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ORIGINAL ARTICLE

NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): evaluation of a national guideline on management of neonatal catheter-related venous thrombosis

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Abstract

Background: In critically ill (preterm) neonates, catheter-related venous thromboembolism (CVTE) can be a life-threatening complication. Evidence on optimal management in the literature is lacking. In the Netherlands, a consensus-based national management guideline was developed to create uniform CVTE management.

Objectives: To evaluate the efficacy and safety of the national guideline.

Methods: This prospective, multicenter, observational study included all infants aged ≤6 months with CVTE in the Netherlands between 2014 and 2019. CVTE was divided into thrombosis in veins and that in the right atrium, with their own treatment algorithms. The primary outcomes were recurrent venous thrombotic events (VTEs) and/or death due to CVTE as well as major bleeding.

Results: Overall, 115 neonates were included (62% male; 79% preterm). The estimated incidence of CVTE was 4.0 per 1000 neonatal intensive care unit admissions. Recurrent thrombosis occurred in 2 (1.7%) infants and death due to CVTE in 1 (0.9%) infant. Major bleeding developed in 9 (7.8%) infants: 2 of 7 (29%) on recombinant tissue plasminogen activator, which was given for high-risk right-atrium thrombosis, and 7 of 63 (11%) on low-molecular-weight heparin (LMWH). Five of the 7 bleedings because of LMWH were complications of subcutaneous catheter use for LMWH administration.

Conclusion: The management of neonatal CVTE according to the Dutch CVTE management guideline led to a low incidence of recurrent VTEs and death due to VTEs. Major bleeding occurred in 7.8% of the infants. Specific guideline adjustments may improve efficacy and, especially, safety of CVTE management in neonates.

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anticoagulation, catheter, neonate, thrombolysis, venous thromboembolism

1 | INTRODUCTION

Among children, neonates have the highest risk of thrombosis [1,2]. The reported incidences of neonatal venous or arterial thrombosis vary, ranging from 2.4 per 1000 neonatal intensive care unit (NICU) admissions in the Canadian registry in the 1990s to 38 per 1000 NICU admissions in more recent registries [3–7]. More than 90% of neonatal venous thrombotic events (VTEs) are associated with central venous catheters [8]. Other thrombotic risk factors for VTEs include sepsis, asphyxia, and congenital heart disease [9]. Data regarding mortality and morbidity of neonatal VTEs are scarce as a result of short follow-up in most studies. Mortality has been reported to vary between 2.4% and 3.7% [10,11]. A systematic review showed recurrent VTEs to occur in ~3% of infants aged <3 months [12]. Mild postthrombotic syndrome, per the modified Villalta Scale, with increased extremity circumference and the formation of collateral veins, developed in 16% of neonates in a retrospective study of children with upper-extremity VTEs that were mostly catheter related [13].

The treatment of neonatal thrombosis is intended to prevent mortality, reduce the risk of extension or embolization, and decrease the risk of recurrent thrombosis and postthrombotic syndrome. Evidence on optimal management of neonates with catheter-related venous thromboembolism (CVTE) in the literature is lacking. Only case series and case reports are available. The American College of Chest Physicians evidence-based guideline of 2012 recommended either the treatment of neonatal CVTE with anticoagulants or monitoring using ultrasonography [14]. If monitoring showed extension of thrombosis, anticoagulation was to be started. Thrombolytic therapy was reserved for major vein occlusion causing critical compromise of organs or the limbs. In the Netherlands, the NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT) working group refined the American College of Chest Physicians 2012 recommendations into a more detailed guideline based on the scarce literature and expert opinion to standardize the treatment of neonatal CVTE nationally. A distinction was made between CVTE in blood veins and CVTE in the right atrium. This national guideline was prospectively evaluated between 2014 and 2019 in the NEOCLOT study, a multicenter, observational cohort study conducted in all 10 NICUs in the Netherlands. In this study, the efficacy and safety of the management of CVTE in infants, as advised in the national guideline, were assessed. In addition, the risk factors for neonatal CVTE, adherence to the

Essentials

- Optimal management of neonatal catheter-related venous thromboembolism (CVTE) is unknown.
- A prospective observational study evaluated a consensus-based national guideline in 115 infants.
- Recurrence occurred in 1.7%, death due to CVTE in 0.9%, and major bleeding in 7.8% of the 115 infants.
- Guideline adjustments may further improve efficacy and safety of CVTE management in neonates.

guideline, and residual thrombosis on the last radiologic imaging scan were determined.

