-105,

2004.
11) Crowley II, Pereira JK, Harris LS et al. Peripherally inserted central catheters: Experience in 523 children. Radiology, 204: 617-21, 1997.
12) Jeng MR, Feusner J Skibola C et al. Central venous catheter complications in sickle cell disease. Am J Hematol, 69: 103-08, 2002.
13) Bollard CM, Teague LR, Berry EW et al. The use of central venous catheters (port a caths) in children with hemophilia. Haemophilia, 6: 66-70, 2000.
14) Raad I. Intravascular-catheter-related infections. Lancet, 351: 893-898, 1998.
15) Climo M, Diekema D, Warren DK et al. Prevalence of use of central access devices within and outside of the intensive care unit: Results of a survey among hospitals in the Prevention Epicenter Program of the Centers for Disease Control and Prevention. Infect Control Hosp Epidemiol, 24: 942-45, 2003.
16) Freytes CO. Vascular access problems revisited: the Multinational Association of Supportive Care in Cancer (MASCC) experience. Support Care Cancer, 6: 13-19, 1998.
17) McGee DC, Gould MK. Preventing complications of central venous catheterization. N Engl J Med, 348: 1123-33, 2003. (full text)
18) Cesaro S, Corro R, Gamba P et al. A prospective survey on incidence and outcome of Broviac/Hickman catheter-related complications in pediatric patients affected by hematological and oncological diseases. Ann Hematol, in press.
19) Mansfield PF, Hohn DC, Fornage BD et al. Complication and failure of subclavian-vein catheterization. N Engl J Med, 331: 1735-38, 1994.
20) Taber SW, Bergamini TM. Long-term venous access: Indications and choice of site and catheter. Semin Vasc Surg, 10: 130-34, 1997.
21) Beck C, Dubois J, Grignon A et al. Incidence and risk factors of catheter-related deep vein thrombosis in pediatric intensive care unit: A prospective study. J Pediatr, 133: 237-41, 1998.
22) Kurecki E, Kaye R, Koehler M. Chylothorax and chylopericardium: A complication of central venous catheter. J Pediatr, 132: 1064-66, 1998.
23) Klerk CPW, Smorenburg SM, Bueller HR. Thrombosis prophylaxis in patient populations with a central venous catheter. Arch Intern Med, 163: 1913-1919, 2003. (full text)
24) Richardson MW, Allen GA, Monahan PE. Thrombosis in children: Current perspective and distinct Challenges. Thromb Haemost, 88: 900-11, 2002.
25) Fratino G, Molinari Ac, mazzola MD et al. Prospective study of indwelling central venous catheter-related complications in children with Broviac or clampless valved catheters. J Pediatr Hematol Oncol, 24: 657-61, 2002.
26) Ingram J, Weitzman S, Greenberg ML et al. Complications of indwelling venous access lines in the pediatric haematology patient: a prospective comparison of external venous catheters and subcutaneous ports. Am J Pediatr Hematol Oncol, 13: 130-36, 1991.
27) Massicotte MP, Dix D, Monagle P et al. Central venous catheter related thrombosis in children : Analysis of the Canadian Registry of venous thromboembolic complications. J Pediatr, 133: 770-76, 1998.
28) Glaser DW, Medeiros D, Rollins N et al. Catheter-related thrombosis in children with cancer. J Pediatr, 138: 255-59, 2001.
29) Miller K, Buchanan GR, Zappa S et al. Implantable venous access devices in children with hemophilia : A report of low infection rates. J Pediatr, 132: 304-98, 1998.
30) Xiang DZ, Verbeken EK, Van Lommel AT et al. Composition and formation of the sleeve enveloping of central venous catheter. J Vasc Surg, 28: 260-71, 1998.
31) Hoch JR. Management of complications of long-term venous access. Semin Vasc Surg, 10: 135-43, 1997.
32) Xiang DZ, Verbeken EK, Van Lommel A et al. Sleeve-related thrombosis: A new form of catheter-related thrombosis. Thromb Res, 104: 7-14, 2001.
