ORIGINAL RESEARCH

Anticoagulants decrease the risk for catheter-related venous thrombosis in patients with chronic intestinal failure: A long-term cohort study

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Abstract

Background: Catheter-related venous thrombosis (CRVT) is a severe complication of home parental nutrition. Although primary prevention of CRVT is crucial, there is no consensus on anticoagulant use to prevent this adversity. The aim was to compare CRVT risk in patients with chronic intestinal failure (CIF) in the presence or absence of anticoagulants, and to identify CRVT risk factors.

Methods: This retrospective cohort study comprised adult patients with CIF with a central venous access device (CVAD) between 2010 and 2020 that were treated at our national CIF referral center. Analyses were performed at a CVAD level.

Results: Overall, 1188 CVADs in 389 patients were included (540.800 CVAD days). Anticoagulants were used in 403 CVADs. In total, 137 CRVTs occurred in 98 patients, resulting in 0.25 CRVTs/1000 CVAD days (95% CI, 0.22–0.29). Anticoagulant use was associated with a decreased CRVT risk (odds ratio [OR] = 0.53; 95% CI, 0.31–0.89; P = 0.02). Left-sided CVAD insertion (OR = 2.00; 95% CI, 1.36–2.94), a history of venous thrombosis (OR = 1.73; 95% CI, 1.05–2.84), and a shorter period postinsertion (OR = 0.78; 95% CI, 0.65–0.92) were independently associated with an increased CRVT risk.

Conclusion: Anticogulants decreased the CRVT risk. In addition, we identified left-sided vein insertion, a history of venous thrombosis, and a shorter period post-CVAD insertion as CRVT risk factors. Further prospective studies should provide guidance whether prophylactic anticoagulant use, especially in higher-risk patients with a left-sided CVAD or a history of venous thrombosis, is justified.

KEYWORDS
anticoagulants, catheter-related venous thrombosis, chronic intestinal failure, home parental nutrition, prevention, thrombosis

CLINICAL RELEVANCY STATEMENT

Patients with chronic intestinal failure (CIF) are lifelong-dependent on home parental nutrition (HPN). Catheter-related venous thrombosis (CRVT) is a severe complication of HPN with potentially devastating consequences such as a vena cava superior syndrome or loss of vascular access. Although prevention of CRVTs is crucial, only limited data are available concerning the optimal prevention strategies in patients with CIF. This study found that anticoagulants were independently associated with a decreased CRVT risk. In addition, several risk factors for CRVTs were identified, including left-sided central venous access device (CVAD) insertion, a history of venous thrombosis, and a shorter period post-CVAD insertion. These results support the use of anticoagulants as secondary prophylaxis.

INTRODUCTION

Patients with chronic intestinal failure (CIF) inadequately absorb nutrients and/or fluids to sustain health and/or growth. These patients therefore depend on lifelong home parenteral nutrition (HPN) that is administered via a central venous access device (CVAD). This is a complex treatment strategy associated with the development of serious complications, mainly central line–associated bloodstream infection (CLABSIs) and catheter-related venous thromboses (CRVTs).[1]

CRVT is defined as a thrombus in the vein adjacent to a CVAD.[2] Factors contributing to the pathogenesis of CRVT include restricted blood flow within the vessel lumen, endothelial damage following CVAD insertion, infusion of high-osmolar parental nutrition formulations, and patient-related factors, such as thrombophilia or active malignancy that lead to a hypercoagulable state.[3,4] The incidence of CRVT in patients with CIF is estimated between 0.02 and 0.20 events per 1.000 CVAD days.[1,5,6] A CLABSI is often mentioned as the most daunting complication of HPN. However, a CRVT may be at least as serious because of the long-term damage to veins and the potentially serious consequences, including vena cava superior syndrome (VCSS) with potential complete loss of options to obtain central venous access. These notions obviate the need for preventive measures.