2 | METHODS

2.1 | Study design

The NEOCLOT study was a national, multicenter, prospective, observational cohort study of all infants aged <6 months with CVTE treated in 1 of the 10 NICUs in the Netherlands according to the national management guideline. The NEOCLOT study's rationale and protocol have been published previously [15]. The Medical Ethics Review Committee confirmed that official approval of this study was not required because the Medical Research Involving Human Subjects Act did not apply to the NEOCLOT study (#14.17.0121). Oral or written informed consent was asked from parents for participation in this study. Regular NEOCLOT study meetings were conducted to diminish inclusion biases. They helped to remind investigators to include all patients with CVTE and, thus, minimized the number of missing patients.

2.2 | Patients and definitions of thrombosis

All preterm and term infants (0-6 months) with CVTE during admission in 1 of the 10 NICUs in the Netherlands between January 1, 2014, and December 31, 2019, were eligible for participation in this study. CVTE could be symptomatic or asymptomatic but had to be confirmed using radiologic imaging. VTE was diagnosed using ultrasonography and/or echocardiography when ≥1 of the following signs were present: a noncompressible segment of a vein, absence of flow, or an echogenic intraluminal thrombus. In the national management guideline, VTE was divided into thrombosis in a vein (obstructive vs nonobstructive) and thrombosis in the right atrium. Thrombosis in veins was defined as a nonobstructive clot if blood flow was still present and as an obstructive clot if blood flow was absent. High-risk thrombosis in veins was defined as thrombosis, which compromised an organ or a limb. Thrombosis in the right atrium was defined as high-risk thrombosis, based on the following criteria: (1) it restricted the outflow from the right atrium via the tricuspid valve; (2) it extended via the tricuspid valve or patent foramen ovale; (3) it caused severe arrhythmias; (4) it caused hemodynamic instability; (5) it was pedunculated, mobile, or snake shaped and mobile; and (6) it increased despite adequate levels of therapeutic heparin. Patients were followed up until cessation of antithrombotic therapy and/or after evaluation of residual thrombosis using ultrasonography or echocardiography.

2.3 | Management protocol

After the diagnosis of CVTE, it was advised to remove the catheter, if possible. Furthermore, in each infant with CVTE, the risks and benefits of all treatment options vs the risks of ongoing thrombosis had to be considered before treatment was started. The relative contraindications for anticoagulation and thrombolysis included invasive surgical procedure(s) and/or intracranial bleeding in the preceding 10 days, invasive surgical procedure(s) scheduled within 3 days, active bleeding, severe asphyxia, very preterm neonates (gestational age at birth < 28 weeks) with a high risk of intraventricular hemorrhage, and severe thrombocytopenia.

Figure 1 shows the management algorithms for CVTE in veins and the right atrium, as suggested in the national guideline. In both the scenarios, thrombolytic therapy had to be considered for high-risk thrombosis, followed by anticoagulant therapy. A wait-and-see policy was advised for nonobstructive vein thrombosis and right-atrium thrombosis obstructing less than half of the atrium, with follow-up Doppler ultrasonography or echocardiography within 5 days, depending on the size of the thrombosis. Anticoagulant therapy was indicated if thrombosis had enlarged during the wait-and-see policy. In obstructive vein thrombosis and right-atrium thrombosis filling (more than) half of the atrium, the guideline advised starting anticoagulant therapy immediately. For thrombolysis, recombinant tissue plasminogen activator (r-tPA) was preferred over urokinase or streptokinase because of assumed increased affinity of r-tPA for fibrin-bound plasminogen. For anticoagulant therapy, the use of low-molecular-weight heparin (LMWH) was preferred over unfractionated heparin (UFH) because of the reduced need for monitoring, potential decreased risk of bleeding, and greater customizability in the Netherlands. The used dosing protocols of r-tPA and LMWH in the guideline have been published previously [15]. The target level of antifactor (F) Xa for LMWH was between 0.5 and 1.0 IU/mL 4 hours after the given LMWH dose.

