Venous thromboembolism (VTE) is a frequent complication of long-term access using central venous catheters, with the highest frequency in hematological diseases, and is one of the leading causes of death in oncology patients. Cohort studies of surgical patients have shown that the incidence of VTE is markedly higher in patients with cancer than in patients without cancer. Post-mortem studies have also demonstrated a higher incidence of VTE in patients with cancer. The association between cancer and VTE arises both as a direct consequence of tumor growth and host inflammatory responses and indirectly as a consequence of cancer treatment, venous stasis, and direct vessel trauma. It is well known that the risk for developing VTE in cancer patients is significantly increased during chemotherapy and as a result of long-term central venous catheter (CVC) placement. Many cancer patients require long-term central venous access for the safe deliverance of chemotherapeutic agents, nutrients and fluids, and transfusion of blood and blood products, as well as for the withdrawal of blood samples from the central circulation. Long-term CVCs may remain in position for months or years, and their role in facilitating patient care is clear. Nevertheless, they are associated with a number of early and late complications, including catheter-related deep vein thrombosis (CVC-related DVT), which represents the second cause for catheter loss, after infection. Though scientific evidences and clinical experience are steadily increasing, many uncertainties still exist about several aspects concerning etiology, pathogenesis, diagnosis, management, and prevention of this complication. The GAVeCeLT (the Italian Study Group for Long Term Central Venous Access) promoted a nationwide consensus, and 12 experts reviewed systematically all the available literature. A preliminary document was presented and discussed during a specific Consensus Meeting, in front of a panel of more than 80 experts (representing different health professions and disciplines). This led to a prefinal document, which was presented to more than 800 health professionals. After peer review by an external board of experts, the final document was prepared. In this article, methodology and results of the consensus are presented.
Methods

The methodology was planned and carried out according to the principles of evidence-based medicine (EBM), with special attention to the recommendations of the Italian National Health Institute (ie, Standards for Planning National Guidelines).7 The guidelines have been developed by using methods that maximize their validity, such as:

• Identification of evidence by systematic review;
• Development by a multidisciplinary group; and
• Use of explicit links between evidence and recommendations, defining the strength of the recommendation according to accepted standards as follows:4

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence</th>
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<tr>
<td>I</td>
<td>Randomized clinical trial of high statistical value or meta-analysis of randomized, clinical trials (RCTs).</td>
</tr>
<tr>
<td>II</td>
<td>RCT of lower statistical value.</td>
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<tr>
<td>III</td>
<td>Case-control study, historical study, nonrandom.</td>
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<tr>
<td>IV</td>
<td>Clinical series and retrospective analysis.</td>
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<tr>
<td>V</td>
<td>Case reports and anecdotal data.</td>
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A committee of 12 experts examined systematically the literature and defined 8 questions to be answered:

1. By what mechanisms may a catheter cause a venous thrombosis?
2. Is there an ideal insertion technique for minimizing the risk?
3. Is there any device or material that may intrinsically reduce the risk?
4. What are the patient's risk factors?
5. What is the role of tip position?
6. If thrombosis occurs, when should the catheter be removed?
7. What is the ideal pharmacological management?
8. Can CVC-related DVT be prevented?

A preliminary document was presented and discussed during a specific consensus meeting, in front of an enlarged panel of more than 80 experts (representing different health professions and different disciplines). This led to a prefinal document, which was presented during a GAVeCeLT Congress in Milan, Italy, to an external board of experts (including international European referees), a final document was prepared.

Recommendation for Clinical Practice Cannot Be Proposed.

2. Is There an Ideal Insertion Technique for Minimizing the Risk?

New techniques have been developed to access central veins with different imaging aides (ie, ultrasound, eco-color-Doppler, digital venography, etc.). The only procedure that is associated with valid scientific data, retrieved in clinical, randomized, controlled studies9 and elaborated in a meta-analysis10 is the ultrasound (US)-guided placement of central venous access.