Although anticoagulants have been shown to be effective as prophylaxis in a range of clinical settings, including (recurrent) deep venous thrombosis, pulmonary embolism, and atrial fibrillation and malignancy, their relevance to prevent CRVTs in patients with a CVAD is not clear.[7–9] As a result, current directives for oncology patients with a CVAD do not recommend primary prophylactic anticoagulant therapy, and most guidelines only recommend secondary prophylaxis in case of a persistent need for a CVAD.[10–13] In addition, only limited data and older guidelines are available to guide prevention strategies in CIF patients.[14–16] The most recent updated ESPEN guidelines do not recommend primary prophylaxis and recommendations for secondary prophylaxis range from 3 months to lifelong anticoagulant use based on limited data from (mostly) retrospective research.[1,17]

Because evidence to bolster effective patient-tailored CRVT preventive strategies in CIF treatment is lacking, we conducted an observational single-center study in our extensive CIF population. Primary aim was to compare the risk for CRVT in patients with CIF in the present or absence of anticoagulant use. Secondary aims were to identify risk factors for CRVTs and assess complications related to the use of anticoagulants and CRVTs.

PARTICIPANTS AND METHODS

Study design

This retrospective cohort study was conducted at our tertiary referral center for CIF, established in 1976.[18] Patient data were retrieved from the Nijmegen IF registry, a web-based Castor Electronic Data Capture database. Patients aged ≥18 years were eligible for inclusion if they met the criteria for CIF and received HPN via a tunneled central venous catheter or subcutaneous port system for a minimum of 3 months between January 2010 and January 2020. Patients with a non-tunneled catheter, a peripheral venous catheter, or an arteriovenous fistula (shunt) were excluded for the time period they only received HPN via this type of CVAD.

Most CVADs were inserted under ultrasound guidance by the vascular surgeon. Before inserting a CVAD, patency of the major neck or femoral veins was established using ultrasound. Preoperatively, fluoroscopy was used to ensure correct positioning of the CVAD and a postoperative x ray was performed to rule out complications, mainly pneumothorax.[2] No screening for CRVTs was performed.

Data collection

The following data were collected: patient characteristics (sex, age, underlying disease leading to CIF, and medical history), medication (anticoagulant use and opiates), CVAD characteristics (starting age, HPN experience, type of CVAD, and side and vein used for insertion), HPN characteristics (type and infusion frequency), complications (CRVT, CLABSI, VCSS, infected thrombosis, and pulmonary embolism), and complications of anticoagulant use (major bleeding, heparin-induced thrombocytopenia, and heparin hypersensitivity).

Outcomes and definitions

The primary aim of this study was to assess, for the first time to our knowledge, the risk for CRVT at CVAD level (as opposed to patient level in previous studies) in patients with CIF in the present or absence of anticoagulant use. Secondary aims were to identify CRVT-related risk factors, and to describe anticoagulant-related side-effects and complications of CRVTs. CRVT was defined as a thrombosis of a vein along the tract or at the tip of the CVAD.[2] The diagnosis was based on clinical symptoms suggestive for CRVT (eg, edema, venous distension,

and swelling) or upon using a diagnostic modality (eg, duplex ultrasound or computed tomography).[2] The first CRVT in a patient was defined as primary and the subsequent event was defined as secondary CRVT. Anticoagulant use was defined as the use of an anticoagulant prior to a CRVT. In case no CRVT occurred during a CVAD period, anticoagulant use was defined as use for >50% of the CVAD days. Anticoagulants were categorized as heparin, coumarin derivatives (intravenous infused or enteral), or direct oral anticoagulants (DOACs). P2Y12-inhibitors and acetylsalicylic acid were not registered as anticoagulants in this setting. A history of venous thrombosis included CRVTs, pulmonary embolism, deep venous thrombosis, or a thrombosis elsewhere. CLABSI was defined according to the definition of Centers for Disease Control and Prevention (CDC).[19] CLABSIs were included if they occurred during the CVAD period. When both CLABSI and CRVT occurred in the same CVAD, the CLABSI was only included when it occurred before or until 30 days after the CRVT. CVAD time is defined as the period from insertion until removal. In case a CRVT occurred, CVAD time is defined as the period from insertion until a CRVT.

Statistical methods

Baseline characteristics were analyzed using descriptive statistics. Continuous variables were expressed as means with SDs, medians with interquartile ranges, or numbers with percentages. CVAD complications were presented as a number of complications per 1.000 CVAD days with 95% CI.[20]

Risk factor analyses were performed at CVAD level using multilevel binary logistic regression. Patients were set as level one, and CVAD was set as level two. A multilevel approach at CVAD level as compared with an evaluation merely at patient level was favored because the former also enables a more detailed analysis of specific CVAD-related variables.