2.4 | Data collection

The following variables were collected in the web-based NEOCLOT database: demographic variables, including gestational age, birth weight, and sex; characteristics of thrombosis, including date of diagnosis, location, diagnostic method used, symptoms, occlusive or nonocclusive, and high risk or low risk; potential risk factors for thrombosis, including type of catheter, size of catheter, insertion location of catheter, catheter days before diagnosis, catheter-related infection according to the National Healthcare Safety Network criteria [16], suspected catheter-related infection, polycythemia (venous hematocrit above 0.65 L/L), presence of disseminated intravascular coagulation [17], shock (hypotension, needing therapy), congenital heart disease, recent surgery (within 7 days of the diagnosis of thrombosis), and maternal diabetes; treatment of thrombosis, including applied policy, catheter removal, duration and dosages of thrombolytic and anticoagulant therapies, effect of applied policy, and complications of therapy (bleeding complications); and follow-up, including death due to thrombosis or other reason, pulmonary embolism (PE), stroke, recurrent thrombosis, residual thrombosis after end of therapy using ultrasonography or echocardiography.

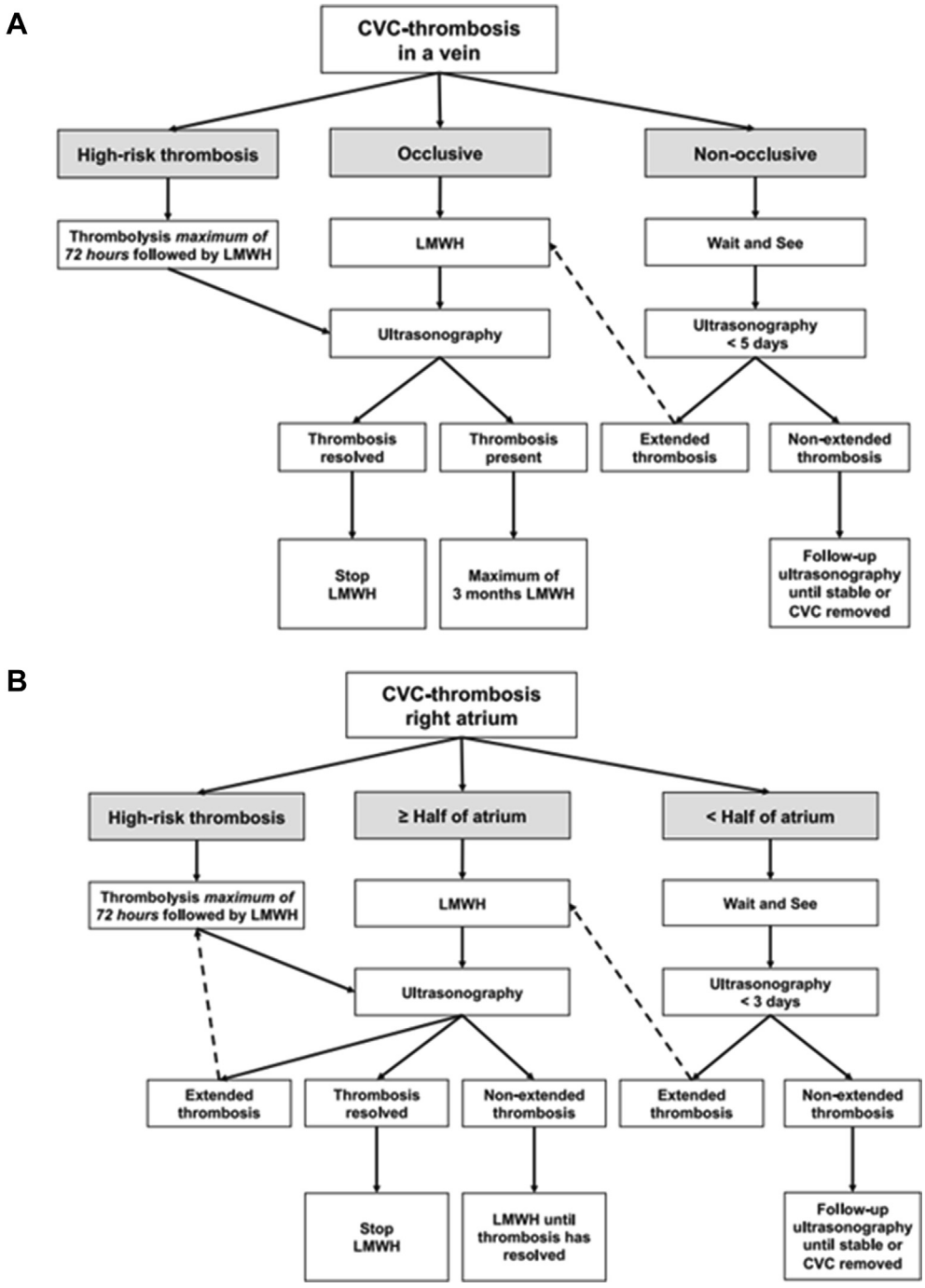

FIGURE 1 Management of catheter-related venous thrombosis in neonates in (A) a vein and (B) the right atrium. CVC, central venous catheter; LMWH, low-molecular-weight heparin.

2.5 | Endpoints

The primary efficacy outcome in the NEOCLOT study was a composite outcome consisting of recurrent VTEs during antithrombotic therapy and death due to CVTE. The primary safety outcome was the incidence of major bleeding complications during thrombolytic and/or anticoagulant therapy.

The secondary efficacy outcomes were individual components of the primary outcome, ie, recurrent VTEs during antithrombotic therapy or death due to CVTE and all-cause mortality. The secondary safety outcomes were clinically relevant nonmajor bleeding (CRNMB) and minor bleeding during thrombolytic and anticoagulant therapies. The outcomes of the secondary aims consisted of frequency of risk factors for CVTE, frequency of protocol variations, and residual thrombosis on the last radiologic imaging scans.