This meta-analysis, taking into account 8 randomized studies, showed that US-guided placement is useful in reducing complications in percutaneous accesses performed with the standard “landmarks” technique, should the operator have little experience. In fact, in such studies, the control arm (unguided percutaneous access) often had an unusually high complication and failure rate (over 40%). Most studies do not exhibit a sufficient follow up, thus leading to an underestimation of costs; it is also well known that a number of late complications (thrombosis included) could arise months after implantation.17

More recently, other articles have addressed this issue with a randomized or prospective approach in the intensive care unit (ICU) setting18 and in oncology,19 pediatric,20 and dialysis patients,21 leading to the conclusion that US guidance improved the success rate of internal jugular vein cannulation, reducing the number of attempts and the failure rate, as well as reduced the incidence of thrombotic complication. The National Institute for Clinical Excellence-UK (Nice-UK)22 made the following recommendations in 2002:

1. 2-D imaging US guidance should be the preferred method when inserting a CVC into the internal jugular vein in adults and children in elective situations.
2. 2-D imaging US guidance should be considered in most clinical situations where CVC insertion is necessary, whether the situation is elective or an emergency.
3. Everyone who uses 2-D imaging US guidance to insert CVCs should have appropriate training to ensure they are competent to use the technique.

Conclusions of the Consensus

There are multiple mechanisms, always including an acute and/or chronic endothelial damage to the vein wall, produced by a foreign intravascular body. Although mechanisms of fibrin sheath formation are well known, their relationship with the thrombotic event is not yet clear.

Results

1. By What Mechanisms May a Catheter Cause Venous Thrombosis?

Soon after the insertion of almost all catheters, a fibrin sheath forms around the catheter. Data from several studies have shown that the sheath develops within 24 hours of catheter insertion.9 In an autopsy study of patients with CVCs, all 55 patients examined developed this sleeve, and, in phlebographic studies, 45 of 57 (78%) patients had a fibrin sheath.9,10 A venographic study showed that 83 of 95 (87%) patients had these sheaths.11 Furthermore, detailed studies by quantitative electron microscopy and by quantitative microbiologic testing of these fibrin sheaths over time have shown that they are always colonized by cocci.12,13

The presence of these sheaths does not predict subsequent DVT of the vessel in which the catheter is placed. In one study, only 1 of 16 patients with a fibrin sheath developed thrombosis over a median of 12.5 months.14

References

With respect to the vein chosen, in one randomized trial, catheter-related thrombosis occurred in 21.5% of the patients with femoral venous catheters and in 19% of those with subclavian venous catheters. In an observational study, the risk of thrombosis associated with internal jugular vein insertion was approximately four times the risk associated with subclavian insertion, thus reinforcing the idea that subclavian vein catheterization carries the lowest risk of catheter-related thrombosis. It should be emphasized that these data were obtained in critically ill patient populations; a trial of oncology patients undergoing long-term cannulation has not been published to date, although an objective need of such a trial is clear. The present state of central venous long-term cannulation, especially for CVCs and ports used in oncology, is confusing. These procedures differ from center to center, and the majority of operators tends to rely on personal experience and professional formation when choosing an approach, the most important factor being their personal confidence with the various possible techniques. Looking at prospective, nonrandomized studies, percutaneous technique and surgical cutdown seem to have the same rate of thrombotic complication.

Conclusions of the Consensus

- To date, to our knowledge, no randomized trials have investigated the relationships between insertion techniques in the long-term setting (eg, percutaneous vs venous cut-down, US-guided vs anatomic landmark techniques) and central venous thrombosis rate.
- Prospective, not randomized, studies have suggested a relationship between minimal insertion damage to vein wall, as obtained with US guidance, and low rate of subsequent thrombotic events.

Strength C Recommendation.

