Reconsidering the GAVeCeLT Consensus on catheter-related thrombosis, 13 years later

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Abstract
Catheter-related thrombosis represents one of the most common complications following central venous access insertion. Despite the amount of available studies, many aspects surrounding catheter-related thrombosis remain controversial. Thirteen years ago, the Italian Study Group for Long Term Central Venous Access (GAVeCeLT) developed a nationwide Consensus in order to clarify some key aspects on this topic. Despite most of them still remain valid, however, knowledge around catheter-related thrombosis has greatly evolved over the last decade, with a natural evolution in terms of catheter technologies, insertion techniques, and management bundles. Aims of this editorial are to readdress conclusions of the 2007 GAVeCeLT Consensus in the light of the new relevant evidences that have been added in the last 13 years and to analyze some unsolved issues that still remain debated.

Keywords
Central venous catheter, catheter-related thrombosis, central venous catheter thrombosis, venous thromboembolism, deep vein thrombosis

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Introduction
Central venous access devices (CVADs) have become routine part of the management of hospitalized patients for the administration of chemotherapy, antimicrobial therapy, and parenteral nutrition and for blood sampling.1 Despite being perceived as essential tools, their use is also inevitably associated with early and late complications. Catheter-related thrombosis (CRT), defined as a mural thrombus extending from the catheter into the lumen of a vessel,2 represents one of the most common complications following central venous access insertion, potentially leading to local signs and symptoms, catheter removal, delay in treatment, post-thrombotic syndrome, and very rarely, life-threatening events such as pulmonary embolism.3–5 Despite the amount of available studies, many aspects surrounding CRT remain controversial. First, its actual incidence is difficult to define, since the rate of CRT ranges from 0% to 71.9%,6–15 due to heterogeneity in study settings in terms of type of CVAD, definition of thrombosis, diagnostic criteria, and inclusion/exclusion of asymptomatic thrombotic events. Furthermore, albeit playing a pivotal role in CRT occurrence, CVAD insertion technique is often neglected in many clinical studies.

Thirteen years ago, the Italian Study Group for Long Term Central Venous Access (GAVeCeLT) developed a nationwide Consensus16 in order to clarify some key aspects on this topic. However, the knowledge around CRT has greatly evolved over the last decade, with a natural evolution in terms of catheter technologies, insertion techniques, and management bundles. The aim of this editorial is to readdress the same eight fundamental questions of the 2007 GAVeCeLT Consensus, on the basis of current knowledge.

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Old answers and relative recommendations will be presented as they originally appeared in the 2007 Consensus. Our answers to the questions will update and integrate the old answers providing recent evidence. Finally, a few unsolved issues related to CRT will be discussed so as to highlight some areas where further studies are warranted.

By which mechanisms may a catheter cause venous thrombosis? Which is the difference between CRT and fibrin sheath?

2007 GAVeCeLT 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.16

Recent findings confirm that pathogenesis of thrombosis is multifactorial.17 In this context, factors involved in the pathogenesis of CRT traditionally include vessel wall injury as a result of needle insertion, venous stasis or occlusion as a result of the relationship between catheter and vein diameter, and patient-related hypercoagulability. While some technical factors may be modified in order to reduce the risk of CRT, hypercoagulability is inevitably related to the patient’s characteristics and comorbidities (hypercoagulable states, malignancies, sepsis, pregnancy or peri-partum, left ventricular dysfunction, prolonged immobility, etc.), thus being susceptible to be modulated only to a limited extent.

Thrombosis and fibroblastic sleeve

The fibroblastic sleeve which surrounds the catheter is not a thrombotic event. This sleeve, erroneously named “fibrin sleeve” or “fibrin sheath,” is a physiological phenomenon which occurs when a foreign body is in prolonged contact with the blood fluid, inside the vessels. The sleeve is made of connective tissue, and it starts with the early deposition of circulating fibronectin over the catheter within 24 h after insertion, with subsequent proliferation of fibroblastic cells and collagen deposition.1 Experimental evidence in rats suggests the hypothesis of a migration of smooth muscle cells from the endothelium, with redifferentiation as fibroblasts.18,19 On the contrary, thrombosis starts from tissue factors released after the endothelial injury:20 the thrombus is a tissue generated by aggregated platelets mixed with a mesh of specialized coagulation proteins (including fibrin). Even if mechanisms of fibroblastic sleeve and thrombosis formation are well-known, their relationship remains still unclear.21

Is there an ideal insertion technique for minimizing the risk?