Major bleeding was defined as reported by Mitchell et al. [18]: (1) fatal bleeding, (2) clinically overt bleeding associated with a decrease in hemoglobin level of at least 20 g/L (ie, 2 g/dL or 1.24 mmol/L) in a

24-hour period, (3) bleeding that is retroperitoneal or pulmonary, or (4) bleeding that requires surgical intervention in an operating room. Intracranial bleeding was categorized as major bleeding as defined by Curley et al. [19] in the Planet-2 study: intraventricular hemorrhage (IVH) (H1, H2, or H3) with ventricular dilatation, IVH (H1, H2, and H3) with parenchymal extension, any evolution of intracranial hemorrhage from IVH or germinal layer hemorrhage to IVH with ventricular dilatation or IVH with parenchymal extension. All intracranial bleedings that were not defined as major bleeding were categorized as nonmajor intracranial bleeding. CRNMB was a composite of overt bleeding for which a blood product was administered and not directly attributable to the patient's underlying medical condition and bleeding that required medical or surgical intervention for restoration of hemostasis, other than in an operating room. Minor bleeding was defined as any overt or macroscopic evidence of bleeding that did not fulfill the above criteria for either major bleeding or CRNMB. The diagnosis of recurrent VTE was made after radiologic confirmation of new VTE during antithrombotic therapy.

2.6 | Statistical analysis

The sample size was determined based on the number of infants during the study period. Data were analyzed using descriptive statistics. Analyses were restricted to infants with complete data on variables needed for the specific analyses. The incidence of CVTE was expressed as incidence per 1000 NICU admissions. Continuous variables were reported as median with an IQR of 25% to 75% and compared using the Mann–Whitney U-test for independent groups. Categorical variables were reported as n (%) and compared using the chi-square or Fisher exact test, as applicable. Statistical significance was assumed at the 5% level. The statistical analyses were performed using the SPSS software, version 22, for Windows.