33) Raad II, Luna M, Khalil SAM et al. The relationship between the thrombotic and infectious complications of central venous catheters. JAMA, 271: 1014-16, 1994.
34) Chesler L, Fuesner J. Use of tissue plasminogen activator in young children with cancer and dysfunctional central venous catheters. J Pediatr Hematol Oncol, 24: 653-58, 2002.
35) Davidson BL. Risk assessment and prophylaxis of venous thromboembolism in acutely and/or critically ill patients. Haemostasis, 30: 77-81, 2000 (suppl S2).
36) Lokich JJ, Becker B. Subclavian vein thrombosis in patients treated with infusion chemotherapy for advanced malignancy. Cancer, 52: 1586-89, 1983.
37) Raaf JH. Results from use of 826 vascular access devices in cancer patients. Cancer, 55: 1312-21, 1985.
38) Lokich JJ, Bothe A, Benotti P et al. Complication and management of implanted venous access catheters. J Clin Oncol, 3: 710-17, 1985.
39) Moss JF, Wagmen LD, Riihimaki DU et al. Central venous thrombosis related to the silastic Hickman-Broviac catheter in an oncolgic population. J Parenter Enteral Nutr, 13: 397-400, 1989.
40) Jansen RF, Wiggers T, van Geel BN. Assessment of insertion tecniques and complication rate of dual lumen central venous catheters in patients with haematological malignancies. World J Surg, 14: 100-04, 1990.
41) Haire WD, Lieberman RP, Edney J et al. Hickman catheter induced thoracic vein thrombosis. Frequency and long term sequelae in patients receiving high dose chemotherapy and marrow transplantation. Cancer, 66: 900-908, 1990.
42) Mueller BU, Skelton J, Callender DP et al. A prospective randomized trial comparing the infectious and non-infectious complications of an externalized catheter versus subcutaneously implanted device in cancer patients. J Clin Oncol, 10: 1943-48, 1992.
43) Wesemberg F, Flaatten H, Janssen CW et al. Central venous catheter with subcutaneous injection port: 8 years clinical follow up with children. Pediatr Hematol Oncol, 10: 233-39, 1993.
44) Soh LT, Ang PT. Implantable subcutaneous infusion ports. Support Care Cancer, 1: 108-10, 1993.
45) Anderson AJ, Krasnow SH, Boyer MW et al. Thrombosis: The major Hickman catheter complication in patients with solid

tumor. Chest, 95: 71-75, 1995.
46) Eastridge BJ, Lefor AT. Complications of indwelling venous access devices in cancer patients. J Clin Oncol, 13: 233-238, 1995.
47) Horne MK III, May DJ, Alexander HR et al. Venographic surveillance of tunneled venous access devices in adult oncology patients. Ann Surg Oncol, 2: 174-78, 1995.
48) Laurenzi L, Fimiani C, Faglieri N et al. Complications with fully implantable venous access systems in oncologic patients. Tumori, 82: 232-36, 1996.
49) Cunningham MJ, Collins MB, Kredentser DC et al. Peripheral infusion ports for central venous access in patients with gynaecologic malignancies. Gynecol Oncol, 60: 397-99, 1996.
50) Nightingale CE, Norman A, Cunningham D et al. A prospective analysis of 949 long-term central venous access catheters for ambulatory chemotherapy in patients with gastrointestinal malignancy. Eur J Cancer, 33: 398-403, 1997.
51) Meisemberg BR, Callaghan M, Sloan C et al. Complications associated with central venous catheters used foe the collection of peripheral blood progenitor cells to support high-dose chemotherapy and autologous stem cell rescue. Support Care Cancer, 5: 223-27, 1997.
52) Wilimas JA, Hudson M, Rao B et al. Late vascular occlusion of central line in pediatric malignancies. Pediatrics, 101: E7,1998.
53) O Neill VJ, Jeffrey Evans TR, Preson J et al. A retrospective analysis of Hickman line-associated complications in patients with solid tumors undergoing infusional chemotherapy. Acta Oncol, 38:1103-07, 1999.