3. Is There Any Device or Material That May Intrinsically Reduce the Risk?

Currently, a wide variety of CVCs are used in medicine. Major design efforts have been undertaken to develop catheters that minimize trauma to blood vessels and are less thrombogenic. The catheter type and materials have undergone major design changes and continue to evolve. Randomized trials and prospective observations have indicated an inherent superiority of silicone and 2nd-3rd-generation polyurethane over more rigid materials, like polyvinylchloride (PVC), tetrafluoroethylene, and polyethylene. Pure silicone, valved catheters exhibited a lower rate of thrombosis compared with barium-added, open-ended silicone ones in a randomized trial. The number of catheter lumens is a major predictor of catheter thrombosis. In one study, triple-lumen, tunneled catheters failed at three times the rate of double-lumen catheters.

Conclusions of the Consensus

- Silicone and 2nd-3rd-generation, polyurethane catheters are less thrombogenic than polyethylene or PVC ones.
- A lower-diameter catheter and a single lumen might be protective against the risk of central venous thrombosis. When the number of therapies demands a multiple-lumen catheter, the number of lumens used should be minimized.

Strength B Recommendation.

4. What Are the Patient's Risk Factors?

The patient risk factors related to CVC thrombosis are many, and most have been studied primarily in oncology patients. As previously discussed, the presence of malignancy generally results in a higher rate of thrombosis; some types of malignancy (eg, adenocarcinoma of the lung or the pancreas) may be associated with higher rates of thrombosis. In a prospective study, 45% of patients with lung cancer developed symptomatic CVC thrombosis, whereas only 9% of those with head and neck cancer did. This may be related to the activation of the coagulation system in these different malignancies, tumor-related changes in blood flow, or levels of tissue factor or tissue-factor-pathway inhibitor.

Inherited thrombophilia has been investigated as possible predictor of CVC thrombosis. One study reported that low antithrombin III levels were associated with a greater risk for thrombosis. Another study found that 32% of patients who had CVC thromboses had diagnoses of a hypercoagulable state; most had elevated anticardiolipin antibody levels, but there was no greater incidence of prothrombin 20210A mutation, Factor V Leiden, protein C deficiency, or protein S deficiency. A case-control study showed that Factor V Leiden carriers with locally advanced or metastatic breast cancer have an increased risk of developing catheter-related DVT during chemotherapy. Last, fibrinogen level and platelet count have been measured in patients with CVC thromboses, but the data are conflicting and most cases are not related to elevations in fibrinogen or platelet count.

Conclusions of the Consensus

- Neoplastic disease and chemotherapy are recognized risk factors for development of central venous thrombosis in patients with a CVC. Pathophysiology is known: It includes direct release of thrombogenic factors by neoplastic cells, decrease of antithrombotic natural factors induced by the tumor, and the procoagulant activity of many antitumor drugs.
- In nonrandomized studies, mutations of Factor V Leiden and/or the prothrombin gene and low antithrombin III levels have been found to be related to a higher incidence of central venous thrombosis in cancer patients with a CVC. Hereditary screening procedures for thrombophilia are not presumably cost effective.

Recommendation for clinical practice cannot be proposed.

5. What Is the Role of Tip Position?

The position of the catheter in the vascular system is a major determinant of CVC-related thrombosis, and tip position has been shown to be the main independent prognostic factor for malfunction and reduced duration of the device. Placement of the catheter tip high in the superior vena cava (SVC) results in a higher incidence of thrombosis than when the catheter tip is placed low in the...
SVC or at atrio-caval junction. Therefore, at least in oncology patients, the atrial-caval junction is apparently the optimal position; hemodialysis could require a full atrial positioning of the catheter tip, at least for cuffed devices. The side of the body where the catheter is inserted has been investigated, with conflicting results; most reports indicate that catheters inserted from the left subclavian vein clotted more commonly.

**Conclusions of the Consensus**

- In many prospective studies, tip position emerged as the main independent prognostic factor for malfunction, thrombosis, and reduced duration of the device. In oncology patients, the atrial-caval junction appears to be the optimal position of the catheter tip, as it minimizes the risk of central venous thrombotic events.