3 | RESULTS

3.1 | Patient characteristics

Between 2014 and 2019, 115 of 29 074 (0.4%) infants admitted to the 10 NICUs in the Netherlands developed CVTE, of whom 71 (62%) were male infants and 44 (38%) were female infants. Figure 2 shows the incidence per year. At diagnosis, the median gestational age was 29 weeks (IQR, 26-36) and the median birth weight was 1100 g (IQR, 795-2325). Ninety-one (79%) infants were born before maturity. In most infants (79%), the diagnosis of CVTE was made within the first 30 postnatal days, with a median age of 14 days (IQR, 9-25).

Most thrombi were related to umbilical vein catheters (59 infants, 51%). Other catheters were those inserted via superficial veins of the limbs (40, 35%), via deep veins of the supraclavicular or infraclavicular area (9, 8%), via the femoral vein (6, 5%), and via the jugular vein (tunneled central venous catheter) (1%). The size of the catheters was known in 102 infants and varied between 1 and 5 gauge. Half of the

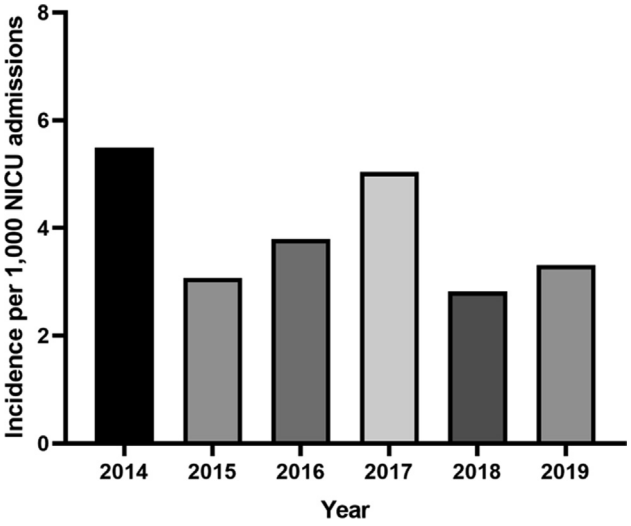

FIGURE 2 Yearly incidence of catheter-related venous thromboembolism per 1000 neonatal intensive care unit admissions. NICU, neonatal intensive care unit.

infants (n = 57, 50%) had double-lumen catheters (single lumen: n = 48, 42%; not reported: n = 10, 9%). The position of the catheter was checked using X-ray (n = 101), ultrasonography (n = 6), or both (n = 4). The most frequent locations of the tip of umbilical vein catheters included the cavoatrial junction (n = 25, 42%), diaphragm (n = 15, 25%), and right atrium (n = 9, 15%). The tip of the other catheters was most often located in the inferior caval vein (n = 16, 29%), cavoatrial junction (8, 14%), brachiocephalic vein (n = 6, 11%), and iliac vein (n = 6, 11%). The median dwell time at VTE diagnosis was 8 days (IQR, 5-11).

3.2 | Thrombosis characteristics

Thrombosis was located in the right atrium in 44 (38%) infants and in ≥1 veins in 71 (62%) infants. The involved sites were the caval, renal, or portal vein (30 infants, 26%); lower extremities (21, 18%); upper extremities (18, 16%); and the jugular vein (2, 2%). The size of right-atrium thrombosis was less than half of the atrium in 35 out of 44 infants. Right-atrium thrombosis was considered a high risk in 9 infants because thrombosis extended via the tricuspid valve and/or patent foramen ovale (n = 7), caused restriction of the outflow from the right atrium via the tricuspid valve (n = 3), was pedunculated and mobile (n = 3), and caused arrhythmia (n = 1) or hemodynamic instability (n = 1). In 5 out of the 9 infants with high-risk thrombosis, thrombosis filled >50% of the right atrium. Occlusive and non-occlusive vein thrombosis occurred in 39 (55%) and 32 (45%) infants, respectively. VTEs were asymptomatic in 18 of the 44 (41%) infants with right-atrium thrombosis and in 10 of 71 (14%) infants with vein thrombosis. The reported signs and symptoms of thrombosis included unexplained thrombocytopenia (n = 50, 43%), ongoing sepsis (n = 30, 26%), swollen limb (n = 28, 24%), occlusion of catheter (n = 6, 5%), collaterals in the skin (n = 3, 3%), chylothorax (n = 1, 1%), and increased creatinine level (n = 1, 1%). Diagnosis was made using

