Received: 25 May 2024 | Accepted: 23 August 2024

DOI: 10.1111/eci.14311

NARRATIVE REVIEW

WILEY

Catheter-related deep vein thrombosis: Where are we at and where are we going? Updates and ongoing unmet clinical needs

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Abstract

Background: Catheter-related thrombosis (CRT) is one of the major complications affecting patients with indwelling venous catheters, usually involving the upper extremity deep venous system. This condition can lead to potentially life-threatening complications such as pulmonary embolism and sepsis. The risk of developing CRT varies depending on type of catheters and patient characteristics. Despite advances in materials and technologies, the actual incidence of CRT is still considerable. Available evidence on CRT management remains controversial, and clinical guidelines base their recommendations on data from non-catheter related upper extremity or lower extremity deep venous thromboses.

Aims: This narrative review aims to describe the epidemiology of CRT, to review the available evidence on its management and to highlight the current unmet needs.

Methods: No formal search strategy was applied for the revision of the literature. The main sources of information used were Medline and guidelines from international societies.

Content: The management of CRT requires a careful balance between the risk of thrombus progression, recurrent events, and systemic embolization and the increased bleeding risk in often fragile patients. Open issues include the optimal management of the catheter and the type and duration of anticoagulant therapy. Direct oral anticoagulants are increasingly prescribed, representing an important alternative to the standard of care low molecular weight heparins in selected cases. The development of new anticoagulant drugs such as factors XI and XII inhibitors may offer further advantages in this context.

Conclusions: The management of CRT is still challenging with constant need for updated evidence to support tailored approaches.

Laura Girardi is the recipient of a research scholarship from Fondazione Cariplo (https://www.fondazionecariplo.it).

KEYWORDS
anticoagulant treatments, catheter-related venous thrombosis, central venous catheters, upper extremity deep vein thrombosis, venous thromboembolism

1 | INTRODUCTION

Catheter-related deep vein thrombosis (CRT) is one of the major complications in patients requiring long-term intravenous accesses, together with arterial cannulation, pneumothorax and infection. Taken together, the composite risk for these complications after central venous access device (CVAD) exposure for 3 days is about 3%.[1] Different types of central venous catheters (CVCs) are available, and they can be classified as tunnelled or non-tunnelled, peripherally inserted central catheters (PICCs), implanted ports and dialysis catheters (Table 1). All CVCs are designed and supposed to be dwelled with their tip ending at the superior vena cava-right atrium junction, within the central venous system.[2] Clot formation associated with CVAD placement may lead to different conditions, that are associated with different clinical implications: (a) fibrin sheath along the length of the device (on the surface of the catheter); (b) catheter lumen occlusion (usually caused by intraluminal clot forming inside catheter's lumen when blood refluxes into the device); (c) ball-valve-thrombosis (which affects aspiration and preserves infusion); and (d) mural thrombosis (partial vein occlusion) leading to deep vein thrombosis (DVT). This latter is conventionally defined as CRT.[2] Most commonly, CRT affects the upper extremity deep venous system, but it may also occur in other venous districts depending on the site of venous catheters placement, such as the jugular veins or the femoral veins. The occurrence of CRT is associated with venous-access loss, risk of pulmonary embolization and related additional costs.[3] The management of CRT is still controversial and challenging, especially among specific subgroups of patients (i.e. cancer patients, haemodialysis, and all conditions associated with high bleeding risk). International guidelines are based on low quality of evidence, mostly extrapolated from data on usual site venous thromboembolism (VTE) (i.e. lower extremities DVT), providing a low level of recommendation, and leading to some heterogeneity in clinical practice.[4] The purpose of this narrative review is to describe the epidemiology and clinical significance of CRT, to review the available evidence on its management, and to highlight current unmet needs that should drive further research on this patient population.

Highlights

- Catheter-related deep vein thrombosis (CRT) is a common complication in patients requiring long-term intravenous accesses.
- Management of CRT is still controversial and local and systemic complications from either the disease or its treatments are not negligible.
- The new anticoagulants against factors XI and XII are promising agents in the management of CRT.

2 | INCIDENCE AND RISK FACTORS FOR CRT

The reported incidence of CRT broadly varies across available studies due to the heterogeneity of study designs (e.g. prospective or retrospective), included populations (e.g. hospitalized medical patients, outpatients with cancer), catheter type and cannulated vein (central or peripheral), diagnostic assessment (e.g. screening of asymptomatic patients or evaluation in case of clinical suspicion) and duration of follow-up.[5] CRT is responsible for the majority of upper extremity DVT (UEDVT) (nearly 70%) and for about 10% of all VTEs.[2,6] The overall annual incidence of CRT is .4–1.0 cases per 10,000 individuals and reaches the highest values in patients admitted to intensive care units and in patients with cancer.[6–8]

Several catheter-related and patient-related characteristics have been evaluated over the years as potential risk factors for CRT development. Available evidence, however, is often misleading and further data are desirable to help clinicians identifying patients who may benefit a stricter clinical surveillance and/or thromboprophylaxis.[9]

Details on different types of catheters and on the principal risk factors associated with CRT are depicted in Tables 1 and 2, respectively.

2.1 | Catheter-related risk factors

The type of catheter represents one of the most important factors affecting the risk of CRT. PICCs are associated with

TABLE 1 Main characteristics of indwelling venous access devices commonly used.

CVAD types	Characteristics	Indications	Durations	Pros	Cons
Tunnelled central venous catheter (CVC) (Hickman®, Groshong®, Broviac®)	Distal end open to the outside with subcutaneous (tunnelled) way	Haemodialysis. Hemodynamic monitoring. Daily blood sampling. Administration of parenteral nutrition and cancer treatments	Months to years	Longer duration. Lower risk of infection and thrombosis	Need for medical radiology, surgery or anaesthesia equipment for insertion. Higher cost. Limited flow
Central venous access device with subcutaneous reservoir (Port or port-a-cath type–PAC)	Special tunnelled venous line connected to a subcutaneous reservoir	Daily blood sampling. Administration of parenteral nutrition and cancer treatments	Months to year	Longer duration. Lower risk of infection and thrombosis. Less visible	Need for medical radiology, surgery or anaesthesia equipment for insertion. Higher cost. Limited flow. 6 weekly flushing. Need for skin puncture to access the device each time
Peripheral insertion central catheter (PICC type)	Inserted by a peripheral vein (basilic, cephalic, etc.) passing through the arm, ending to superior vena cava/right atrium junction	Administration of parenteral nutrition and cancer treatments	Months	Easier to insert and remove. Lower cost	Increased risk of infection and thrombosis
Midline[a]	Same insertion as PICCs but ending into a deep vein (usually axillary or subclavian veins)	Administration of medium or long-term selected treatments (e.g. antibiotics)	Medium-term (1–6 weeks) or long-term (up to 3 months)	Easier to insert and remove. Lower cost	Increased risk of infection and thrombosis. Limited use due to peripheric position

[a]Not a proper central venous catheter, but peripheric (not reaching the right atrium).

TABLE 2 Risk factors for CRT.