**Strength B Recommendation.**

6. *If Thrombosis Occurs, When Should the Catheter Be Removed?*

The majority of clinical reports about pharmacology treatment of catheter-related DVT have focused on clinically overt and imaging-diagnosed thromboses. These studies have not always indicated the fate of the catheter; only 7 retrospective articles that indicated this problem could be retrieved; and those 7 articles reported a rate of successful catheter preservation ranging from 45.5% to 96% (N = 235). No clear advantages could be obtained by catheter removal after the thrombosis was established, and the clinical outcome did not seem influenced by this measure. In addition, local thrombolytic treatment may require the presence of the catheter and a poor peripheral vein status could represent a major limiting factor for most therapies, after the catheter has been removed.

A risk of embolization during or immediately after catheter removal has been clinically confirmed by many anecdotal reports. The mandatory indications to catheter removal in case of thrombosis include infected thrombus, malposition of the tip (primary or secondary to migration), and irreversible occlusion of the lumen.

**Conclusions of the Consensus**

- Catheter removal or maintenance does not influence the outcome.
- Although local thrombolytic treatment may require the presence of the catheter, a poor peripheral vein status could represent a major limiting factor for most therapies, if the catheter has been removed.
- In case of clinically overt or imaging-diagnosed DVT, a risk of embolization during or immediately after catheter removal has been clinically confirmed.
- Catheter should be removed in case of:
  - Infected thrombus;
  - Malposition of the tip (radiologic reposition of the tip often fails, as a consequence of the inability to reach it inside the thrombus); or
  - Irreversible occlusion of the lumen.

**Strength C Recommendation.**

7. *What is the Ideal Pharmacological Management?*

This topic has been investigated exclusively by retrospective studies and a small clinical series of monocentric experiences. In general, thrombolytic drugs showed higher efficacy when used in acute symptomatic cases (diagnosis made less than 24 hours after the first symptoms arising). The efficacy of systemic versus local thrombolysis is still matter of debate; the latter may require the availability of an interventional radiology suite and specific expertise when a second, smaller catheter is directed percutaneously into a large thrombus to deliver locally a thrombolytic agent. Catheter-directed, low-dose infusion of a thrombolytic agent for a defined period of time is safely done on the nursing units and often in alternative-care settings such as ambulatory infusion clinics.

Another unresolved issue is the long-term treatment of patients who experienced symptomatic catheter-related DVT. Most institutions and authorities prescribe warfarin therapy as long as cancer is active; nevertheless, the effectiveness of warfarin in preventing VTE recurrence is lower in patients with cancer than without cancer, whereas the risk of bleeding may be higher in patients with malignancy. Warfarin carries the additional disadvantage of having substantial inter- and intraindividual variability in dose requirement and the need for frequent dose monitoring. Several low-molecular-weight heparins (LMWHs) have demonstrated superior efficacy to warfarin in the prevention of recurrent VTE. Specifically, dalteparin demonstrated superior efficacy to warfarin in a large trial of patients with cancer and VTE without increasing the risk of bleeding. Thus, compared with warfarin, the LMWHs exhibit a superior safety profile and more predictable antithrombotic effects and can usually be given once daily, without the need for dose monitoring. It is important that possible antineoplastic effects of LMWHs may alter the natural history of malignant disease.

**Conclusions of the Consensus**

- Thrombolytic drugs should be used in acute symptomatic cases (diagnosis <24 hours after the first symptoms). Efficacy of systemic versus local thrombolysis is still matter of debate, especially for large thrombi.
- Chronic symptomatic cases should be treated with a combination of LMWH and then oral anticoagulants, or LMWH long term alone, depending on the clinical setting. Compared with warfarin, the LMWHs exhibit a superior safety profile and more predictable antithrombotic effects and can usually be given once daily in a unit dose without the need for dose monitoring.