Possible covariates were sex, age at CVAD insertion, underlying mechanism of CIF, history of venous thrombosis (pulmonary embolism, deep venous thrombosis, or venous thrombosis elsewhere), hypercoaguable state, history of malignancy (active malignancy or ongoing treatment), history of inflammatory bowel disease, type of CVAD, side of CVAD insertion (right or left), vein used for CVAD insertion (jugular, subclavian, femoral), fluids or nutrition administered through the CVAD, number of infusion days per week, CVAD time (years), and occurrence of CLABSI. Covariates with a *P*-value ≤ 0.10 in a univariate analysis were included in the final multivariate analyses. Previously reported risk factors (history of venous thrombosis, hypercoaguable state, active malignancy, and side of CVAD insertion) were included as fixed confounders. Missing values were excluded from analyses. All analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp Armonk, NY, USA).

Ethical approval

This study was reviewed and approved by the research ethics committee of the Radboudumc in Nijmegen, the Netherlands (reference number 2020-6119). This study was reported according to STROBE guidelines.[21]

RESULTS

Study population

Overall, 389 patients with 1.188 CVADs were observed for a total of 540.800 CVAD days; 403 CVADs in the anticoagulant group (183.881 CVAD days) and 785 CVADs in the nonanticoagulant group (356.919 CVAD days). A detailed flowchart of the excluded CVADs can be found in Figure S1.

Coumarin derivatives were mainly used as anticoagulant (75.4%) and DOACs the least (5.5%). Baseline characteristics at CVAD level are presented in Table 1 and at patient level in Table S1. Indications for anticoagulant use comprised history of CRVT (*n* = 116), thrombosis at another site (*n* = 173), previous shunt occlusion (*n* = 19), shunt (*n* = 17), atrial fibrillation (*n* = 16), miscellaneous (*n* = 39), or unknown (*n* = 23).

CRVT characteristics

In total, 137 CRVTs were reported in 137 CVADs of 98 patients (Table 2). Eighty-four CRVTs were primary and 53 secondary related. In 70% of CRVTs, a patient experienced one or more complaints (*n* = 96, Figure 1). In 19 (68%) of 28 asymptomatic thromboses a diagnostic modality was performed because of the placement of a new CVAD. In the remaining nine thromboses, the CRVT was an accidental finding. In 53% of the CVADs with a CRVT, the CRVT was the reason for CVAD removal.

In total, 84 patients developed a primary CRVT during the observation period (Figure 2). Fourteen percent of the patients who started with anticoagulants after a primary CRVT developed a secondary CRVT. In contrast, 60% of the patients who did not receive anticoagulants developed a secondary CRVT. The overall median time to a CRVT was 4.5 months (interquartile range [IQR], 1.2–13.8). Eighteen of 84 primary CRVTs (21%) occurred in the first CVAD of a patient with a median time from start HPN until the first CRVT of 38.9 months (IQR, 14.0–76.7). The median time from the primary to secondary CRVT was 6.4 months (IQR, 4.5–20.0).

Risks for CRVT

The overall CRVT rate was 0.25/1000 CVAD days (95% CI, 0.22–0.29). CRVT rates in the anticoagulant and nonanticoagulant groups were 0.27/1000 CVAD days (95% CI, 0.21–0.34) and 0.24 (95% CI, 0.20–0.29), respectively (Table 2). The main outcome, anticoagulant use, was associated with a decreased CRVT risk (adjusted OR = 0.53; 95% CI, 0.31–0.89; *P* = 0.02) (Table 3). The results of the univariable logistic regression analysis are shown in Table S2.