2007 GAVeCeLT Consensus: To date, to our knowledge, no randomized trials have investigated the relationships between insertion techniques in the long-term setting (e.g., percutaneous vs venous cut-down, US-guided vs anatomic landmark techniques) and central venous thrombosis rate. Prospective, non-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.16

US guidance is nowadays considered a standard of care for catheter insertion and appropriate vein choice.22 Since 2008, an extensive body of evidence has demonstrated that real-time ultrasound-guided venipuncture reduces the risk of CRT.23 US guidance has shown to reduce puncture attempts, technical failures, and mechanical complications, thus minimizing vessel wall trauma, a key element in CRT development. A recent meta-analysis8 which included only studies where catheter insertion had been performed according to good clinical practice (US-guided venipuncture, appropriate catheter size choice, and proper verification of tip location) showed a low incidence of CRT. As a result, US guidance is currently recommended in all bundles aimed at catheter-related complication prevention.23,24

Is there any device or material that may intrinsically reduce the risk?

2007 GAVeCeLT Consensus: Silicone and second- and third-generation polyurethane catheters are less thrombogenic than polyethylene or polyvinylchloride. 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.16

The choice of the device in terms of type of venous approach, material, and size plays an important role in order to minimize thrombotic risk and ensure good catheter performance.22

Type. Type of central venous approach results in different risks of CRT. Femorally inserted central catheters (PICCs) have the highest risk of CRT, with a rate of 5%–15% in adult patients. Furthermore, lower limb CRT is associated with a fourfold increase in risk of pulmonary embolism.6 No hard data about the actual incidence of venous thrombosis related to centrally inserted central catheters (CICCs) are available, with reported rates ranging between 3% and 5%, depending on catheter size, cannulation route, and insertion technique. As for peripherally inserted central catheters (PICCs), current evidence shows that if they are inserted respecting the proper indications and paying attention to a few technical aspects, the rate of symptomatic CRT is 3% or less in both oncologic and non-oncologic patients and a little higher (5%–6%) in hematologic patients.7 Moreover, PICC-related pulmonary embolism is extremely rare.9,10,12 Thus, in terms of prevention of
thrombosis-related morbidity and mortality, the use of PICCs should be recommended over CICCs and FICCs.\textsuperscript{13,14}

**Materials.** Experimental and clinical evidence confirmed that polytetrafluoroethylene and polyethylene are more thrombogenic compared with silicone and second-/third-generation polyurethane.\textsuperscript{25}

In recent years, two different types of medicated PICCs have been released into the market, with supposed antithrombogenic activity: Angiodynamics BioFlo\textsuperscript{6} PICCs with Endexo\textsuperscript{8} technology and Arrow PICCs with Chloragard technology\textsuperscript{8}. Endexo\textsuperscript{8} is a low-molecular-weight fluorine-oligomeric additive that self-locates in the first few nanometers of the surface of the material. It is not a catheter coating, but rather it is incorporated into the polyurethane. As a result, antithrombogenic properties are located on the internal, external, and cutting surfaces of PICC. This substance inhibits platelet adhesion, suppresses the formation of protein procoagulants, and reduces thrombus formation.\textsuperscript{26}

Nevertheless, at present, there is scarce evidence suggesting the effectiveness of Endexo\textsuperscript{8} technology in reducing the risk of CRT and no convincing evidence of its cost-effectiveness.\textsuperscript{26,27}

As regards chlorhexidine-coated PICCs (Chloragard\textsuperscript{8}), in one recent experimental study, they have been associated with a non-significant reduction of fibroblastic sleeve, with no effect on CRT.\textsuperscript{28}

Therefore, at the moment, no conclusion can be drawn from available evidences about the role of medicated catheters in CRT reduction.

**Size.** The presence of the catheter itself inside the vein invariably reduces blood flow. Retrospective observations reported a greater risk of CRT when using larger catheters, especially when inserted in small veins, as it occurs with PICCs and with any CV AD in children.\textsuperscript{29,30} In the ultrasound era, the possibility of measuring the vein diameter has introduced the concept of catheter/vein ratio. In vitro and in vivo studies have confirmed that catheter/vein ratio may be more relevant than catheter diameter per se. An ideal catheter/vein ratio has not yet been defined. On the basis of the in vitro study by Nifong et al.,\textsuperscript{19} many institutions have adopted the rule of 33%. Similarly, the international WoCoVA-GA VenCeLT-WINFOCUS Consensus suggests that the external diameter of the catheter should not exceed one-third of the internal diameter of the vein.\textsuperscript{23}

The rule of the 33% has also the advantage of being easy to remember, easy to teach, easy to learn, and easy to apply. In fact, in practical terms, according to that rule, for a 3 mm vein, one will choose a 3 Fr catheter, for a 4 mm vein a 4 Fr catheter, for a 5 mm vein a 5 Fr, and so on.