**8. Can We Prevent Catheter-Related Central Venous Thrombosis?**

The benefit of systemic prophylaxis with LMWHs or warfarin has not been well established. Although many older studies support the use of low-dose warfarin and LMWHs, most recent stud-
ies do not. In a 1990 randomized, open, prospective study of oncology patients, Bern et al compared the administration of 1 mg/day of warfarin with no warfarin for 90 days.76 All patients underwent a venogram at the time of thrombotic symptoms or at 90 days. Total thrombosis rates determined by venographic methods were 37.5% (15/40) for patients without warfarin and 9.5% (4/42) for patients given warfarin. Symptomatic thrombi occurred in 13 of 40 (32.5%) patients without warfarin and in 4 of 42 (9.5%) patients given warfarin (p = 0.001). Boraks et al obtained similar results in a nonrandomized study in which patients received 1 mg/day warfarin prophylactically and were assessed for venographically verified thrombi.78 In those patients treated with minidoses of warfarin, symptomatic thrombi occurred in 5 of 108 (5%) patients compared with 15 of 115 (13%) patients in a historical control group that did not receive warfarin (p = 0.03). Furthermore, the time to thrombosis was a median of 72 days in those who received warfarin but was 16 days in those who did not receive warfarin.

Since the studies discussed above, a number of other studies have been performed to assess the utility of low-dose warfarin prophylaxis. Three have shown a probable benefit of low-dose warfarin, which was of borderline statistical significance given the small number of patients studied.77-79 Three more recent studies did not show any benefit of low-dose warfarin. In a nonrandomized study of 160 patients with melanoma or renal cell cancer being treated with interleukin-2, 1 mg/day warfarin did not reduce the CVC thrombosis rate.80 Heaton et al randomized 88 patients with double-lumen, subclavian, tunneled catheters to receive either 1 mg/day warfarin or no therapy.81 After 90 days, there was no difference in the rates of clinically significant thrombi between those treated with warfarin and those not treated: 8 of 45 (18%) patients treated with warfarin and 5 of 43 (12%) patients not treated had clinically evident thrombi. Coban et al randomized 255 cancer patients to receive warfarin 1 mg daily or placebo.82 The overall incidence of symptomatic CVC-related DVT was 4.3%: 6 of 130 patients (4.6%) in the warfarin group and 5 of 125 patients (4.0%) in the placebo group. Moreover, the incidence of serious bleeding was 2% in the warfarin group and 0 in the placebo-treated group.

This discrepancy in the results probably reflects the inadequate number of patients in the old clinical trials but may also be due to better catheter care, superior catheter design, and more attention to implantation technique.

Similar trends were observed for LMWH-based prophylaxis. In an early, randomized, open-label, prospective study by Monreal et al, oncology patients with Port-a-Cath (Smiths Medical, Saint Paul, MN) catheters received 2500 units/day dalteparin or no therapy and underwent a venogram at the time of symptoms or at 90 days. The overall incidence of symptomatic CVC-related DVT was 4.3%; 6 of 130 patients (4.6%) in the warfarin group and 5 of 125 patients (4.0%) in the placebo group. Moreover, the incidence of serious bleeding was 2% in the warfarin group and 0 in the placebo-treated group.83

Of the 16 patients who received dalteparin, only 1 developed a thrombosis, and this thrombosis was symptomatic. Of the 13 patients who received no treatment, 8 (62%) developed thromboses, and of those, 7 were symptomatic. Because of the highly statistically significant difference in outcome (p = 0.002), the study was closed early to accrual.