Patient-related risk factors	Catheter-related risk factors
Hypercoagulable state: • malignancy • inherited thrombophilia (factor V Leiden and prothrombin gene mutations, protein C and S deficiencies, antithrombin deficiency) • acquired thrombophilia (antiphospholipid syndrome) • inflammation • sepsis	CVAD type and characteristics: • noncuffed CVC > cuffed tunnelled CVC • midlines ≅ PICCs > CVCs • CVC diameter (larger > smaller) • number of lumens (triple > double > single) • synthetic material (polyethylene or polyvinylchloride > silicon or polyurethane, polyurethane > silicon)
Older age (> 64 years)	Insertion site (femoral > subclavian > internal jugular)
Obesity (BMI > 25 kg/m^2)	Side of insertion (left > right)
Immobility, hospitalization	Multiple insertion attempts
History of previous thrombosis	Non-ultrasound-guided insertion
Leukocytosis, thrombocytosis, anaemia	Tip location (proximal to SVC > atriocaval junction)
A, B or AB blood groups >0-blood group	Fibrin sheath
Concomitant prothrombotic treatments (e.g. anti-cancer therapies, oral contraceptives, erythropoiesis stimulating factors, blood products infusion, etc.)	CLABSI

Abbreviations: BMI, body mass index; CLABSI, central line-associated blood stream infection; CRT, catheter-related deep vein thrombosis; CVAD, central venous access device; CVC, central venous catheter; PICC, peripherally inserted central catheter; SVC, superior vena cava.

a roughly three fold increased risk of CRT compared to standard CVCs (i.e. directly inserted into a central vein), with a reported incidence of 2% in the general population, which increases up to 5% in patients with hematologic cancer.[8,10,11] Although the incidence of CRT is considerable also in patients with cancer and implantable ports (roughly 4%), it appears to be lower than that of PICC.[12,13] Midline catheters are a potentially attractive alternative to PICCs in patients needing peripheral infusions. Midlines share the same peripheral insertion of PICCs, but they do not reach the right atrium, ending into the upper extremity deep vein system (typically subclavian and axillary veins). The incidence of midline-related UEDVT and pulmonary embolism (PE) is not negligible and is similar to that of PICC.[14,15] The site of insertion is, in fact, relevant in determining the catheter-related risk of CRT, as the lumen may be completely filled in by the catheter when a peripheral vein is used.[16] Ultrasound-guided catheter insertion in a larger vein (e.g. above the elbow or shoulder), choosing the smallest needed catheter size and the lowest needed lumen number, reducing the insertion attempts and positioning the tip in the largest achievable vein segment may reduce the risk of CRT through a lower compression or friction to the vessel wall.[17,18] The relevance of the site of insertion is not limited only to the type of vein cannulated, but is also determined by the arm used. It has been reported that the left-sided insertion of the CVC leads to an increased risk of thrombotic complications compared to the right-sided one.[19,20] PICC placement in the right arm may further reduce CRT risk possibly due to a shorter and more direct route to the superior vena cava.[17,21] Hence, the institution of a dedicated vascular access team for the standardization of the insertion techniques and the maintenance of CVCs may provide beneficial results.[2]

As for catheter materials, there is limited evidence on whether the use of antibiotic or heparin coated catheters may decrease the rates of CRT.[22–24] Results from a recent meta-analysis showed that silicone and polyurethane PICCs were associated with a similar rate of thrombotic complications.[22] Another option to reduce thrombotic risk may be represented by the use of new materials able to prevent central line-associated blood stream infections (CLABSI), for example through the impregnation of CVCs with various forms of antimicrobials (either with an antiseptic or with antibiotics). Infection and thrombosis of catheters, indeed, are

strictly intertwined and preventing infection may reduce the incidence of CRT.[25] Data from a prospective study including 105 patients with haematological malignancies showed that patients with infection had an increased risk (up to 17-fold) of CRT compared to patients without infection.[26] On the other hand, the risk of infection was increased (up to 2-fold) in patients with CRT in a prospective study including 265 ICU admitted patients.[27] A Cochrane review showed controversial findings on the use of impregnated CVCs, which seem to prevent catheter colonization in studies conducted in ICUs, whereas no such benefit was found for CLABSI.[23] Furthermore, no significant differences were detected between the impregnated and non-impregnated groups in the rates of adverse effects, including thrombosis.[23] Finally, pretreatment with nucleases has been shown to reduce thrombogenicity by limiting inflammatory response incited by foreign materials or microorganism invasion (i.e. immunothrombosis).[28] Further studies on preventing the formation of neutrophil extracellular traps (NETs) around the catheters and the aggregation effects of NETs on platelets are needed to increase the evidence of this promising strategy in the setting of CRT.

All these improvements in insertion modalities and materials of catheters have resulted in a reduction in the incidence of CRT over the last years.[2]

2.2 | Patient-related risk factors

CRT also shares some patients-related risk factors with usual site VTE. Older age (>64 years) and a body mass index (BMI) >25 kg/m^2 have been associated with an increased risk of CRT.[9] Conversely, no association was reported among CRT, sex and ethnicity, while inconsistent results were available for other clinical conditions (e.g. diabetes, arterial hypertension, hypercholesterolemia).[9]

Thrombophilia (e.g. factor V Leiden and prothrombin gene mutations, protein C and protein S deficiencies and antithrombin III deficiency) increases the risk of CRT both in patients with and without cancer,[29–32] while the role of personal history of VTE remains controversial.[9] An interesting finding of recent studies is that patients with A, B or AB blood groups may have with a significantly higher risk of CRT compared with those with 0-blood group.[33,34]

Cancer is a well-known risk factor for VTE. Implantable ports and long-term CVCs have brought a significant improvement in oncology practice for their multiple utilities, such as administration of chemotherapies and parenteral nutrition, facilitation of blood sampling and transfusion of blood components. The risk of developing cancer-associated CRT is not negligible depending on the characteristics of the underlying malignancy (e.g. site and stage) and on cancer-specific therapy (e.g. chemotherapy or chest radiotherapy).[5,11,12,35] In patients with cancer most of CRT occur within the first 100 days from catheter insertion and specific surveillance programme may ameliorate patients' morbidity and prognosis.[13] The role of risk assessment models (e.g. Khorana, Caprini and Michigan risk scores) to predict CRT has been investigated in small studies and requires further validation.[36,37] A recent meta-analysis evaluating the performance of six available models, however, identified the Michigan risk score as the most accurate in stratifying the risk of CRT.[38]

3 | PATHOPHYSIOLOGY, DIAGNOSIS AND IMPLICATIONS OF CRT

3.1 | Pathophysiology of CRT

As any other venous thrombosis, CRT occurs as the result of a complex multifactorial mechanism classically represented by the Virchow's triad, including endothelial damage, alteration in blood flow and hypercoagulability. In the specific context of CRT, risk of vessel injury and therefore of endothelial damage is intrinsically connected with catheter insertion and its long-lasting presence in the venous system. The role of contact pathway activation on artificial surfaces has been studied in vivo, with demonstration of prompt vessel occlusion due to thrombosis occurring in animal models following device placement in a blood vessel (i.e. a vascular catheter).[39] The contact pathway starts with the activation of coagulation factor XII (FXII) following direct contact between blood and surfaces of medical devices. Activated FXII (FXIIa) further cleaves coagulation factor XI (FXI) into the activated form (FXIa) which sustains downstream activation of the coagulation cascade leading to the formation and propagation of blood clot.[2]

3.2 | Diagnosis of CRT

A great proportion of patients with CRT are asymptomatic. The reported incidence of CRT found with venography studies ranged between 27% and 66%, most of which were asymptomatic.[40] When clinically overt, patients may complain of classic signs and symptoms of venous thrombosis, such as pain and tenderness along the vein, with severity often influenced by number and location of veins and amount of collateral venous flow. Frequently, signs and symptoms of CRT cannot distinguish between fibrin sheaths and superficial or DVT of the arm and neck.[41]

Other possible clinical manifestations of CRT are represented by catheter dysfunction and/or fever, derived from possible concomitant CVAD-associated infection.[42] Catheter dysfunction has been reported in 14%–36% of patients within the first 2 years of CVC implantation, of which 60% are due to thrombosis.[43]

In case of clinical suspicion, the initial diagnostic approach for CRT is represented by duplex ultrasound (US), a non-invasive, rather inexpensive and easily available test.

Duplex US for the diagnosis of UEDVT has reported average sensitivity and specificity around 91% and 93%, respectively.[44] Computed tomography (CT) angiography or magnetic resonance imaging (MRI) scans are alternative diagnostic strategies in case of strong suspicion and non-diagnostic US, especially for certain CRT locations,[5] and occasionally can report incidental findings of asymptomatic CRT when they are done for other reasons.

The role of D-dimer as a potential useful biomarker in the diagnostic process of CRT remains controversial. In this regard, a recent systematic review and meta-analysis showed that high levels of D-dimer and platelets count were associated with the development of CRT.[45] Conversely, a recent retrospective case–control study highlighted the limited diagnostic efficacy of the use of D-dimer in this setting.[46]

A few clinical prediction rules, for example the Constans score which combines clinical items and includes the presence of a CVC,[47] have been proposed to help clinicians with the diagnosis of UEDVT and CRT. Additionally, a diagnostic algorithm comprising Constans score, D-dimer levels and US showed potential utility in case of suspected UEDVT, although no data directly addressing CRT are available.[48] In conclusion, CRT-specific prediction rule has not been developed yet, and further effort is still needed with this intent.