TABLE 1 Baseline characteristics of CVADs

Baseline characteristics	CVADs with anticoagulation (n = 403)	CVADs without anticoagulation (n = 785)
Patient characteristics		
Female, N (percentage)	305 (76)	571 (73)
Age start HPN, mean (±SD), year	48 ± 16	50 ± 15
Pathological mechanism, N (percentage)		
Short bowel syndrome	190 (47)	316 (40)
Gastrointestinal motility disorder	170 (42)	312 (40)
Extensive small bowel mucosal disease	14 (4)	35 (5)
Intestinal fistula	7 (2)	45 (6)
Mechanical obstruction	7 (2)	20 (3)
Other	15 (4)	57 (7)
Medical history, N (percentage)		
Inflammatory bowel disease	68 (17)	205 (26)
Active malignancy	2 (1)	40 (5)
History of venous thrombosis	300 (74)	130 (17)
Hypercoagulable state	34 (8)	10 (1)
CVAD characteristics		
CLABSI, N (percentage)	97 (24)	160 (20)
Anticoagulants, N (percentage)		
Coumarin derivatives	303 (75)	
DOACs	22 (6)	
Heparin	77 (19)	
Opiates, N (percentage)	190 (47)	318 (41)
Unknown	3 (1)	19 (2)
Age start CVAD, mean (±SD), years	53 (±15)	52 (±16)
HPN experience at start CVAD, median (IQR), years	3 (0.8–7)	0.8 (0–3)
Type of CVAD, N (percentage)		
Tunneled catheter	323 (80)	596 (76)
Subcutaneous port system	80 (20)	189 (24)
CVAD lumen, N (percentage)		
Single lumen	363 (90)	682 (87)
Multilumen	34 (8)	60 (8)
Unknown	6 (2)	43 (6)
Side of vein insertion, N (percentage)		
Left	163 (40)	319 (41)
Right	229 (57)	438 (56)
Other	4 (1)	0 (0)
Unknown	7 (2)	28 (4)
Vein used for insertion, N (percentage)		
Jugular	219 (54)	487 (62)
Subclavian	70 (17)	210 (27)
Femoral	90 (22)	25 (3)
Other	16 (4)	6 (1)
Unknown	8 (2)	57 (7)

(Continues)

TABLE 1 (Continued)

Baseline characteristics	CVADs with anticoagulation (n = 403)	CVADs without anticoagulation (n = 785)
Type of infusion, N (percentage)		
Nutrition	375 (93)	653 (83)
Fluids	27 (7)	127 (16)
Unknown	1 (0.2)	5 (1)
Infusion, N per week, mean (±SD)	6 (±1)	6 (±1)
Lock solution, N (percentage)		
2% taurolidine	360 (89)	646 (82)
Saline	34 (8)	44 (6)
Heparin	2 (1)	36 (5)
1.35% taurolidine, 4% citrate	0 (0)	12 (2)
Unknown	7 (2)	47 (6)

Notes: Because of the analysis at CVAD level, patients could be included multiple times when having had several CVADs, and possibly in both groups.
Abbreviations: CLABSI, central line–associated bloodstream infection; CVAD, central venous access device; DOAC, direct oral anticoagulant; HPN, home parental nutrition; IQR, interquartile range.
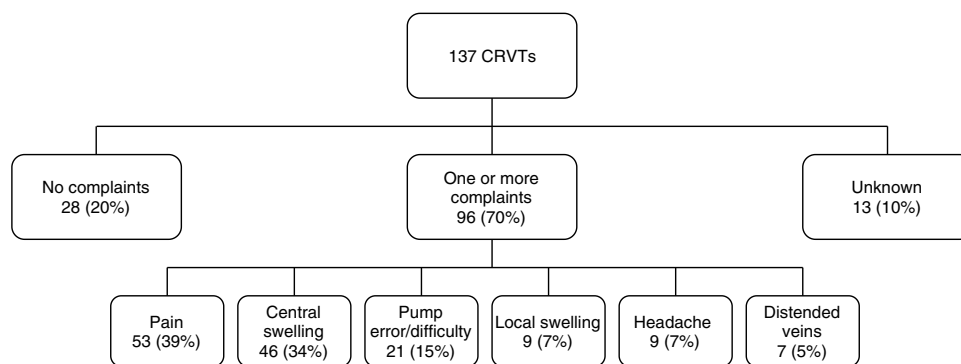

FIGURE 1 Clinical symptoms reported prior to a catheter-related venous thrombosis (CRVT) diagnosis
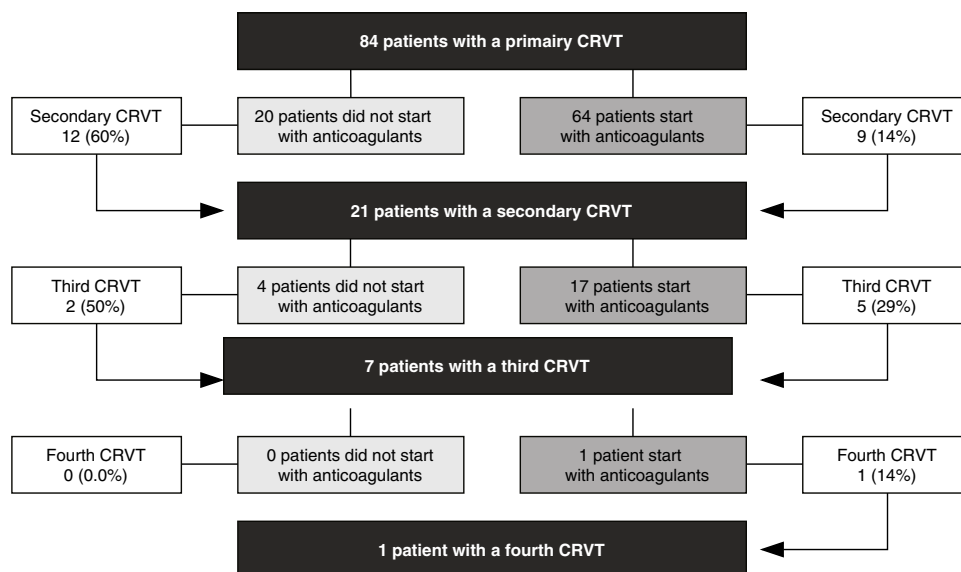