**Micro-introducers.** Vessel wall trauma as a result of catheter insertion is one of the main mechanisms at the basis of CRT occurrence. Therefore, the use of small introducer kits (21G echogenic needle, atraumatic 0.018" nitinol guidewire, 3 or 4 Fr micro-introducers) represents an obvious benefit during catheter insertion in order to limit vessel injury. The use of micro-introducers has been included in evidence-based insertion bundles\textsuperscript{30,31–33} for catheter-related complication prevention, and their widespread use reflects recent advances in terms of technical development and awareness of factors related to catheter-related thrombotic events.

**Proper securement.** Catheter stabilization has emerged as an important aspect in minimizing catheter-related complications.\textsuperscript{34} Inadequate securement is associated not only with the risk of dislodgment but also with in and out movements of the catheter at the exit site, which may cause prolonged trauma to the vein wall trauma and enhance bacterial contamination by the extraluminal route.\textsuperscript{35} Strategies of proper securement include (a) appropriate choice of the exit site, with mid-upper arm and infraclavicular area being the preferred catheter exit sites, (b) use of sutureless\textsuperscript{36} devices or subcutaneously anchored systems (SAS) and (c) semipermeable transparent dressing.\textsuperscript{34} Proper catheter securement techniques have shown to reduce phlebitis, local infection, catheter migration, and dislodgement, all known risk factors for CRT.\textsuperscript{37} However, the impact of securement techniques on CRT has not been fully demonstrated yet. Some authors have shown that securement devices help reducing catheter-related bloodstream infections (CRBSI) and improve cost-effectiveness in patients with non-tunneled CVADs, including PICCs.\textsuperscript{38} Finally, a recent meta-analysis\textsuperscript{39} showed that transparent dressing might reduce CRBSI. It is possible that this type of dressing, improving the stability of the catheter, may also be helpful in reducing CRTs.

**What are the patient’s risk factors?**

2007 GAVeCeLT Consensus: Neoplastic disease and chemotherapy are recognized risk factors for the development of central venous thrombosis in patients with a central venous catheter. Pathophysiology includes direct release of thrombogenic factors by neoplastic cells, decrease of antithrombotic natural factors induced by the tumor, and the procoagulant activity of many antineoplastic drugs. In non-randomized 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 central venous catheter. Hereditary screening procedures for thrombophilia are not presumably cost-effective.\textsuperscript{16}

Oncology patients are at higher risk of CRT as they combine CVAD-related risk factors together with procoagulant features typical of neoplastic disease. Direct vessel trauma due to the insertion and the presence of the CVAD and the hypercoagulable state of the host caused by cancer-related activation of coagulation cascade are the two main mechanisms involved in cancer patient CRT.\textsuperscript{39} In
particular, the tumor itself produces procoagulant and anti-fibrinolytic factors, such as plasminogen activation inhibitor-1, tissue factor, and podoplanin,\textsuperscript{41} and these substances, through the expression of adhesion molecules and the release of cytokines and angiogenic factors, cause an increase in thrombin and fibrin formation, therefore leading to a hypercoagulable state.\textsuperscript{40,42} In addition, many anti-tumor drugs exert a clotting activation.\textsuperscript{43,44}

Not all oncology patients have the same thrombotic risk. In fact, patients with certain types of tumors such as gastric and pancreatic adenocarcinoma, ovarian cancer, and especially, onco-hematological diseases are at increased risk for CRT.