3.3 | Clinical implications of CRT

CRT may have a relevant impact on patients' morbidity and costs. Although relatively uncommon, possible complications of CRT include PE, recurrent DVT, post-thrombotic syndrome and sepsis.[41,49] The most common consequence of CRT is represented by functional impairment of the catheter, which may require replacement and cause substantial delays in the delivery of treatments. When CRT occurs, therapeutic anticoagulation is required and patients are therefore exposed to an increased risk of bleeding complications, especially in the most fragile subgroups such as patients with cancer and those with end-stage renal disease. Other local complications usually determined by delayed diagnosis include superior vena cava syndrome and chronic venous stenosis, which impact the possibility to place other long-term venous accesses.[2]

4 | MANAGEMENT OF CRT

The management of CRT includes a timely start of anticoagulation and an adequate duration of secondary prevention, a careful evaluation of the need for removal of the device and possible additional treatment strategies. Treatment goals include saving of vascular access, relief of symptoms, prevention of thrombosis progression and/or pulmonary embolization. A practical algorithm for the management of CRT in different settings is proposed in Figure 1.

4.1 | Anticoagulant treatment

Only few and relatively small retrospective or prospective studies evaluated the use of anticoagulants for the treatment of CRT, and no randomized studies are currently available to establish the optimal intensity or duration of anticoagulation. Thus, management of CRT is mostly based on indirect evidence originated from studies on the treatment of DVT of the lower extremity. In addition, since most studies evaluated CRT management in patients with cancer, data in patients without cancer are even more limited.[50–52] In a meta-analysis of 20 studies including 1473 patients with UEDVT, 60% of whom had an indwelling catheter, the incidence of recurrent VTE, major bleeding, clinically relevant non-major bleeding (CRNMB) and all-cause mortality in the subgroup of patients with an indwelling catheter was 3% (95% CI 2%–4%), 5% (95% CI 3%–8%), 5% (95% CI 2%–9%) and 8% (95% CI 4%–14%), respectively.[53] Patients received either direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs) or low molecular weight heparins (LMWHs); however, the relatively low number of events and patients precluded a more in-depth analysis by type of anticoagulant.[53] Similar findings were reported in another recent systematic review,[54] while another meta-analysis reported lower risk of recurrent VTE and a higher incidence of major bleeding.[55]

In the absence of direct comparisons between anticoagulant agents, decision on the type of anticoagulant treatment still needs to be taken on a case-by-case basis. While LMWHs remain the most commonly used anticoagulants in particular for patients with cancer, DOACs now represent a valid option in this setting. The International Initiative on Thrombosis and Cancer (ITAC) 2022 guidelines on the treatment and prophylaxis of VTE in patients with cancer suggest CRT treatment with either LMWH or unfractionated heparin (UFH) for a minimum of 3 months or as long

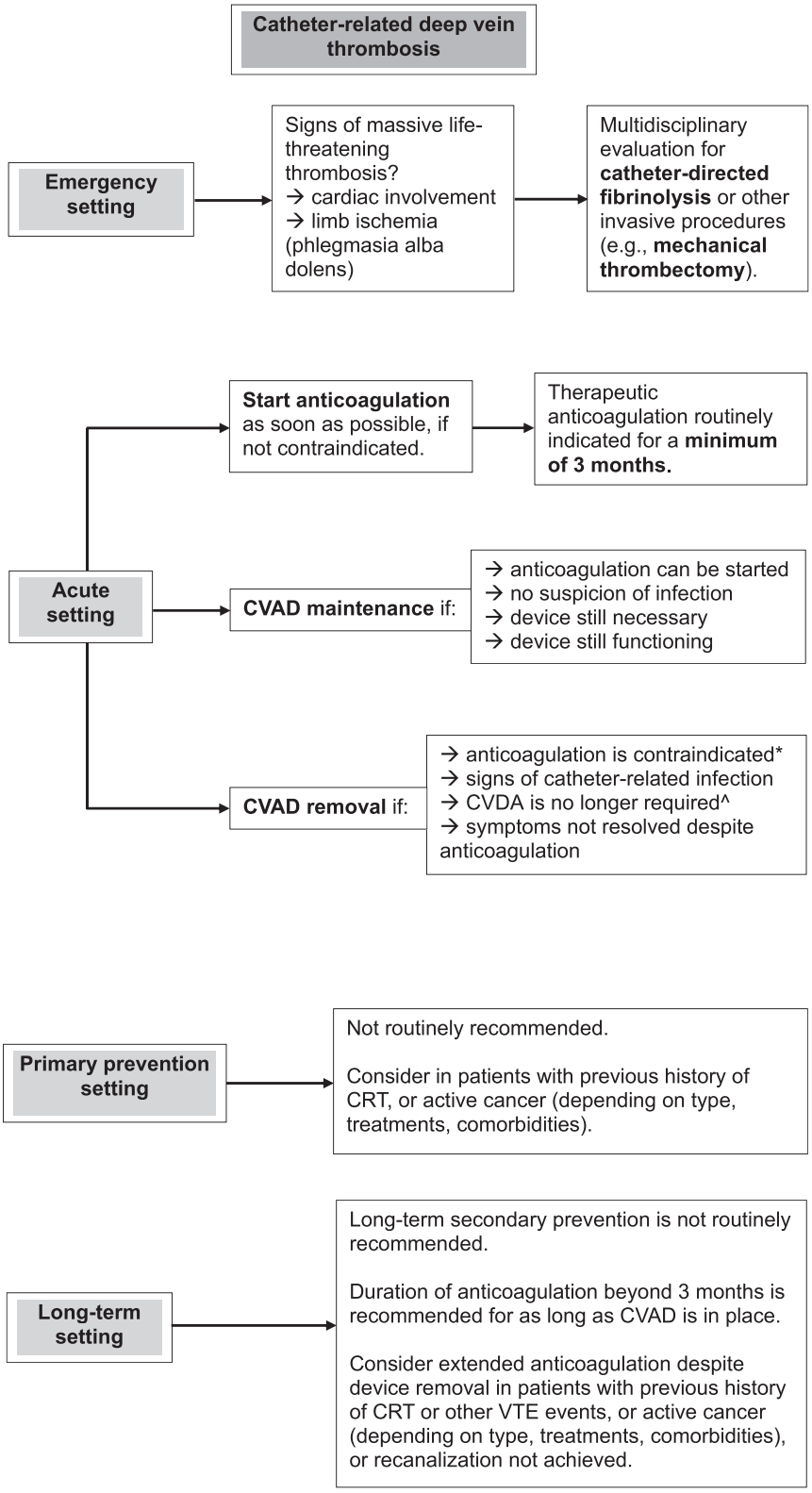

FIGURE 1 Management algorithm of CRT. *Alternative to catheter removal, in this case, is follow with serial imaging and start anticoagulation as soon as contraindication is resolved. ^In this case, anticoagulation for 3–7 days is recommended before CVDA removal. CRT, catheter-related deep vein thrombosis; CVAD, central venous access device; VTE, venous thromboembolism.

as the CVC is in place, with no specific recommendation for DOACs or VKAs (Table 3).[50] No mention on CRT treatment is available in the guidelines of the American Society of Haematology (ASH).[51] The recently released guidelines of the European Society of Medical Oncology (ESMO) also suggest LMWH as the first option for the treatment of CRT, with VKAs and DOACs as potential alternatives based on a low grade of evidence.[52] In the absence of contraindications, the same dose and regimen as for DVT of the lower extremity may be considered for CRT.

The duration of anticoagulant treatment for CRT also remains controversial, with a wide spectrum of

TABLE 3 Guideline recommendations on CRT management.