FIGURE 2 Flowchart of patients developing CRVTs after a primary event. CVAD only patients with a primary CRVT were selected for this figure. CRVT, catheter-related venous thrombosis; CVAD, central vascular access device

TABLE 2 Incidence rates of CRVTs and complications of CRVTs and anticoagulants

	CVADs with anticoagulants (n = 403)			CVADs without anticoagulants (n = 785)			Total (n = 1188)		
	Events	CVAD days	Rate per 1.000 CVAD days (95% CI)	Events	CVAD days	Rate per 1.000 CVAD days (95% CI)	Events	CVAD days	Rate per 1.000 CVAD days (95% CI)
CRVTs	50	183.881	0.27 (0.21–0.34)	87	356.919	0.24 (0.20–0.29)	137	540.800	0.25 (0.22–0.29)
Complications of CRVT									
Infected thrombosis	7	183.881	0.04 (0.02–0.08)	6	356.919	0.02 (0.01–0.04)	13	540.800	0.02 (0.01–0.04)
VCSS	6	183.881	0.03 (0.02–0.07)	10	356.919	0.03 (0.02–0.05)	16	540.800	0.03 (0.02–0.05)
Complications of anticoagulants									
Major bleeding	19	183.881	0.10 (0.07–0.16)	13	356.919	0.04 (0.02–0.06)	32	540.800	0.06 (0.04–0.08)

Notes: Rates are unadjusted and presented as events per 1.000 CVAD days.
Abbreviations: CRVT, catheter-related venous thrombosis; CVAD, central venous access device; VCSS, vena cava superior syndrome.

TABLE 3 Multivariate multilevel logistic regression of factors associated with a catheter-related venous thrombosis in patients with chronic intestinal failure

Variable	Odds ratio (95% CI)	P-value
Anticoagulants		
No	*Reference*	
Yes	0.53 (0.31–0.89)	0.02
History of venous thrombosis		
No	*Reference*	
Yes	1.73 (1.05–2.84)	0.03
Hypercoagulable state		
No	*Reference*	
Yes	2.16 (0.84–5.56)	0.11
Active malignancy		
No	*Reference*	
Yes	0.43 (0.10–1.93)	0.27
CLABSI		
No	*Reference*	
Yes	1.48 (0.96–2.28)	0.08
CVAD time, years	0.78 (0.65–0.92)	0.004
Side of vein insertion		
Right	*Reference*	
Left	2.00 (1.36–2.94)	0.00
Vein used for insertion		
Jugular vein	*Reference*	
Subclavian vein	1.05 (0.66–1.66)	0.85
Femoral vein	1.64 (0.89–3.02)	0.11
Subclavian vein	*Reference*	
Femoral vein	1.58 (0.80–3.09)	0.19

Note: Risk factors were analyzed using multivariate multilevel logistic regression. Variables with $P \leq 0.10$ in the univariable analysis and/or fixed confounders were included. Fixed confounders included active malignancy, history of venous thrombosis, hypercoagulable state, and side of insertion. Abbreviations: CLABSI, central line–associated bloodstream infection; CVAD, central venous access device.

Other risk factors independently associated with an increased CRVT risk were left-sided CVAD insertion (adjusted OR, 2.00; 95% CI, 1.36–2.94; $P = 0.00$), history of venous thrombosis (adjusted OR, 1.73; 95% CI, 1.05–2.84; $P = 0.03$), and a shorter period post-CVAD insertion (adjusted OR, 0.78; 95% CI, 0.65–0.92; $P = 0.004$) (Table 3).