TABLE 1 Management and residual thrombosis of 115 infants with catheter-related right atrium and vein thrombosis.

Location thrombosis	Number	Management	Recanalization at last follow-up imaging	Follow-up time(d) (mean)
Right atrium				
High risk	*n* = 2	r-tPA, LMWH	Normalized *n* = 1, improved *n* = 1	23
n = 9	*n* = *5*	*LMWH*	Normalized *n* = 2, improved = 3	46
	n = *2*	*LMWH/UFH, r-tPA, LMWH/UFH*	Normalized *n* = 2	80
<50% atrium	*n* = 23	WS	Normalized *n* = 11, improved *n* = 10, nf *n* = 2	57
n = 35	*n* = 4	WS, LMWH	Normalized *n* = 2, improved *n* = 1, nf *n* = 1	67
	n = 1	WS, LMWH, r-tPA, LMWH	Normalized	14
	n = *5*	*LMWH*	Normalized *n* = 1, improved *n* = 4	66
	n = *1*	*LMWH, r-tPA, LMWH*	Normalized	79
	n = *1*	*LMWH, UFH*	Improved	5
Vein				
Obstructive	*n* = 24	LMWH	Normalized *n* = 13, improved *n* = 9, unchanged *n* = 2	67
n = 39	*n* = 1	LMWH, UFH	Normalized	60
	n = 1	LMWH, r-tPA, LMWH	Unchanged	145
	n = 1	UFH	Normalized	8
	n = *5*	*WS, LMWH*	Normalized *n* = 2, improved *n* = 1, no change *n* = 2	48
	n = *7*	*WS*	Normalized *n* = 3, improved *n* = 1, no change *n* = 1, nf *n* = 2	154
Nonobstructive	*n* = 20	WS	Normalized *n* = 9, improved *n* = 6, no change *n* = 1, nf *n* = 4	25
n = 32	*n* = 6	WS, LMWH	Normalized *n* = 2, improved *n* = 3, nf *n* = 1	34
	n = 1	WS, UFH	Normalized *n* = 1	36
	n = *5*	*LMWH*	Normalized *n* = 1, improved *n* = 3, no change *n* = 1	54

Deviations of the protocol are in italics.

LMWH, low-molecular-weight heparin; nf, no follow-up imaging after last type of therapy; r-tPA, recombinant tissue plasminogen activator; UFH, unfractionated heparin, WS, wait-and-see.

Doppler ultrasonography in 72 (63%) infants, echocardiography in 35 (30%) infants, and both the imaging tools in 8 (7%) infants. The most frequent additional risk factors for CVTE were catheter sepsis, with bacteriologic confirmation, in 50 (43%) infants; suspected catheter sepsis in 18 (16%) infants, shock in 13 (11%) infants, recent surgery in 14 (12%) infants, congenital heart disease in 11 (10%) infants, and maternal diabetes in 7 (6%) infants.

3.3 | Management of thrombosis

The catheter was removed without anticoagulation in 102 of the 115 infants shortly before or after the diagnosis of VTE. In 13 of the 115 (11%) infants, anticoagulation was started before catheter removal for a median period of 4 days (IQR, 3-6). No symptomatic PE occurred after catheter removal with and without prior anticoagulation.

Table 1 shows the antithrombotic management and residual thrombosis during follow-up of the infants with CVTE. Most infants (*n* = 84, 73%) were treated as suggested by the guideline; in 31 (27%) infants, deviation from the treatment guideline occurred (italics in Table 1) for various reasons, as described below. Nineteen (16%) infants received more conservative treatment and 12 (10%) infants received more intensive treatment than that advised by the guideline.