Guideline	Anticoagulant treatment	Catheter removal	Thrombolysis/catheter directed therapy
NCCN 2021[65]	Anticoagulation for at least 3 months or as long as CVC in place	Consider if symptoms persist, catheter is infected, dysfunctional or no longer necessary or contraindication to anticoagulation	Consider catheter-directed pharmacomechanical or mechanical thrombectomy in appropriate candidates
ESC 2022[56]	Anticoagulation in patients with cancer and CVC-associated VTE for at least 3 months or as long as CVC in place	–	–
ASH 2021[51]	–	Consider removal if infected, mispositioned or malfunctioning, in patients no longer requiring the CVC or who cannot receive anticoagulant treatment	–
ESMO 2023[52]	Anticoagulant treatment for a minimum of 3 months or as long as CVC in place. LMWH suggested, VKAs or DOACs alternatives	Remove if CVC not needed, infected, anticoagulant treatment is contraindicated or there is clinical deterioration due to thrombus extension despite treatment	–
ITAC 2022[50]	Anticoagulant treatment for a minimum of 3 months or as long as CVC in place. LMWH suggested	Remove if CVC malfunctional, infected, symptoms persist despite anticoagulant treatment	–

Abbreviations: CRT, catheter-related deep vein thrombosis; CVC, central venous catheter; DOACs, direct oral anticoagulants, LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

anticoagulant treatment courses reported in the literature, ranging from weeks to months. A general consensus is to provide anticoagulant treatment for a minimum of 3 months, regardless of CVC removal, with the option to continue as long as the catheter is in place.[56] In case of recurrent thrombosis, consideration may be given to indefinite anticoagulation, although no randomized controlled trials specifically evaluated this strategy in patients with CRT.

4.2 | Other treatment options

The use of systemic or catheter-directed thrombolysis and thrombectomy has been reported in small, retrospective series and is generally not recommended. While these strategies are sometimes considered in patients with extensive or massive CRT, evidence showing superior or similar efficacy compared with conventional anticoagulation is lacking. Based on indirect evidence on extensive DVT of the lower extremity, consideration to catheter-directed thrombolysis may be given in carefully selected patients with thrombosis progression and limb-threatening CRT despite conventional treatment who have a low bleeding risk. Similarly, experience with vena cava filters remains scarce and their use may be considered on a case-by-case basis for patients with CRT who have absolute contraindications to anticoagulation.

Local thrombolytic therapy with intraluminal instillation of low doses of fibrinolytic agents, such as alteplase (2 mg/2 mL), is often used on an outpatient basis for CVC obstruction caused by fibrin sheaths around the catheter or by thrombus on the tip of the catheter which impairs the flow into and out of the catheter interfering with aspiration or infusion through the catheter lumen.[57] These episodes of catheter dysfunction are usually distinguished from CRT and can be managed with local thrombolytic treatment, with a good chance of restoring CVC function, without significant increase of bleeding risks.[57] A limitation of alteplase is represented by its long dwell time (i.e. up to 4 h) to achieve catheter clearance. Newer thrombolytic agents, such as reteplase, tenecteplase and recombinant urokinase, were found to be equally safe and effective for the treatment of CVC obstruction, with the advantage of requiring shorter dwell times than alteplase.[57] If the CVC remains obstructed, a course of few days of anticoagulant treatment may be considered and, if not successful, catheter removal may be necessary. It is important to acknowledge that catheter obstructions can also be due to a non-thrombotic internal occlusion, such as precipitation of medications or parenteral nutrition constituents, which can be successfully cleared with a 70% ethanol solution.[57]

The use of graduated compression stockings or bandages for patients with acute symptomatic CRT is generally not recommended due to very limited data on their effectiveness.[4]

4.3 | Thromboprophylaxis in patients with CVC

Although flushing of the CVC with heparin or saline is standard practice in several centres, the efficacy of this approach remains unclear.[42] Similarly, the role of anticoagulant primary prophylaxis for CRT is uncertain. Studies evaluating either low, fixed-dose warfarin or LMWH led to controversial results, substantially failing to show a significant benefit for both patients with cancer and patients without cancer.[58] More promising results are shown in a post-hoc analysis of the AVERT trial, where primary thromboprophylaxis with apixaban in patients with CVC and cancer was associated with a reduced risk of VTE, without an increased bleeding risk.[59] Additional insights on the use of weight-adjusted twice-daily apixaban as primary thromboprophylaxis in the context of indwelling catheters are shown by a recent phase 3, open-label, randomized controlled trial on children affected by acute lymphoblastic leukaemia or lymphoma (the PREVAPIX-ALL trial).[60] When compared to standard of care (i.e. no anticoagulation), the use of apixaban was associated with a decreased risk of VTE, though not statistically significant (RR .69, 95% CI .45–1.05; $p = .08$).[60] This occurred at the cost of a higher incidence of CRNMB events, mainly epistaxis (RR 3.67, 95% CI 1.04–12.97, $p = .03$), suggesting that apixaban is a potentially safe alternative in patients at significantly higher thrombotic risk.[60] Based on the available evidence, most guidelines including ASH, ESMO and ITAC do not recommend the routine use of thromboprophylaxis in cancer patients with CVC.[50–52] Recent preliminary evidence on new target anticoagulants (i.e. against coagulation factor XI) in this setting are described in the following paragraphs.[61]

4.4 | Catheter removal

Since the catheter itself represents a provoking factor for thrombosis, a critical decision in patients with CRT is whether and when removal of the catheter is required. Importantly, many patients undergoing line removal still need central venous access and insertion of another CVC may not be straightforward and could further increase the thrombotic risk. Current guidelines suggest that in patients with CRT the removal of the catheter should be considered in case of infection or malfunctioning of the CVC, when the line is no longer needed, if the patient cannot receive anticoagulant treatment, or when the patient remains symptomatic for CRT despite anticoagulation.[50–52]

In a large retrospective study including 628 patients with haematological malignancy and CRT, 480 of whom were treated with anticoagulants, the risk of PE within 1 week of UEDVT was low and comparable between patients who underwent early (within 48 h) CVC removal compared with delayed or no removal (.78% vs. .44%).[62]

If catheter removal is being considered based on one or more of the conditions above, this could be attempted within the first 1–2 weeks of CRT diagnosis in the absence of contraindications including very high risk of bleeding or hemodynamic instability. Before CVC removal, consideration on a case-by-case basis may be given to a period of few days of anticoagulation, particularly in patients with large proximal thrombosis at increased risk of embolization.[63–65] In case of need for catheter replacement, no strong evidence is available to provide specific recommendations on indications and timing. The preferred option seems to assess the venous anatomy of the contralateral arm, before removing the affected non-functioning device.[66] The possibility to use the same site previously affected by thrombosis may be taken into consideration, if no better options are available. Since the best timing and modalities represent an ongoing unsolved question, a case-by-case evaluation considering various individual factors is strongly advised.

5 | SPECIAL CONDITIONS FOR CRT

5.1 | Children

The presence of a CVAD is reported being the most common provoking factor for VTE in the paediatric inpatient population, followed by surgery and trauma.[67] Additional risk factors associated with CRT in this subgroup of patients are infant age (<1 year old) and the presence of malignancy, along with renal and cardiac diseases, especially congenital heart disease requiring cardiac surgery.[67,68] The reported incidence of CRT in the paediatric population varies from 2% to 81%, based on the differences in patient populations.[69] The rates of this complication have shown an increasing trend over the past decades,[70] though most recent evidence suggests a possible inversion of the trend towards lower rates.[69] Evidence on rates of asymptomatic CRT among paediatric population widely varies from 5% to 50%, and most of them are detectable within first few days of catheterization.[71,72] Current clinical guidelines suggest no removal of a functioning CVAD in paediatric patients with symptomatic CVAD-related thrombosis who continue to require venous access.[73] Removal is suggested in cases of nonfunctioning or unneeded CVAD in paediatric patients with symptomatic CRT,[73] and may be preceded by few days of anticoagulation to reduce the risk of PE or paradoxical stroke.[73] As for CVAD-related superficial vein thrombosis, guidelines

suggest using either anticoagulation or no anticoagulation in paediatric patients.[73] After the first few days of anticoagulation, either LMWHs or VKAs should be used in paediatric patients with symptomatic VTE.[73] Data on DOACs in this setting are available from a pre-defined analysis of the CVC-VTE cohort of the EINSTEIN-Jr trial, showing the potential advantage of rivaroxaban to reduce clot burden when compared with standard anticoagulation.[74] Other promising results on the use of DOACs are given by a systematic review and meta-analysis pooling data on primary prophylaxis for cardiac surgery and VTE treatment among paediatric patients.[75] A limited course of anticoagulation (i.e. maximum 3 months) is usually preferred for CRT, given it is broadly considered as a provoked event.[73] Longer courses may be considered on a case-by-case basis in patients with ongoing additional risk factors. As regards thromboprophylaxis, there are no standardized recommendation on its routine use, although the results of the recent phase 3 trial PREVAPIX-ALL, suggest the use of weight-adjusted apixaban as a safe alternative for patients at increased thrombotic risk.[60]