54) Lagro SW, Verdonck LF, Borel Rinkes IH et al. No effect of Nadroparin prophilaxys in the prevention of central venous catheter (CVC)-associated thrombosis in bone marrow transplant recipients. Bone Marrow Transplant, 26: 1103-1106, 2000.
55) Lyon RD, Griggs KA, Johnson AM et al. Long-term follow-up of upper extremity implanted venous access devices in oncology patients. J Vasc Interv Radiol, 10: 463-71, 1999.
56) Knofler R, Siegert E, Lauterbach I et al. Clinical importance of prothrombotic risk factors in pediatric patients with malignancy: Impact of central venous lines. Eur J Pediatr, 158: 147-50, 1999.
57) Schwarz RE, Coit DG, Groeger JS et al. Transcutaneously tunnelled central venous lines in cancer patients: An analysis of device-related morbidity factors based on prospective data collection. Ann Surg Oncol 7: 441-49, 2000. (full text)
58) Biffi R, De Braud F, Orsi F et al. A randomized prospective trial of central venous ports connected to standard open-end or Groshong catheters in adult oncology patients. Cancer, 92: 1204-12, 2001.
59) Molinari AC, Castagnola E, Mazzola C et al. Thromboembolic complications related to indwelling central venous catheters in children with oncological/haematological diseases: a retrospective study of 362 catheters. Support Care Cancer, 9: 539-44, 2001.
60) Coccaro M, Bochicchio AM, Capobianco AM et al. Long-term infusional systems: Complications in cancer patients. Tumori, 87: 308-11, 2001.
61) Fijnheer R, Paijmans B, Verdonck LF et al. Factor V Leiden in central venous catheter-associated thrombosis. Br J Haematol, 118: 267-70, 2002.
62) Harter C, Salwender HJ, Bach A et al. Catheter-related infection and thrombosis of the internal jugular vein in hematologic-oncologic patients undergoing chemotherapy: A prospective comparison of silver coated and uncoated catheters. Cancer, 94:245-51, 2002.
63) Bern MM, Lokich JJ, Wallach SR, et al. Very low dose of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. Ann Intern Med, 112: 423-428, 1990.
64) Monreal M, Alastrue A, Rull M, et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices-prophylaxis with a Low-Molecular Weight Heparin (Fragmin). Thromb Haemost, 75: 251-253, 1996.
65) Balestrieri L, De Cicco M, Matovic M et al. Central venous catheter-related thrombosis in clinically asymptomatic oncologic patients: A phlebographic study. Eur J Radiol, 20: 108-11, 1995.
66) De Cicco M, Matovic M, Balestrieri L et al. Central venous thrombosis: An early and frequent complication in cancer patients bearing long term silastic catheter. A prospective study. Thromb Res, 86: 101-13, 1997.
67) Van Rooden CJ, Rosendaal FR, Barge RMY et al. Central venous catheter related thrombosis in haematology patients and prediction of risk by screening with Doppler-ultrasound. Br J Haematol, 123: 507-512, 2003.
68) Ratcliffe M, Broadfoot C, Davidson M, et al. Thrombosis, markers of thrombotic risk, indwelling CVC and antithrombotic prophylaxis using low-dose warfarin in subjects with malignant disease. Clin Lab Haem, 21: 353-357, 1999.
69) Ljung R, Petrini P, Lindgren AK et al. Implantable central venous catheter facilitates prophylactic treatment in children with hemophilia. Acta Paeditr, 81: 918-20, 1992.
70) Mourkazel AA, Haddad I, Ament ME et al. 230 patient years of experience with home long-term parenteral nutrition in childhood: Natural history and life of central catheters. J Pediatr Surg, 29: 1323-27, 1994.
71) Martin C, Viviand X, Saux P et al. Upper extremity deep vein thrombosis after central venous catheterization via axyllary vein. Crit Care Med, 27: 2626-29, 1999.