Complications of CRVT and anticoagulants

CRVT-related complications were reported in 28 CVADs (2.4%), 13 infected thromboses, and 16 VCSS. In total, 32 major bleedings occurred and were predominantly gastrointestinal in origin ($n = 17$). Other major bleedings were postsurgical ($n = 6$), intramuscular ($n = 4$), urinary tract ($n = 2$), cerebral ($n = 1$), intra-articular ($n = 1$), or unknown

(n = 1) (Table 2). Overall, 30 other thrombotic events occurred, of which 13 deep venous thrombosis (0.02/1000 CVAD days [95% CI, 0.01–0.04)) and 17 pulmonary embolisms (0.03/1000 CVAD days [95% CI, 0.02–0.05)). Three pulmonary embolisms were most likely secondary to a CRVT and one secondary to a deep venous thrombosis. Thirty-eight percent of the patients used anticoagulants prior to a deep venous thrombosis and 24% prior to a pulmonary embolism. There were no patients with heparin-induced thrombocytopenia and only one patient with possible heparin hypersensitivity.

DISCUSSION

Patients with CIF are at risk for CVAD-related complications, including CRVTs. This retrospective cohort study aimed to compare the risk for CRVTs in patients with CIF based on anticoagulant use. Also, we assessed CRVT-related risk factors and complications related to CRVTs and anticoagulant use.

Our results suggest that CRVT risk was reduced in patients with CIF while using anticoagulants. Previous work by Barco et al showed a nonsignificant decrease in incidence rate of the first venous thrombosis in patients using anticoagulants with an adjusted hazard ratio of 0.72.[22] It is important to note that these authors reported a combined end point of all venous thrombotic events, which might explain their rather high incidence (0.31/1000 CVAD days vs our 0.25/1000 CVAD days) and reference literature data (0.08–0.20/1000 CVAD days).[6,23–25]

The available literature is seriously hampered by the absence of a uniform definition to coin CRVT, ranging from asymptomatic to symptomatic CRVTs with varying incidence rates that may or may not be based on imaging techniques. Future research would obviously benefit from a uniform definition. In the present study, we reported both asymptomatic and symptomatic CRVTs, which contribute to our higher incidence rate. Notably, up to 20% of CRVTs was asymptomatic in this study, and even sums up to two-third in the literature.[6,26] In contrast, the only recent prospective study in patients with CIF to establish asymptomatic and symptomatic CRVTs did not pick up any asymptomatic thromboses which, might suggest a power issue.[4] Nevertheless, these findings suggest an urgency for robust studies on the relevance of a screening policy to pick up (asymptomatic) CRVTs in patients with CIF at an earlier stage.

Although our cohort revealed three risks factors, that is, left-sided CVAD insertion, history of venous thrombosis, and a shorter period post-CVAD insertion, we did not pick up known risk factors as malignancy and hypercoagulable state, probably due to a lack of power.

We previously identified left-sided CVAD insertion as a strong risk factor for CRVT.[2] Although this association has not been described in populations with CIF yet, the finding is echoed in other conditions.[13,27,28] There is some discussion whether left-sided CVADs are at increased risk of malpositioning and hence thrombosis. We therefore only included CVADs with a life span >2 days. This, of course does not rule out a more difficult placement procedure that causes problems later on.

The second CRVT risk factor concerned a shorter period post-CVAD insertion, most probably reflecting per procedural vascular damage. Also, in patients with other CRVT risk factors, the CVAD most likely establishes as an additional threat that manifests early after CVAD insertion. Our data support findings by Barco et al, who reported a higher incidence rate of venous thromboses in the first year after CVAD placement.[22] Our median time to the onset of thrombosis (4.5 months) closely resembles previous data (3.8 months) of Brandt et al.[23] Overall, these findings indicate that we should be most concerned about CRVTs within the first year after insertion and routine screening at this early stage might be indicated.