Nine of the 44 (20%) infants with right-atrium thrombosis had high-risk thrombosis. The national guideline advised to treat high-risk right-atrium thrombosis with thrombolysis. Two infants were treated with thrombolysis, followed by LMWH. Anticoagulation (LMWH, *n* = 6; UFH, *n* = 1) instead of thrombolysis was started in 7 infants because of increased risk of bleeding as judged by the treating physicians. In 5 of them, thrombosis decreased with LMWH and lost its high-risk features. In 2 infants, heparin was changed to r-tPA because of extension of thrombosis, as detected using echocardiography, after 4 and 8 days. In these infants, thrombolysis was followed by LMWH (*n* = 1) and UFH (*n* = 1). The starting and maximum dosages of r-tPA varied between 0.1 and 0.3 and between 0.3 and 0.5 mg/kg/h, respectively. The duration of thrombolysis varied between 6 and 24 hours.

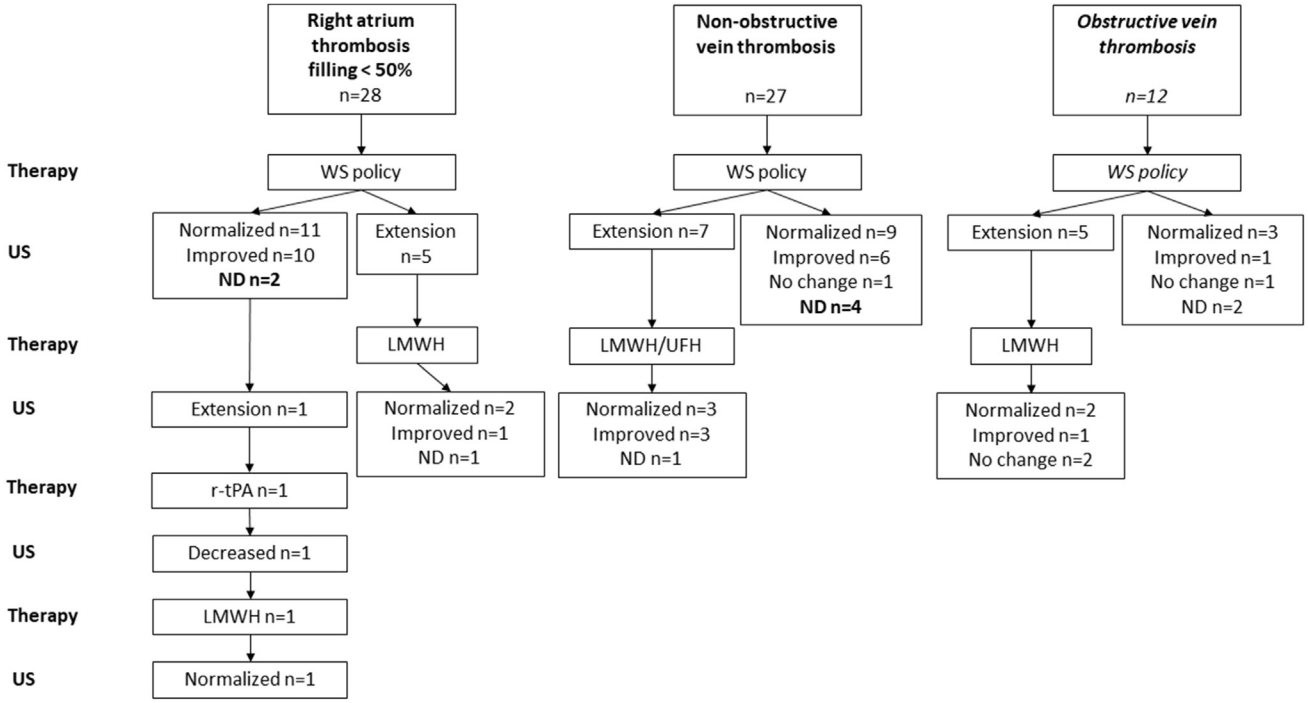

FIGURE 3 Management and residual thrombosis of infants managed with the wait-and-see policy. Deviations of the protocol are in italics. ND, not done; LMWH, low-molecular-weight heparin; r-tPA, recombinant tissue plasminogen activator; UFH, unfractionated heparin; US, ultrasonography or echocardiography; WS, wait-and-see.