5.2 | Haemodialysis

Haemodialysis is the most widely used renal replacement therapy for end-stage renal disease (ESRD), followed by peritoneal dialysis. Haemodialysis consists in an extracorporeal hemofiltration, continuous or intermittent, which can be provided through an arteriovenous fistula, arteriovenous graft or CVC. The last technique is more common in the acute emergency setting, given its relative ease in insertion and the ability to initiate dialysis immediately, but it is associated with higher rates of complications, such as CVC infections and thrombosis. Despite several attempts to limit their use in favour of arteriovenous accesses, which are still considered the preferred choice by clinical guidelines,[76] CVCs' use in haemodialysis has been constantly increasing worldwide.[77–79] The management of haemodialysis CVC-associated venous thrombosis consists in a prompt initiation of anticoagulation since delay in treatment could lead to inadequate dialysis, permanent vascular access loss and increased patient morbidity. The preferred anticoagulant agent is UFH, or alternatively LMWH, followed by oral anticoagulation with VKA for a minimum duration of 6 weeks and/or as long as the catheter is in place.[80] Removal of CVC is not mandatory, especially in cases of limited options for vascular accesses. In case of mural thrombosis, presence of atrial thrombus, or evidence of systemic sepsis caused by the catheter itself, the device should be removed or exchanged immediately. A randomized placebo-controlled trial evaluating low-dose warfarin for the prevention of late malfunction in tunnelled, cuffed haemodialysis catheters, showed no benefits of warfarin thromboprophylaxis.[81] New anticoagulants targeting contact activation pathway seem as an important option for anticoagulation in patients with VTE and end-stage renal impairment, given their clearance barely depending on kidney function and their minimal impact on the haemostatic process, resulting in limited bleeding risk for this fragile population. A number of phase 2 trials exploring FXI inhibition in patients with kidney failure on haemodialysis showed that the reduction of FXI levels was associated with lower risk of haemodialysis circuit clotting with similar or lower risk of bleeding compared to placebo.[82–85] Official results of other phase 2 trials in the context of anti-FXI administration among ESRD patients are awaited.[86–88] Additionally, the use of these agents in rabbit model of catheter thrombosis resulted in prolongation of the time to catheter occlusion compared with control,[89] opening the way for further investigation in the setting of VTE prevention in haemodialysis patients with indwelling venous catheters.

6 | FUTURE: ANTI-XI AND ANTI-XII FOR CRT

The burden of CRT management is still high due to costs and complication rates, especially in fragile subgroups of patients (e.g. cancer and haemodialysis patients), who are exposed to an increased risk of bleeding. During the last decade, research has focused on the development of novel anticoagulant agents that can be effective in preventing and treating thromboembolic events without increasing the bleeding risk. The novel coagulation targets are represented by factor XI (FXI) and factor XII (FXII), which are involved in the contact activation pathway and play an important role in thrombus formation and propagation, without significant impact in the haemostatic process.[90,91] Moreover, inhibition of contact activation has shown promising results in terms of reduction of device-associated clotting without the bleeding risks of traditional anticoagulants.[92,93] Following the promising results of several phase 2 trials on different inhibitors of FXI for thromboprophylaxis in orthopaedic surgery,[94–97] these agents have been recently proposed also in the context of CRT thromboprophylaxis. The results of a phase 2 clinical trial with gruticibart, an anti-FXI monoclonal antibody (previously known as AB023), in the context of prevention of CRT in 22 ambulatory cancer patients undergoing central line placement, have been recently published.[61] The overall incidence of CRT was 12.5% and 40.0% in the interventional and the control study, respectively, with no significant difference in adverse or bleeding-related events.[61] Gruticibart, aside from preserving tissue factor-mediated

TABLE 4 Ongoing studies for CRT.

ID	Title	Topic	Estimated enrolment	Estimated completion date
NCT06149533	A randomized, multicenter, open-label, control, clinical trial to evaluate the efficacy and safety of edoxaban on prevention of catheter-related thrombosis (CRT) in cancer patients	Primary prevention for CRT in cancer patients	366	30 November 2026
NCT04924322	Age-dependent heterogeneity in the efficacy of prophylaxis with enoxaparin against catheter-associated thrombosis in critically ill children	Age-dependent primary prevention for CRT in critically ill children	258	31 July 2026
NCT04548713	Control of line complications with kiteLock (CLiCK) in the critical care unit: a multi-center, cluster-randomized, double-blinded, crossover trial investigating the effect of a novel locking fluid on central line complications in the critical care population	Critical care unit	1524	31 December 2024
NCT04067245	Tetrasodium EDTA central venous catheter lock solution in home parenteral nutrition patients: ease of use and cost analysis	Home parenteral nutrition	20	01 March 2025
NCT04117217	Analysis of laboratory markers to predict risk of catheter related thrombosis	Predictive laboratory markers for CRT in paediatric patients	350	December 2026

Abbreviation: CRT, catheter-related deep vein thrombosis.

coagulation, had minimal to null impact on platelet activation.[61] These results align with a previous phase 2 randomized, double-blind, placebo-controlled trial on haemodialysis patients, where AB023 was well tolerated and reduced dialyzer clotting and thrombin-antithrombin complexes compared with placebo.[84] While promising, these findings remain preliminary and require confirmation in larger prospective trials to establish the efficacy and safety of gruticibart or other FXI inhibitors as prophylaxis for CRT.

Table 4 provides information on the ongoing trials on CRT, highlighting the constant need for updated evidence, in order to improve clinicians' armamentarium for the management of this challenging condition.

7 | CONCLUSIONS

The increasing use of central venous accesses brought to a significant increase of device-associated VTE. Despite the constant concomitant improvement in techniques and materials, the incidence of CRT remains substantial. Current evidence in the management of CRT is still limited but highlights non-negligible rates of treatment-related complications, such as bleeding events, especially among more fragile subgroups of patients. New anticoagulants directed against the contact pathway represent a promising option for the prevention and management of CRT.

AUTHOR CONTRIBUTIONS

Laura Girardi contributed to conceptualization; writing part of the original draft, tables and figures; writing review and editing, bibliography review. Marcello Di Nisio, Matteo Candeloro and Emanuele Valeriani contributed to writing part of the original draft, writing review and editing. Walter Ageno contributed to conceptualization, writing review and editing, validation, supervision, and project administration.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

L. Girardi, M. Candeloro and E. Valeriani report no conflicts of interests. M. Di Nisio received personal fees as an invited speaker from Bayer, Daiichi Sankyo, and Viatris, personal fees for advisory board membership from Leo

Pharma and Pfizer, and institutional funding from Leo Pharma, all outside the submitted work. W. Ageno reports advisory board honoraria from Astra Zeneca Bayer, BMS/Pfizer, Leo Pharma, Norgine, Sanofi and Viatris outside the submitted work.

DATA AVAILABILITY STATEMENT

This paper does not include original data, since it is a review on the available evidence on the topic. Data related to articles selection may be available if expressively requested.