Lastly, a history of venous thrombosis was associated with a higher risk for CRVT, which is in line with the literature.[3] This was supported by the fact that 25% of patients with a primary CRVT developed a second episode, of which 60% in those without anticoagulants and only 14% in the presence of anticoagulants (Figure 2). Although descriptive in nature, these data show that anticoagulants as secondary prophylaxis should be considered, in line with guidelines for patients with a malignancy using long-term CVADs.[10–13]

Permanent vascular damage, for instance in the form of VCSS, is the most devastating consequence of CRVTs. This may result in a necessity to use less favorable veins to create a venous access or ultimately results in a loss of venous access. In our cohort, we found a VCSS incidence slightly below previous literature data (0.05–0.12/1000 CVAD days).[22,29,30] To prevent such problems, optimal timing to start anticoagulants is crucial. In contrast, anticoagulants may have serious side-effects. The incidence of major bleedings in the anticoagulant group was 2.5-fold higher than in the nonanticoagulant group, yet without any fatal bleeding in either group. These rates are comparable to data from Barco et al.

Given the potential side-effects of anticoagulants, the dilemma remains which patients should be started on primary prophylaxis. The consideration to start primary prophylaxis is more delicate compared with secondary prophylaxis because of the relatively low incidence of primary CRVTs. To balance these risks and benefits, we should consider the possibly devastating consequences of even a single CRVT episode, including VCSS, against the side-effects of anticoagulants. In the absence of strong evidence at this point, the decision to start with primary prophylaxis at the individual level seems most prudent. Identification of formerly mentioned risk factors for CRVTs helps to stratify these patients. At this point the evidence to justify starting anticoagulants as primary prophylaxis, seems too thin in the absence of guidance by prospective clinical data and additional risk factor analyses.

The main strengths of this study are the multilevel analysis at CVAD level rather than only patient level and the comprehensive available information on CVAD characteristics and complications. Therefore, we were able to correct for multiple confounders. It has to be considered that most patients with CIF depend on their CVAD for the rest of their lives; during this long period many changes are made in prescribed medications, HPN treatment, and different types of CVAD may be used within one patient. Another strength is the substantial number of patients and CVAD days evaluated from a single-center, with less variability in patient/caregiver training and technical procedures.

The main limitation of this study is its retrospective design with the associated biases. Despite the detailed patient reports and data capturing in the database and the electronic health records since 2010, missing data always remains a concern. Also, we were unable to retrieve all data on anticoagulants (coumarin derivates) monitoring, which in the Netherlands is performed by an external service. Lastly, due to power issues, we were unable to perform subgroup analyses of the different anticoagulant groups.

In conclusion, our study showed that anticoagulants substantially decreased the risk for CRVTs in patients with CIF. In addition, several risk factors for CRVTs were found, including left-sided CVAD insertion, history of venous thrombosis and a shorter period post-CVAD insertion. Our results support the use of secondary prophylaxis; however, we consider the evidence too weak at this point to justify starting anticoagulants as primary prophylaxis, even in patients with the previously mentioned risk factors. Based on these notions, a prospective, adequately powered exploration of the efficacy of anticoagulants in a well-defined population of (high-risk) patients with CIF for primary CRVT prophylaxis seems indicated.

CONFLICT OF INTEREST

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study. Veerle E.L.M. Gillis and Thijs van Houdt conducted the research, provided essential material, performed statistical analysis, and drafted the manuscript. All authors critically revised the manuscript for important intellectual content, agree to be fully accountable for ensuring the integrity and accuracy of the work, and gave final approval.

DATA AVAILABILITY STATEMENT

Data described in the manuscript, code book, and analytic code will be made available upon request pending approval.

CONFERENCE PRESENTATION

Oral presentation ESPEN (2021) and Dutch Digestive Disease Days (2021).