72) Luciani A, Clement O, Halimi P. et al. Catheter-related upper extremity deep venous thrombosis in cancer patients: A prospective study based on Doppler US. Radiology, 220: 655-60, 2001. (full text)
73) Prandoni P, Polistena P, Bernardi E, et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med, 157: 57-62, 1997.
74) Tolar B, Gould GR. The prognostic significance of the ball-valve effect in Groshong catheters. Support Care Cancer, 4: 34-38, 1996.
75) Haire WD, Lieberman RP, Lund GB et al. Thrombotic complications of silicone rubber catheters during autologous bone marrow and peripheral stem cell transplantation: Prospective comparison of Hickman and Groshong Catheters. Bone Marrow Transplant, 7: 57-59, 1991.
76) Grove JR, Pevec WC. Venous thrombosis related to peripherally inserted central catheters. J Vasc Interv Radiol, 11: 837-40, 2000.
77) Allen AW, Megargell JL, Brown DB et al. Venous thrombosis associated with the placement of peripherally inserted central catheters. J Vasc Interv Radiol, 11: 1309-14, 2000.
78) Duerksen DR, Papineau N, Siemens J et al. Peripherally inserted central catheters for parenteral nutrition: A comparison with

centrally inserted catheters. J Parenter Enteral Nutr, 23: 85-89, 1999.
79) Cowl CT, Weinstock JV, Al-Jurf A et al. Complications and cost associated with parenteral nutrition delivered to hospitalized patients through either subclavian or peripherally inserted central catheters. Clin Nutr, 19: 237-43, 2000.
80) Ma TY, Yoshinaka R, Banaag A et al. Total parenteral nutrition via multilumen catheters does not increase the risk of catheter-related sepsis: A randomized prospective study. Clin Infect Dis, 27: 500-03, 1998.
81) Borow M, Crowley JG. Evaluation of central venous catheter thrombogenicity. Acta Anaesthesiol Scand, 81: 59-64, 1985 (suppl 3).
82) Gould JR, Carloss HW, Skinner WL et al. Groshong-associated subclavian venous thrombosis. Am J Med, 95: 419-23, 1993.
83) Craft PS, May J, Dorigo A et al. Hickman catheters: Left-sided insertion, male gender and obesity are associated with an increased risk of complications. Aust NZ Med, 26: 33-39, 1996.
84) Puel V, Caudry M, Metayer P et al. Superior vena cava thrombosis related to catheter malposition in cancer chemotherapy given through implanted ports. Cancer, 72: 2248-52, 1993.
85) Petersen J, Delaney JH, Brakstad MT et al. Silicone venous access devices positioned with their tip high in the superior vena cava are more likely to malfunction. Am J Surg, 178: 78-79, 2000.
86) Kearns PJ, Coleman S, Wehner Jh et al. Complications of long-term catheters: Randomized trial of central vs peripheral tip location. J Parent Enter Nutr, 20: 20-24, 1996.
87) Merrer J, De Jonghe B, Golliot F et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trail. JAMA, 286: 700-07, 2001.
88) Timsit JF, Farkas JC, Boyer JM et al. Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis. Chest, 114: 207-213, 1998. (full text)
89) McBride KD, Fisher R, Warnock N et al. A comparative analysis of radiological and surgical placement of central venous catheters. Cardiovasc Intervent Radiol, 20: 17-22, 1997.
90) Koksoy C, Kuzu A, Erden I et al. The risk factors in central venous catheter-related thrombosis. Aust NZ J Surg, 65: 796-98, 1995.
91) Brown DF, Muirhead MJ, Travis PM et al. Mode of chemotherapy does not affect complications with an implantable venous access device. Cancer, 80: 966-72, 1997.
92) Sletnes KE, Holte H, Halvorsen S et al. Activation of coagulation and deep vein thrombosis after bone marrow harvesting and insertion of a Hickman catheter in ABMT patients with malignant lymphoma. Bone Marrow Transplant, 17: 577-581, 1996.
93) Mitchell L. Sutor AH, Andrew M. Hemostasis in childhood acute lymphoblastic Leukemia: Coagulopathy induced by disease and treatment. Semin Thromb Hemost, 21: 390-401, 1995.