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REFERENCES

1. Teja B, Bosch NA, Diep C, et al. Complication rates of central venous catheters: a systematic review and meta-analysis. *JAMA Intern Med*. 2024;184(5):474. doi:10.1001/JAMAINTERNMED.2023.8232
2. Baumann Kreuziger L, Jaffray J, Carrier M. Epidemiology, diagnosis, prevention and treatment of catheter-related thrombosis in children and adults. *Thromb Res*. 2017;157:64-71. doi:10.1016/J.THROMRES.2017.07.002
3. Debourdeau P, Farge D, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. *J Thromb Haemost*. 2013;11(1):71-80. doi:10.1111/JTH.12071
4. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315-352. doi:10.1016/J.CHEST.2015.11.026
5. Citla Sridhar D, Abou-Ismail MY, Ahuja SP. Central venous catheter-related thrombosis in children and adults. *Thromb Res*. 2020;187:103-112. doi:10.1016/J.THROMRES.2020.01.017
6. Kucher N. Clinical practice. Deep-vein thrombosis of the upper extremities. *N Engl J Med*. 2011;364(9):861-869. doi:10.1056/NEJMcp1008740
7. Abbruzzese C, Guzzardella A, Consonni D, et al. Incidence of asymptomatic catheter-related thrombosis in intensive care unit patients: a prospective cohort study. *Ann Intensive Care*. 2023;13(1):106. doi:10.1186/S13613-023-01206-W
8. Chopra V, Anand S, Hickner A, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. *Lancet*. 2013;382(9889):311-325. doi:10.1016/S0140-6736(13)60592-9
9. Leung A, Heal C, Perera M, Pretorius C. A systematic review of patient-related risk factors for catheter-related thrombosis. *J Thromb Thrombolysis*. 2015;40(3):363-373. doi:10.1007/S11239-015-1175-9
10. Balsorano P, Virgili G, Villa G, et al. Peripherally inserted central catheter-related thrombosis rate in modern vascular access era-when insertion technique matters: a systematic review and meta-analysis. *J Vasc Access*. 2020;21(1):45-54. doi:10.1177/1129729819852203
11. Haggstrom L, Parmar G, Brungs D. Central venous catheter thrombosis in cancer: a multi-centre retrospective study investigating risk factors and contemporary trends in management. *Clin med insights Oncol*. 2020;14:14. doi:10.1177/1179554920953097
12. Decousus H, Bourmaud A, Fournel P, et al. Cancer-associated thrombosis in patients with implanted ports: a prospective multicenter French cohort study (ONCOCIP). *Blood*. 2018;132(7):707-716. doi:10.1182/BLOOD-2018-03-837153
13. Saber W, Moua T, Williams EC, et al. Risk factors for catheter-related thrombosis (CRT) in cancer patients: a patient-level data (IPD) meta-analysis of clinical trials and prospective studies. *J Thromb Haemost*. 2011;9(2):312-319. doi:10.1111/J.1538-7836.2010.04126.X
14. Bahl A, Karabon P, Chu D. Comparison of venous thrombosis complications in midlines versus peripherally inserted central catheters: are midlines the safer option? *Clin Appl Thromb Hemost*. 2019;25:25. doi:10.1177/1076029619839150
15. Bahl A, Diloreto E, Jankowski D, Hijazi M, Chen NW. Comparison of 2 midline catheter devices with differing antithrombogenic mechanisms for catheter-related thrombosis: a randomized clinical trial. *JAMA Netw Open*. 2021;4(10):e2127836. doi:10.1001/JAMANETWORKOPEN.2021.27836
16. Nifong TP, McDevitt TJ. The effect of catheter to vein ratio on blood flow rates in a simulated model of peripherally inserted central venous catheters. *Chest*. 2011;140(1):48-53. doi:10.1378/CHEST.10-2637
17. Brewer C. Reducing upper extremity deep vein thrombosis when inserting PICCs. *Br J Nurs*. 2012;21(14):S12-S17. doi:10.12968/BJON.2012.21.SUP14.S12
18. Orme RMLE, McSwiney MM, Chamberlain-Webber RFO. Fatal cardiac tamponade as a result of a peripherally inserted central venous catheter: a case report and review of the literature. *Br J Anaesth*. 2007;99(3):384-388. doi:10.1093/BJA/AEM181
19. De Cicco M, Matovic M, Balestreri L, et al. Central venous thrombosis: an early and frequent complication in cancer patients bearing long-term silastic catheter. A prospective study. *Thromb Res*. 1997;86(2):101-113. doi:10.1016/S0049-3848(97)00054-6
20. Craft PS, May J, Dorigo A, Hoy C, Plant A. Hickman catheters: left-sided insertion, male gender, and obesity are associated with an increased risk of complications. *Aust NZ J Med*. 1996;26(1):33-39. doi:10.1111/J.1445-5994.1996.TB02904.X
21. Hamilton H. Central venous catheters: choosing the most appropriate access route. *Br J Nurs*. 2004;13(14):862-870. doi:10.12968/BJON.2004.13.14.14317
22. Seckold T, Walker S, Dwyer T. A comparison of silicone and polyurethane PICC lines and postinsertion complication rates: a systematic review. *J Vasc Access*. 2015;16(3):167-177. doi:10.5301/JVA.5000330
23. Lai NM, Chaiyakunapruk N, Lai NA, O'Riordan E, Pau WSC, Saint S. Catheter impregnation, coating or bonding for reducing central venous catheter-related infections in adults. *Cochrane Database Syst Rev*. 2016;3(3):CD007878. doi:10.1002/14651858.CD007878.PUB3
24. Shah PS, Shah N. Heparin-bonded catheters for prolonging the patency of central venous catheters in children. *Cochrane Database Syst Rev*. 2014;2014(2):CD005983. doi:10.1002/14651858.CD005983.PUB3
25. Boersma RS, Jie KSG, Verbon A, van Pampus ECM, Schouten HC. Thrombotic and infectious complications of central