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REFERENCES

1. Pironi L, Arends J, Bozzetti F, et al. ESPEN guidelines on chronic intestinal failure in adults. *Clin Nutr*. 2016;35(2):247-307.
2. Wouters Y, Roosenboom B, Causevic E, Kievit W, Groenewoud H, Wanten GJA. Clinical outcomes of home parenteral nutrition patients using taurolidine as catheter lock: a long-term cohort study. *Clin Nutr*. 2018;38(5):2210-2218.
3. Kucher N. Deep-vein thrombosis of the upper extremities. *N Engl J Med*. 2011;364(9):861-869.
4. Cuerda C, Joly F, Corcos O, et al. Prospective study of catheter-related central vein thrombosis in home parenteral nutrition patients with benign disease using serial venous Doppler ultrasound. *Clin Nutr*. 2016;35(1):153-157.
5. Brandt CF, Tribler S, Hvistendahl M, et al. Home parenteral nutrition in adult patients with chronic intestinal failure: catheter-related complications over 4 decades at the main Danish Tertiary Referral Center. *JPEN J Parenter Enteral Nutr*. 2018;42(1):95-103.
6. Allan P, Lal S. Intestinal failure: a review. *F1000Research*. 2018;7:85-85.
7. Franco L, Giustozzi M, Agnelli G, Becattini C. Anticoagulation in patients with isolated distal deep vein thrombosis: a meta-analysis. *J Thromb Haemost*. 2017;15(6):1142-1154.
8. Mai V, Bertoletti L, Cucherat M, et al. Extended anticoagulation for the secondary prevention of venous thromboembolic events: an updated network meta-analysis. *PLoS One*. 2019;14(4):e0214134.
9. Becattini C, Verso M, Munoz A, Agnelli G. Updated meta-analysis on prevention of venous thromboembolism in ambulatory cancer patients. *Haematologica*. 2020;105(3):838-848.
10. Farge D, Frere C, Connors JM, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2019;20(10):e566-e581.
11. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e419S-e496S.
12. Schiffer CA, Mangu PB, Wade JC, et al. Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2013;31(10):1357-1370.
13. Sousa B, Furlanetto J, Hutka M, et al. Central venous access in oncology: ESMO clinical practice guidelines†. *Ann Oncol*. 2015;26:v152-v168.
14. Koletzko B JK, Verwied-Jorky S, et al. *Guidelines on Parenteral Nutrition from the German Society for Nutritional Medicine*. DGEM; 2009.
15. Gillanders L, Angstmann K, Ball P, et al. AuSPEN clinical practice guideline for home parenteral nutrition patients in Australia and New Zealand. *Nutrition*. 2008;24(10):998-1012.
16. David August M, Teitelbaum D, Albina J, et al. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr*. 2002;26(1 Suppl):1sa-138sa.
17. Cuerda C, Pironi L, Arends J, et al. ESPEN practical guideline: clinical nutrition in chronic intestinal failure. *Clin Nutr*. 2021;40(9):5196-5220.
18. Wouters Y, Vissers RK, Groenewoud H, Kievit W, Wanten GJA. Repair of damaged central venous catheters is safe and doubles catheter survival: a home parenteral nutrition patient cohort study. *Clin Nutr*. 2019;38(4):1692-1699.
19. Centers for Disease Control and Prevention. *Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection)*. Centers for Disease Control and Prevention; 2022:6-7. Accessed September 18, 2021. https://www.cdc.gov/nhsn/pdfs/pscManual/4PSC_CLABScurrent.pdf.
20. Sergeant ESG. *Epitools Epidemiological Calculators*. Ausvet. Accessed September 18, 2021. http://epitools.ausvet.com.au.
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12(12):1495-1499.
22. Barco S, Heuschen CB, Salman B, et al. Home parenteral nutrition-associated thromboembolic and bleeding events: results of a cohort study of 236 individuals. *J Thromb Haemost*. 2016;14(7):1364-1373.

23. Brandt CF, Tribler S, Hvistendahl M, et al. Home parenteral nutrition in adult patients with chronic intestinal failure: catheter-related complications over 4 decades at the main Danish Tertiary Referral Center. *JPEN J Parenter Enteral Nutr*. 2018;42(1):95-103.

24. Cotogni P, Mussa B, Degiorgis C, De Francesco A, Pittiruti M. Comparative complication rates of 854 central venous access devices for home parenteral nutrition in cancer patients: a prospective study of over 169,000 catheter-days. *JPEN J Parenter Enteral Nutr*. 2020;45(4):768-776.

25. Lorentsen R, Munck LK, Wildt S. Parenteral therapy and complications in patients with intestinal failure in a regional unit. *Scand J Gastroenterol*. 2017;52(12):1326-1330.

26. Dibb M, Lal S. Home parenteral nutrition: vascular access and related complications. *Nutr Clin Pract*. 2017;32(6):769-776.

27. 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.

28. Rooden CJ, Tesselaar ME, Osanto S, Rosendaal FR, Huisman MV. Deep vein thrombosis associated with central venous catheters—a review. *J Thromb Haemost*. 2005;3(11):2409-2419.

29. Beers TR, Burnes J, Fleming CR. Superior vena caval obstruction in patients with gut failure receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1990;14(5):474-479.

30. Buchman AL, Misra S, Moukarzel A, Ament ME. Catheter thrombosis and superior/inferior vena cava syndrome are rare complications of long term parenteral nutrition. *Clin Nutr*. 1994;13(6):356-360.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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