94) Andrew M, Monagle P, Brooker L. Thromboembolic complications during infancy and childhood. Hamilton, Ontario: BC Decker, 2000.
95) Stephens LC, Haire WD, Schmit-Pokorny K et al. Granulocyte-macrophage colony-stimulating factor: High incidence of apheresis catheter thrombosis during peripheral stem cell collection. Bone Marrow Transplant, 11: 5154, 1993.
96) Eastman M, Khorsand M, Maki D et al. Catheter-related bacteremia and thrombosis in patients treated with moderate dose, continuous infusion interleukin-2. Proc Am Soc Clin Oncol, 17:437a, 1998 (Abst).
97) De Cicco M, Matovic M, Balestrieri L. et al. Antithrombin III deficiency as a risk factor for catheter-related central vein thrombosis in cancer patients. Thromb Res, 78: 127-37, 1995.
98) Riordan M, Weiden PL. Factor V Leiden mutation does not account for central venous catheter-related thrombosis. Am J Hematol, 58: 150-52, 1998.
99) Wermes C, von Depka Prondzinsky, Lichtinghagen R et al. Clinical relevance of genetic risk factors for thrombosis in paediatric oncology patients with central venous catheters. Eur J Pediatr, 158: 143-46, 1999.
100) Ruud E, Holmstrom H, Natvig S et al. Prevalence of thrombophylia and catheter-associated neck vein thrombosis in 41 children with acncer: A prospective study. Med pediatr Oncol, 38:405-10. 2002.
101) Monreal M, Dvant E. Thrombotic complications of central venous catheters in cancer patients. Acta Haematol, 106: 69-72,2001.
102) Rello J, Ochagavia A, Sabanes E et al. Evaluation of outcome of intravenous catheter-related infections in critical ill patients. Am J Respir Crit Care Med, 162: 1027-30, 2000. (full text)
103) Viot M. Intravenous access: related problems in oncology. Internat J Antimicrob Agents, 16:165-168, 2000.
104) Groeger JS, Lucas AB, Thaler HT, et al. Infectious morbidity associated with long-term use of venous access device in patients with cancer. Ann Intern Med, 119: 1168-1174, 1993. (full text)
105) Maki DG, Weise CE and Sarafin HW. A semiquantitative culture metod for identifying intravenous-catheter-related infection. N Engl J Med, 296: 1305-1309, 1977.
106) Raad I, Darouiche R, Dupuis J et al. Central venous catheters coated with mynocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections: A randomized, double-blind trial. Ann Intern Med, 127: 267-74, 1997. (full text)
107) Karthaus M, Doellmann T, Klimasch T et al. Central venous catheter infections in patients with acute leukemia. Chemotherapy, 48:154-57, 2002.
108) Wechsler RJ, Spirm PW, Conant EF et al. Thrombosis and infection caused by thoracic venous catheters: Pathogenesis and imaging findings. Am J Roentgenol, 8:461-71, 1993.
109) Mustafa BO, Rathbun SW, Whitsett TL, et al.: Sensitivity and specificity of ultrasonography in the diagnosis of upper extremity deep vein thrombosis. A systematic review. Arch Intern Med, 162: 401-404; 2002.
110) Knudson GJ, Wiedmeyer DA, Erickson SJ, et al.: Color doppler sonographic imaging in the assessment of upper extremity deep venous thrombosis. AJR, 154: 399-403; 1990.
111) Sottiurai VS, Towner k, McDonnell AE, et al.: Diagnosis of upper extremity deep venous thrombosis using noninvasive technique. Surgery, 91: 582-585; 1982.
112) Baxter GM, Kincaid W, Jeffrey RF, et al.: Comparison of colour doppler ultrasound with venography in the diagnosis of axillary and subclavian vein thrombosis. Br J Radiol, 64: 771-781; 1991.

113) Male C, Chait P, Ginsberg JS, et al.: Comparison of venography and ultrasound for the diagnosis of asymptomatic deep vein thrombosis in the upper body in children. Results of the PARKAA study. Thromb Haemost, 87: 593-598; 2002.