Critically ill patients are also at increased risk for CRT. In fact, in addition to general venous thromboembolism risk factors, intensive care unit (ICU) patients are exposed to ICU-acquired risk factors, such as prolonged sedation, immobilization, and vasopressors use. In particular, the incidence of CRT in the ICU setting is higher in the elderly, in septic patients, and in patients with FICCs, especially if placed in emergency.\textsuperscript{6,40}

**What is the role of central venous catheter tip positioning?**

2007 GAVeCeLT Consensus: In many prospective studies, tip positioning emerged as the main independent prognostic factor for malfunction, thrombosis, and reduced duration of the device. In oncology patients, the cavoatrial junction appears to be the optimal position of the catheter, as it minimizes the risk of central venous thrombotic events.\textsuperscript{16,45} All current guidelines agree that an incorrect tip position is a major risk factor for CRT, arrhythmias, valve, and heart lesions.\textsuperscript{45} The distal tip of the catheter should be placed at the junction between superior vena cava and the right atrium.\textsuperscript{46} Post-operative chest X-ray has been traditionally considered the gold standard for central catheter’s tip location for many years. As an alternative, fluoroscopy has been used diffusively worldwide for both tip location and tip navigation. However, recent guidelines\textsuperscript{47} recommend non-invasive intra-procedural methods for tip location, such as intracavitary electrocardiography (IC-EKG) or transthoracic echocardiography (TTE).

IC-EKG and TTE have several advantages over radiology: as opposed to chest X-ray, they are intra-procedural, allowing real-time verification of correct tip position; also, they are more accurate and less expensive,\textsuperscript{48} especially compared to fluoroscopy.\textsuperscript{49} Also, they are safer for both patients and operators, avoiding ionizing radiation exposure.

**If thrombosis occurs, when should the catheter be removed?**

2007 GAVeCeLT 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 deep vein thrombosis (DVT), a risk of embolization during or immediately after catheter removal has been clinically confirmed. Catheter should be removed in case of (a) infected thrombus, (b) malposition of the tip, and (c) irreversible occlusion of the lumen.\textsuperscript{16}

International guidelines\textsuperscript{2,22,46,50} recommend the maintenance of the catheter in the presence of CRT if the catheter is necessary for the patient, still functioning, correctly positioned with the distal tip placed at the cavoatrial junction, and with no signs or symptoms of infection. Increased risk of pulmonary embolism due to mobilization of the thrombus is reported during or immediately after the VAD removal.\textsuperscript{51,52} in particular when the CRT involves the tip of the catheter and the thrombus is recent and partially floating.\textsuperscript{51,52}

Should the catheter be removed, it is wise to do it only after a short course of treatment with low-molecular-weight heparin (LMWH; 3–5 days according to the 2015 European Society for Medical Oncology (ESMO) guidelines).\textsuperscript{53} In case of a PICC-related thrombosis localized in the veins of the arm, even if there is no data, removal is probably safe after 72 h of treatment. At the moment, there are no recommendations by available guidelines about the need of ultrasound evaluation before removal of a catheter complicated by thrombosis. In this context, it is noteworthy to say that the aim of the short course of LMWH before catheter removal is not to dissolve the whole thrombus but to stabilize it, by dissolving only the friable part of the thrombus. However, while not routinely suggested, US evaluation by mean of CUS (compressive ultrasound) technique before catheter removal might be a reasonable option in case of risk factors for clot embolism, such as a floating thrombus.

**What is the ideal pharmacological management?**

2007 GAVeCeLT Consensus: Thrombolytic drugs should be used in acute symptomatic cases (diagnosis <24 h after the first symptoms). Efficacy of systemic versus local thrombolysis is still a 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.\textsuperscript{16}

Goals of CRT management are to reduce mortality and acute morbidity, minimizing post-thrombotic sequelae and preventing embolization. The recommended anticoagulation
regimen does not differ from the one usually adopted for non-CRT of the deep veins of the lower limbs. Treatment starts with parenteral anticoagulants, subcutaneous LMWH, or fondaparinux; some guidelines suggest to shift later to a vitamin K antagonist (warfarin), while others recommend to continue with LMWH. LMWH is usually preferred to warfarin in CRT patients with cancer due to a more favorable risk profile. Most guidelines recommend LMWH (Dalteparin 200IU/kg/day o.d., Enoxaparin 1mg/kg b.i.d.) for at least 3 months (or until removal of the CVAD, should the CVAD stay in place for more than 3 months after the CRT episode).

Thrombolysis represents a therapeutic option only in specific cases. It may be considered in case of very acute presentation with severe symptoms refractory to conventional therapy and/or thrombosis extension in superior vena cava, in patients with low bleeding risk.

Can we prevent catheter-related central venous thrombosis?

2007 GAVeCeLT 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 central venous catheter, either with LMWHs or with mini-dose warfarin, remains unsupported by evidence-based medicine. GAVeCeLT suggests considering prophylaxis with a daily single dose of LMWH 100IU/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).