venous catheters in patients with hematological malignancies. *Ann Oncol*. 2008;19(3):433-442. doi:10.1093/ANNONC/MDM350
26. Van Rooden CJ, Schippers EF, Barge RMY, et al. Infectious complications of central venous catheters increase the risk of catheter-related thrombosis in hematology patients: a prospective study. *J Clin Oncol*. 2005;23(12):2655-2660. doi:10.1200/JCO.2005.05.002
27. 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*. 1998;114(1):207-213. doi:10.1378/CHEST.114.1.207
28. Wallace A, Albadawi H, Patel N, et al. Anti-fouling strategies for central venous catheters. *Cardiovasc Diagn Ther*. 2017;7(Suppl 3):S246-S257. doi:10.21037/CDT.2017.09.18
29. Van Rooden CJ, Rosendaal FR, Meinders AE, Van Oostayen JA, Van Der Meer FJM, Huisman MV. The contribution of factor V Leiden and prothrombin G20210A mutation to the risk of central venous catheter-related thrombosis. *Haematologica*. 2004;89(2):201-206.
30. Dentali F, Gianni M, Agnelli G, Ageno W. Association between inherited thrombophilic abnormalities and central venous catheter thrombosis in patients with cancer: a meta-analysis. *J Thromb Haemost*. 2008;6(1):70-75. doi:10.1111/J.1538-7836.2007.02823.X
31. De Cicco M, Matovic M, Balestreri L, et al. Antithrombin III deficiency as a risk factor for catheter-related central vein thrombosis in cancer patients. *Thromb Res*. 1995;78(2):127-137. doi:10.1016/0049-3848(95)00041-0
32. Abdelkefi A, Romdhane N, Ben KA, et al. Prevalence of inherited prothrombotic abnormalities and central venous catheter-related thrombosis in haematopoietic stem cell transplants recipients. *Bone Marrow Transplant*. 2005;36(10):885-889. doi:10.1038/sj.bmt.1705156
33. Koo CM, Vissapragada R, Sharp R, et al. ABO blood group related venous thrombosis risk in patients with peripherally inserted central catheters. *Br J Radiol*. 2018;91(1082):20170560. doi:10.1259/BJR.20170560
34. Zhang Q, Peng H, Hu L, Ren R, Peng X, Song J. Association between ABO blood group and venous thromboembolism risk in patients with peripherally inserted central catheters: a meta-analysis and systematic review. *Front Oncol*. 2022;12:12. doi:10.3389/FONC.2022.906427
35. Wang P, He L, Yuan Q, et al. Risk factors for peripherally inserted central catheter-related venous thrombosis in adult patients with cancer. *Thromb J*. 2024;22(1):6. doi:10.1186/S12959-023-00574-4
36. Yue J, Zhang Y, Xu F, et al. A clinical study of peripherally inserted central catheter-related venous thromboembolism in patients with hematological malignancies. *Sci Rep*. 2022;12(1):9871. doi:10.1038/S41598-022-13916-5
37. Yuen HLA, Zhao J, Tran H, Chunilal SD. Development of a risk score to predict peripherally inserted central catheter thrombosis in active cancer. *Intern Med J*. 2022;52(10):1733-1740. doi:10.1111/IMJ.15557
38. Hu Z, He R, Zhao Y, Luo M, Fan Y, Li J. Risk assessment models for PICC-related venous thrombosis in adult patients with cancer: a network meta-analysis. *Thromb Res*. 2024;239:109030. doi:10.1016/J.THROMRES.2024.05.003
39. Wang X, Cheng Q, Xu L, et al. Effects of factor IX or factor XI deficiency on ferric chloride-induced carotid artery occlusion in mice. *J Thromb Haemost*. 2005;3(4):695-702. doi:10.1111/J.1538-7836.2005.01236.X
40. Paauw JD, Borders H, Ingalls N, et al. The incidence of PICC line-associated thrombosis with and without the use of prophylactic anticoagulants. *JPEN J Parenter Enteral Nutr*. 2008;32(4):443-447. doi:10.1177/0148607108319801
41. Grant JD, Stevens SM, Woller SC, et al. Diagnosis and management of upper extremity deep-vein thrombosis in adults. *Thromb Haemost*. 2012;108(6):1097-1108. doi:10.1160/TH12-05-0352
42. Rajasekhar A, Streiff MB. How I treat central venous access device-related upper extremity deep vein thrombosis. *Blood*. 2017;129(20):2727-2736. doi:10.1182/BLOOD-2016-08-693671
43. Baskin JL, Pui CH, Reiss U, et al. Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. *Lancet*. 2009;374(9684):159-169. doi:10.1016/S0140-6736(09)60220-8
44. Di Nisio M, Van Sluis GL, Bossuyt PMM, Büller HR, Porreca E, Rutjes AWS. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8(4):684-692. doi:10.1111/J.1538-7836.2010.03771.X
45. Cardoso PC, Rabelo-Silva ER, Martins Bock P, Chopra V, Saffi MAL. Biomarkers associated with thrombosis in patients with peripherally inserted central catheter: a systematic review and meta-analysis. *J Clin Med*. 2023;12(13):4480. doi:10.3390/JCM12134480
46. Liu W, He L, Zhou J, Zeng W, Zeng S, Gong Z. Different diagnostic strategies using D-dimer for peripherally inserted central catheter-related upper extremity deep vein thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2023;11(3):565-572. doi:10.1016/J.JVSV.2022.07.018
47. Constans J, Salmi LR, Sevestre-Pietri MA, et al. A clinical prediction score for upper extremity deep venous thrombosis. *Thromb Haemost*. 2008;99(1):202-207. doi:10.1160/TH07-08-0485
48. Kleinjan A, Di Nisio M, Beyer-Westendorf J, et al. Safety and feasibility of a diagnostic algorithm combining clinical probability, D-dimer testing, and ultrasonography for suspected upper extremity deep venous thrombosis: a prospective management study. *Ann Intern Med*. 2014;160(7):451-457. doi:10.7326/M13-2056
49. Geerts W. Central venous catheter–related thrombosis. *Hematology*. 2014;2014(1):306-311. doi:10.1182/ASHEDUCATION-2014.1.306
50. Farge D, Frere C, Connors JM, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. *Lancet Oncol*. 2022;23(7):e334-e347. doi:10.1016/S1470-2045(22)00160-7
51. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv*. 2021;5(4):927-974. doi:10.1182/BLOODADVANCES.2020003442
52. Falanga A, Ay C, Di Nisio M, et al. Venous thromboembolism in cancer patients: ESMO clinical practice guideline. *Ann Oncol*. 2023;34:452-467. doi:10.1016/J.ANNONC.2022.12.014

53. Valeriani E, Di Nisio M, Porceddu E, et al. Anticoagulant treatment for upper extremity deep vein thrombosis: a systematic review and meta-analysis. *J Thromb Haemost*. 2022;20(3):661-670. doi:10.1111/JTH.15614
54. Elias A, Debourdeau P, Espitia O, et al. Central venous catheter associated upper extremity deep vein thrombosis in cancer patients: diagnosis and therapeutic management. *Arch Cardiovasc Dis*. 2024;117(1):72-83. doi:10.1016/J.ACVD.2023.11.011
55. Wang TF, Kou R, Carrier M, Delluc A. Management of catheter-related upper extremity deep vein thrombosis in patients with cancer: a systematic review and meta-analysis. *J Thromb Haemost*. 2023;7:749-764. doi:10.1016/J.JTHA.2023.11.017
56. Lyon AR, López-Fernández T, Lancellotti P, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the international cardio-oncology society (IC-OS): developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). *Eur Heart J Cardiovasc Imaging*. 2022;23(10):e333-e465. doi:10.1093/EHJCI/JEAC106
57. Baskin JL, Reiss U, Wilimas JA, et al. Thrombolytic therapy for central venous catheter occlusion. *Haematologica*. 2012;97(5):641-650. doi:10.3324/HAEMATOL.2011.050492
58. Kahale LA, Tsolakian IG, Hakoum MB, et al. Anticoagulation for people with cancer and central venous catheters. *Cochrane Database Syst Rev*. 2018;6(6):CD006468. doi:10.1002/14651858.CD006468.PUB6
59. Brandt W, Brown C, Wang TF, et al. Efficacy and safety of apixaban for primary prevention of thromboembolism in patients with cancer and a central venous catheter: a subgroup analysis of the AVERT trial. *Thromb Res*. 2022;216:8-10. doi:10.1016/J.THROMRES.2022.05.014
60. O'Brien SH, Rodriguez V, Lew G, et al. Apixaban versus no anticoagulation for the prevention of venous thromboembolism in children with newly diagnosed acute lymphoblastic leukaemia or lymphoma (PREVAPIX-ALL): a phase 3, open-label, randomised, controlled trial. *Lancet Haematol*. 2024;11(1):e27-e37. doi:10.1016/S2352-3026(23)00314-9
61. Pfeffer MA, Kohs TCL, Vu HH, et al. Factor XI inhibition for the prevention of catheter-associated thrombosis in patients with cancer undergoing central line placement: a phase 2 clinical trial. *Arterioscler Thromb Vasc Biol*. 2024;44(1):290-299. doi:10.1161/ATVBAHA.123.319692
62. Houghton DE, Billett HH, Gaddh M, et al. Risk of pulmonary emboli after removal of an upper extremity central catheter associated with a deep vein thrombosis. *Blood Adv*. 2021;5(14):2807-2812. doi:10.1182/BLOODADVANCES.2021004698
63. Zwicker JI, Connolly G, Carrier M, Kamphuisen PW, Lee AYY. Catheter-associated deep vein thrombosis of the upper extremity in cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(5):796-800. doi:10.1111/JTH.12527
64. Sousa B, Furlanetto J, Hutka M, et al. Central venous access in oncology: ESMO clinical practice guidelines. *Ann Oncol*. 2015;26(Suppl 5):v152-v168. doi:10.1093/ANNONC/MDV296
65. Streiff MB, Holmstrom B, Angelini D, et al. Cancer-associated venous thromboembolic disease, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw*. 2021;19(10):1181-1201. doi:10.6004/JNCCN.2021.0047
66. Frank DA, Meuse J, Hirsch D, Ibrahim JG, Van Den Abbeele AD. The treatment and outcome of cancer patients with thromboses on central venous catheters. *J Thromb Thrombolysis*. 2000;10(3):271-275. doi:10.1023/A:1026503526188
67. Takemoto CM, Sohi S, Desai K, et al. Hospital-associated venous thromboembolism in children: incidence and clinical characteristics. *J Pediatr*. 2014;164(2):332-338. doi:10.1016/J.JPEDS.2013.10.025
68. Manlhiot C, Menjak IB, Brandão LR, et al. Risk, clinical features, and outcomes of thrombosis associated with pediatric cardiac surgery. *Circulation*. 2011;124(14):1511-1519. doi:10.1161/CIRCULATIONAHA.110.006304
69. Smitherman AB, Alexander T, Connelly M, et al. The incidence of catheter-associated venous thrombosis in noncritically ill children. *Hosp Pediatr*. 2015;5(2):59-66. doi:10.1542/HPEDS.2014-0041
70. Boulet SL, Grosse SD, Thornburg CD, Yusuf H, Tsai J, Hooper WC. Trends in venous thromboembolism-related hospitalizations, 1994–2009. *Pediatrics*. 2012;130(4):e812-e820. doi:10.1542/PEDS.2012-0267
71. Dubois J, Rypens F, Garel L, David M, Lacroix J, Gauvin F. Incidence of deep vein thrombosis related to peripherally inserted central catheters in children and adolescents. *CMAJ*. 2007;177(10):1185-1190. doi:10.1503/CMAJ.070316
72. Beck C, Dubois J, Grignon A, Lacroix J, David M. Incidence and risk factors of catheter-related deep vein thrombosis in a pediatric intensive care unit: a prospective study. *J Pediatr*. 1998;133(2):237-241. doi:10.1016/S0022-3476(98)70226-4
73. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv*. 2018;2(22):3292-3316. doi:10.1182/BLOODADVANCES.2018024786
74. Thom K, Lensing AWA, Nurmeev I, et al. Safety and efficacy of anticoagulant therapy in pediatric catheter-related venous thrombosis (EINSTEIN-Jr CVC-VTE). *Blood Adv*. 2020;4(19):4632-4639. doi:10.1182/BLOODADVANCES.2020002637
75. Giossi R, Menichelli D, D'Amico F, et al. Efficacy and safety of direct oral anticoagulants in the pediatric population: a systematic review and a meta-analysis. *J Thromb Haemost*. 2023;21(10):2784-2796. doi:10.1016/J.JTHA.2023.07.011
76. Lok CE, Huber TS, Lee T, et al. KDOQI clinical practice guideline for vascular access: 2019 Update. *Am J Kidney Dis*. 2020;75(4):S1-S164. doi:10.1053/J.AJKD.2019.12.001/ATTACHMENT/3116 1DA0-0384-4B50-99B9-DAD4DDA7C16F/MMC4.PDF
77. Ethier J, Mendelssohn DC, Elder SJ, et al. Vascular access use and outcomes: an international perspective from the dialysis outcomes and practice patterns study. *Nephrol Dial Transplant*. 2008;23(10):3219-3226. doi:10.1093/NDT/GFN261
78. Chouhani BA, Kabbali N, Chiba Bennani S, El Bardai G, Sqalli HT. Tunneled catheters in hemodialysis: indications and complications. *J Méd Vasc*. 2022;47(2):87-93. doi:10.1016/J.JDMV.2022.04.007
79. Johansen KL, Chertow GM, Gilbertson DT, et al. US renal data system 2022 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2023;81(3):A8-A11. doi:10.1053/j.ajkd.2022.12.001
80. Gunawansa N, Sudusinghe DH, Wijayaratne DR. Hemodialysis catheter-related central venous thrombosis: clinical approach to evaluation and management. *Ann Vasc Surg*. 2018;51:298-305. doi:10.1016/J.AVSG.2018.02.033