114) Falanga A, Moia M, Cortelezzi A et al. A prospective observational study on catheter-related complications in patients with hematological malignancies (CATHEM). Abstract accepted for the 18th International Congress on Thrombosis, Lubjana, June 20-24, 2004.
115) Haire WD, Lynch TG, Lieberman RP, et al.: Utility of duplex ultrasound in the diagnosis of asymptomatic catheter-induced subclavian vein thrombosis. J Ultrasound Med, 10: 493-496; 1991.
116) Haire WD, Lynch T, Lund GB, et al.: Limitation of magnetic resonance imaging and ultrasound-directed (duplex) scanning in the diagnosis of subclavian vein thrombosis. J Vasc Surg, 12: 391-397; 1991.
117) Shankar KR, Abernethy LJ, Das KS, et al.: Magnetic resonance venography in assessing venous patency after multiple venous catheters. J Pediatr Surg 37: 175-179; 2002.
118) Forneris G, Quarello F, Pozzato M, et al.: Spiral x-ray computed tomography in the diagnosis of central venous catheterization complications. Nephrologie, 22: 495-499; 2001.
119) Schutgens RE, Haas FJ, Gerritsen WB, van der Horst F, Nieuwenhuis HK, Biesma DH. The usefulness of five D-dimer assays in the exclusion of deep venous thrombosis. J Thromb Haemost, 1:976-81;2003.
120) Boraks P, Seale J, Price J, et al.: Prevention of central venous catheter associated thrombosis using minidose warfarin in patients with haematological malignancies. Brit J Haematol, 101: 483-486; 1998.
121) Massicotte P, Julian JA, Gent M, et al.: An open-label randomized controlled trial of low molecular weight heparin for the prevention of central venous line related thrombotic complications in children: the PROTEKT study. Thromb Haemost, (suppl July 2001); (abstr).
122) Reichardt P, Kretzschmar A, Biakhov M, et al.: A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of daily low-molecular-weight-heparin (dalteparin sodium) in preventing catheter-related complications (CRCs) in cancer patients with central venous catheters (CVCs). Proceedings of 38th annual ASCO meeting (vol 21) 2002; (abstr).
123) Lagro SW, Verdonck LF, Borel Rinkes IH, et al.: No effect of nadroparin prophylaxis in the prevention of central venous catheter (CVC)-associated thrombosis in bone marrow transplant recipients. Bone Marrow Transplant, 26: 1103-1106; 2000.
124) Heaton DC, Han DY, Inder A: Minidose (1 mg) warfarin as prophylaxis for central vein catheter thrombosis. Intern Med J, 32: 84-88; 2002.
125) Couban S, Goodyear M, Burnell M, et al.: a randomized double blind placebo-controlled study of low dose warfarin for the prevention of symptomatic central venous catheter-associated thrombosis in patients with cancer. Blood, 100 (11): 703a; 2002 (abstr n° 2769).
126) Randolph AG, Cook DJ, Gonzales CA, et al.: Benefit of heparin in central venous and pulmonary artery catheters. A meta-analysis of randomized controlled trials. Chest, 113: 165-171; 1998. (full text)
127) Mismetti P, Mille D, Laporte S, et al.: low-molecular-weight heparin (nadroparin) and very low doses of warfarin in the prevention of upper extremity thrombosis in cancer patients with indwelling long-term central venous catheters: a pilot randomized trial. Haematologica, 88: 67-73; 2003.
128) Geerts WH, Heit JA,Clagett,P et al. Prevention of Venous Thromboembolism. Chest, 119:132S 175S; 2001. (full text)
129) Savage KJ, Wells PS, Schulz V, et al.: Outpatient use of low molecular weight heparin (dalteparin) for the treatment of deep vein thrombosis of the upper extremity. Thromb Haemost, 82:1008-1010;1999.
130) Lee AY, Levine MN, Baker RI et al. Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. N Engl J Med, 349:146-53; 2003.