Several randomized trials have evaluated LMWH, low-dose warfarin, or unfractionated heparin as an attempt to reduce the risk of CRT in adult patients with cancer or critical illness. However, a clinical benefit coming from these interventions has not been proven yet. A recent meta-analysis including 13 randomized controlled trials (RCTs) on 3420 patients found a moderate evidence that LMWH prophylaxis may reduce CRT if compared to controls. However, the analysis did not confirm or exclude a beneficial or detrimental role of prophylactic LMWH on mortality, major and minor bleeding. In the same meta-analysis, low-dose warfarin did not show any beneficial or detrimental effect on symptomatic CRT compared to controls. Furthermore, the evidence was not conclusive for the effect of LMWH on mortality and risk of symptomatic CRT if compared to warfarin.

As a result, based on the current lack of evidence in terms of meaningful clinical endpoints, experts do not recommend routine pharmacological prophylaxis in cancer patients with indwelling central VAD to prevent CRT. However, LMWH prophylaxis can be considered in high-risk patients, including those who have hereditary anomalies associated with thrombophilia or previously suffered from CRT or DVT related to the neoplastic disease. In these patients, clinicians should balance the possible benefit of reduced thromboembolic complications with the possible arms of anticoagulation.

Unanswered issues

Asymptomatic CRT natural history

The natural history of asymptomatic thrombosis is an often neglected aspect surrounding CRT, which may play an essential role in terms of diagnostic and therapeutic approaches. At the moment, an extensive body of literature is available for symptomatic events where the presence of symptoms allows early diagnosis and treatment, leading to a low rate of serious adverse events, such as pulmonary embolism and post-thrombotic syndrome. However, little is known about asymptomatic events in adult patients, which mostly appear to be incidental findings during diagnostic screening procedures. In this context, asymptomatic CRT natural history in pediatric patients has been elegantly evaluated by Jones et al. In their study, thrombus extension, clinical pulmonary embolism, and post-thrombotic syndrome appeared to be uncommon events when asymptomatic thrombotic events were not treated. Further investigation is warranted in adult patients, so as to determine whether asymptomatic upper extremity CRT should be screened and treated or whether it represents an uneventful, not clinically relevant event.

Length of treatment

Recommendations on anticoagulation for CRT (i.e. 3 months of treatment) are mainly extrapolated from data on non-CRT of deep veins of the lower limb. However, the latter phenomenon is quite different from CRT in terms of pathophysiology. Prolonged anticoagulation is not devoid of risks, while the optimal duration of treatment following CVAD removal is not clear, due to lack of good quality data. In this context, length of treatment is often variable between different institutions, reflecting personal preferences and believes. Therefore, also in this field, further studies are warranted in order to reach a more coherent and uniform approach.

Conclusion

Thrombosis is a pathophysiological phenomenon which follows any trauma to the vessel wall, and venous cannulation makes no exception. As such, CRT can be regarded as an inevitable side-effect of venous access, since vein injury can be minimized but not avoided.
In the last decade, our understanding of CRT risk factors has greatly improved. Based on new evidence, the implementation of insertion and management bundles have been shown to be effective in reducing catheter-related complications. In fact, CRT rates have been steadily decreasing over the years, thanks to the adoption of appropriate strategies, such as ultrasound guidance, proper selection of vein and catheter size, adequate tip placement, and adequate catheter securement.8,23

Understanding the clinical relevance of CRT is another key challenge today. Since the natural history of symptomatic CRT is well-known, we can intervene with prompt diagnosis and effective treatment and ensure a positive clinical outcome. On the contrary, the natural history of asymptomatic thrombosis is quite mysterious, so that a precautionary behavior still influences our approach toward this poorly understood phenomenon.60,61

Also, some pharmacological aspects in the management of CRT are not yet well defined.2,25 The actual length of treatment is not known. The indications to prophylaxis with LMWH are still controversial. The reduction of CRT rates “at any cost” may not necessarily lead to better clinical outcomes. However, pharmacologic prophylaxis might be considered in high-risk patients after careful consideration of related risks and benefits.59

While many of the recommendations of the original GAVeCeLT Consensus on CRT are still valid, new relevant evidences have been added in the last 13 years. These new insights have greatly improved our knowledge surrounding CRT prevention and risk minimization, leading us to a new perspective, where CVAD insertion should reflect actual clinical needs, without fearing iatrogenic complications.

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