81. Mokrzycki MH, Jean-Jerome K, Rush H, Zdunek MP, Rosenberg SO. A randomized trial of minidose warfarin for the prevention of late malfunction in tunneled, cuffed hemodialysis catheters. *Kidney Int*. 2001;59(5):1935-1942. doi:10.1046/J.1523-1755.2001.0590051935.X
82. Winkelmayer WC, Lensing AWA, Thadhani RI, et al. A phase II randomized controlled trial evaluated antithrombotic treatment with fesomersen in patients with kidney failure on hemodialysis. *Kidney Int*. 2024;106(1):145-153. doi:10.1016/J.KINT.2024.02.024
83. Weitz JI, Tankó LB, Floege J, et al. Anticoagulation with osocimab in patients with kidney failure undergoing hemodialysis: a randomized phase 2 trial. *Nat Med*. 2024;30(2):435-442. doi:10.1038/S41591-023-02794-7
84. Lorentz CU, Tucker EI, Verbout NG, et al. The contact activation inhibitor AB023 in heparin-free hemodialysis: results of a randomized phase 2 clinical trial. *Blood*. 2021;138(22):2173-2184. doi:10.1182/BLOOD.2021011725
85. Walsh M, Bethune C, Smyth A, et al. Phase 2 study of the factor XI antisense inhibitor IONIS-FXIRx in patients with ESRD. *Kidney Int Rep*. 2021;7(2):200-209. doi:10.1016/J.EKIR.2021.11.011
86. Study Details. Global Study of MK-2060 (Anti-Factor XI Monoclonal Antibody) in Participants With End Stage Renal Disease Receiving Hemodialysis (FXI Hemodialysis Study) (MK-2060-007). Accessed August 13, 2024. https://clinicaltrials.gov/study/NCT05027074
87. Study Details. Study to Investigate the Safety of a Drug Called Osocimab at Low and High Doses in Adult Patients With Kidney Failure Requiring Regular Hemodialysis. Accessed August 13, 2024. https://clinicaltrials.gov/study/NCT04523220
88. Study Details. A Study of ISIS 416858 Administered Subcutaneously to Participants With End-Stage Renal Disease (ESRD) on Hemodialysis. Accessed August 13, 2024. https://clinicaltrials.gov/study/NCT03358030
89. Yau JW, Liao P, Fredenburgh JC, et al. Selective depletion of factor XI or factor XII with antisense oligonucleotides attenuates catheter thrombosis in rabbits. *Blood*. 2014;123(13):2102-2107. doi:10.1182/BLOOD-2013-12-540872
90. Gailani D, Bane CE, Gruber A. Factor XI and contact activation as targets for antithrombotic therapy. *J Thromb Haemost*. 2015;13(8):1383-1395. doi:10.1111/JTH.13005
91. Stavrou E, Schmaier AH. Factor XII: what does it contribute to our understanding of the physiology and pathophysiology of hemostasis & thrombosis. *Thromb Res*. 2010;125(3):210-215. doi:10.1016/J.THROMRES.2009.11.028
92. Larsson M, Rayzman V, Nolte MW, et al. A factor XIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk. *Sci Transl Med*. 2014;6(222):222ra17. doi:10.1126/SCITRANSLMED.3006804
93. Wallisch M, Lorentz CU, Lakshmanan HHS, et al. Antibody inhibition of contact factor XII reduces platelet deposition in a model of extracorporeal membrane oxygenator perfusion in nonhuman primates. *Res Pract Thromb Haemost*. 2020;4(2):205-216. doi:10.1002/RTH2.12309
94. Weitz JI, Strony J, Ageno W, et al. Milvexian for the prevention of venous thromboembolism. *N Engl J Med*. 2021;385(23):2161-2172. doi:10.1056/NEJMOA2113194
95. Büller HR, Bethune C, Bhanot S, et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med*. 2015;372(3):232-240. doi:10.1056/NEJMOA1405760
96. Weitz JI, Bauersachs R, Becker B, et al. Effect of Osocimab in preventing venous thromboembolism among patients undergoing knee arthroplasty: the FOXTROT randomized clinical trial. *JAMA*. 2020;323(2):130-139. doi:10.1001/JAMA.2019.20687
97. Verhamme P, Yi BA, Segers A, et al. Abelacimab for prevention of venous thromboembolism. *N Engl J Med*. 2021;385(7):609-617. doi:10.1056/NEJMOA2105872

How to cite this article: Girardi L, Di Nisio M, Candeloro M, Valeriani E, Ageno W. Catheter-related deep vein thrombosis: Where are we at and where are we going? Updates and ongoing unmet clinical needs. *Eur J Clin Invest*. 2025;55:e14311. doi:10.1111/eci.14311