Similar studies done with larger numbers of patients failed to show any difference in CVC thrombosis rates. Pucheu et al prospectively compared patients given 2500 anti-Xa U/day dalteparin subcutaneously with untreated historical controls using US done at Months 1, 3, and 12 to screen for thrombosis.84 Documented thrombi occurred in 3 of 46 (6.5%) patients who received dalteparin, and all were without symptoms. In the historical control group, 11 of 72 (15%) patients developed documented clots, not a statistically significant difference. Two recent, large, randomized, blinded, placebo-controlled studies failed to demonstrate a benefit from prophylactic use of LMWHs in cancer patients. In the first,149 patients received placebo injections and 294 received 5000 IU/day dalteparin subcutaneously for 16 weeks.85 Clinical thrombosis occurred in 5.3% of placebo-treated and 5.8% of dalteparin-treated patients, not a statistically significant difference. There was no difference in infection rates. In the second study,86 385 patients were randomly assigned to receive the LMWH enoxaparin, 40 mg daily for 42 days, or placebo. The primary endpoints were CVC-related DVT of the upper limbs screened by venography or clinically overt pulmonary embolism, confirmed by objective testing. Venography was performed at 6 weeks or earlier in case of clinical suspicion of thrombosis. CVC-related thrombosis was found in 22 (14.1%) of the 155 patients in the enoxaparin group and 28 (18%) of the placebo group, corresponding to a 22% (not statistically significant) risk reduction in the rate of CVC-related DVT (p = 0.35).

Conclusions of the Consensus

- Although some open-label, early trials suggested a benefit of oral, low-dose daily warfarin or daily subcutaneous dose of LMWHs, more recent randomized, double-blind, placebo-controlled, and sufficiently powered trials did not find any advantages for either of these prevention strategies.
- The choice to start a prophylaxis of venous thromboembolic events in all oncology patients bearing a CVC, either with LMWHs or with minidose warfarin, remains unsupported by evidence-based medicine.
- GAVeCeLT suggests considering prophylaxis with a daily single dose of LMWH 100 IU/kg only in high-risk population (including those who have a family history or previously suffered from idiopathic venous thrombotic events of the upper or lower vena cava district).

Strength C Recommendation.

Final Remarks

On a population basis, CVC-related thrombosis is associated with considerable morbidity and expense. When CVC-related DVT occurs, it seriously complicates the clinical management of the patient because of the need for anticoagulant treatment and the occasional need to start another central line. DVT may be particularly troublesome in a patient who already has compromised venous access because of multiple courses of chemotherapy.

Two important areas of investigation deserve additional, substantive efforts: prevention and treatment. Future prevention studies should also focus on achieving a better understanding of the risk factors for CVC thrombosis, contributing to a better definition of risk patient population. Certain patient groups, including those with a hematological malignancy undergoing intensive chemotherapy as well as those with a hereditary thrombophilia.
or with a prior history of unprovoked thrombosis, may have an elevated risk of developing this complication, making them potential candidates for prophylaxis. Future trials evaluating antithrombotic prophylaxis in these special patient groups should concentrate on the potential reduction in risk of bacterial colonization and catheter-related infection.

Current available prophylactic agents are not optimal for the prevention of thrombosis, especially in the cancer patient. Certainly, larger, placebo-controlled studies of LMWHs or low-dose warfarin prophylaxis in patients with CVCs could be useful overcoming the intrinsic limits of previous studies, but it may be more appropriate to consider instead the use of newer factor-Xa inhibitors, such as pentasaccharide, or direct thrombin inhibitors, such as ximelegatran, which, at the present time, are available for investigational use only. The former appears from early trials to be a more effective prophylactic agent of venous thromboembolism and is associated with less bleeding than LMWH. The latter may be a more stable oral anticoagulant than warfarin by not being affected by diet or antibiotics. Clearly, such agents would first have to undergo evaluation in large Phase III trials in this clinical setting.

Last, the timing of onset and the type and duration of prophylaxis have not been yet fully investigated. Given that fibrin sheaths and occlusive or nonocclusive thrombi seem to occur soon after catheter placement, early prophylaxis is probably warranted, but the duration of therapy has not been studied.

References
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