131) Drakos PE, Nagler A, Or R, et al.: Low molecular weight heparin for Hickman catheter-induced thrombosis in thrombocytopenic patients undergoing bone marrow transplantation. Cancer, 70: 1895-1898; 1992.
132) Horne MK 3rd, Mayo DJ: Low-dose urokinase infusions to treat fibrinous obstruction of venous access devices in cancer patients. J Clin Oncol, 15:2709-2714; 1997.
133) Pucheu A, Dierhas M, Leduc B, et al.: Fibrinolysis of deep venous thrombosis on implantable perfusion devices. Apropos of a consecutive series of 57 cases of thrombosis and 32 cases of fibrinolysis. Bull Cancer Paris, 83: 293-299; 1996.
134) Rubenstein M, Creger WP: Successful streptokinase therapy for catheter-induced subclavian vein thrombosis. Arch Intern Med, 140: 1370-1371; 1980.
135) Rodenhuis S, van t Hek LGFM, Vlasveld LT, et al.: Central venous catheter associated thrombosis of major veins: thrombolytic treatment with recombinant tissue plasminogen activator. Thorax, 48: 558-559; 1993.
136) Haire WD, Atkinson JB, Stephens LC, et al.: Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double blinded, randomized trial. Thromb Haemost, 72: 543-547; 1994.
137) Fraschini G, Jadeja J, Lawson M, et al.: Local infusion of urokinase for the lysis of thrombosis associated with permanent central venous catheters in cancer patients. J Clin Oncol, 5: 672-678; 1987.
138) Schindler J, Bona RD, Chen HH, et al.: Regional thrombolysis with urokinase for central venous catheter-related thrombosis in patients undergoing high-dose chemotherapy with autologous blood stem cell rescue. Clin Appl Thromb Haemost, 5: 25-29; 1999.
139) Spence LD, Gironta MG, Malde HM, et al.: Acute upper extremity deep venous thrombosis: safety and effectiveness of superior vena caval filters. Radiology, 210: 53-58; 1999. (full text)
140) Ascher E, Hingorani A, Tsemekhin B, et al.: Lesson learned from a 6-year clinical experience with superior vena cava Greenfield filters. J Vasc Surg, 32: 881-887; 2000.
141) Haire WD, Lieberman RP: Thrombosed central venous catheters: restoring function with 6-hour urokinase infusion after failure of bolus urokinase. J Parenter Enteral Nutr, 16: 129-132; 1992.
142) Ponec D, Irwin D, Haire WD, et al.: Recombinant tissue plasminogen activator (alteplase) for restoration of flow in occluded central venous access devices: a double-blind placebo-controlled trial--the Cardiovascular Thrombolytic to Open Occluded Lines (COOL) efficacy trial. J Vasc Interv Radiol, 12: 951-955; 2001.
143) Shen V, Li X, Murdock M, Resnansky L, McCluskey ER, Semba CP; COOL Investigators. Recombinant tissue plasminogen

activator (alteplase) for restoration of function to occluded central venous catheters in pediatric patients. J Pediatr Hematol Oncol, 25:38-45; 2003.
144) Juve ME. Intravenous catheter declotting: same outcomes with lower dose urokinase?. J Infus Nurs, 26: 245-51; 2003.

Marco Moia
Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Department of Hematology, IRCCS Maggiore Hospital and University of Milan, Milan, Italy

Agostino Cortelezzi
Department of Hematology, IRCCS Maggiore Hospital and University of Milan, Milan, Italy

Anna Falanga
Department of Hematology-Oncology, Ospedali Riuniti, Bergamo, Italy

Correspondence to: Anna Falanga, MD
Department of Hematology-Oncology,
Ospedali Riuniti di Bergamo
Largo Barozzi, 1 - 24128 Bergamo, Italy
Phone +39.035.269491
Fax +39.035.266659
E-mail annafalanga@yahoo.com

Abbreviations

CR: complete response OR CVC-related
DVT: deep vein thrombosis
LMWH: low molecular weight heparin
PE: pulmonary embolism
VTE: venous thomboembolism