In 35 of the 44 (80%) infants with right-atrium thrombosis, thrombosis filled <50% of the right atrium and had no high-risk features. The wait-and-see policy, as advised by the guideline, was initially applied to 28 infants. Twelve of them had signs or symptoms, including unexplained thrombocytopenia (n = 8), ongoing sepsis (n = 4), and catheter occlusion (n = 1). Two infants did not undergo radiologic follow-up. Ultrasonography showed an increase in thrombosis in 5 of 28 infants (including 4 with symptoms) after a median duration of 4 days (IQR, 3-6 days), and LMWH was started. In 1 infant, extension of thrombosis was observed using echocardiography after 7 days of LMWH, and thrombolysis was administered, followed by LMWH. In 7 infants with thrombosis filling <50% of the right atrium, LMWH was started directly after diagnosis instead of the wait-and-see policy, mostly because of suspicion of infected thrombosis. In 1 infant, this was changed to UFH because of rapid clinical deterioration. This infant died because of an underlying disease. After 8 days of LMWH, 1 other infant had extension of thrombosis, as detected using echocardiography, and received thrombolysis, followed by LMWH.

Of the 39 infants with obstructive vein thrombosis, 27 (69%) infants were started on anticoagulation (LMWH, n = 26; UFH, n = 1), as advised by the guideline. One infant had extension of thrombosis, as detected using ultrasonography, 2 days after the start of LMWH; thrombolysis was started for 1 day, followed by LMWH for a total of 3 months. In 1 infant, this was switched to UFH because of a very poor clinical condition and increased risk of bleeding. In 12 infants, the wait-and-see policy was applied because of a severe risk of bleeding (n = 2), an expected poor outcome (n = 1), and unknown reasons (n = 9). Two children did not undergo radiologic follow-up while the wait-and-see policy was being applied. In 5 of the 12 infants managed with the wait-and-see policy, ultrasonography showed extension of thrombosis after a median duration of 4 days (IQR, 2-3 days), and LMWH was started.

Most infants with nonobstructive vein thrombosis (n = 27, 84%) were managed with the wait-and-see policy, as suggested by the guideline; 20 of them had signs and symptoms: persistent thrombocytopenia (n = 13), ongoing sepsis (n = 9), swollen limb (n = 3), occluded catheter (n = 2), and collaterals in the skin (n = 1). Four infants did not undergo radiologic follow-up. In 7 (all symptomatic) of the 27 infants, the wait-and-see policy was switched to anticoagulation (LMWH, n = 6; UFH, n = 1) after a median duration of 3 days because of extension of thrombosis, as detected using ultrasonography (n = 6), or suspicion of infected thrombosis (n = 1) with *Staphylococcus aureus*. In 5 of 32 (16%) infants with nonobstructive vein thrombosis, LMWH was started directly instead of the wait-and-see policy: 1 infant had symptoms of swollen painful leg, 1 infant had persistent unexplained thrombocytopenia, and 2 children were suspected of having infected thrombosis. In 1 infant with nonoccluding thrombosis in the inferior caval vein, the reason for deviation from the guideline was unknown. LMWH was stopped after 2 weeks because of major bleeding.

The wait-and-see policy, as advised by the national guideline, was applied to 55 infants: 28 of 35 (80%) infants with thrombosis filling <50% of the right atrium and 27 of 32 (84%) infants with nonobstructive vein thrombosis (Figure 3). Signs and symptoms of

TABLE 2 Outcome of 115 infants with catheter-related venous thrombosis.

Outcome	Right atrium thrombosis *n* = 44	Vein thrombosis *n* = 71	All VTE *n* = 115
Efficacy			
Composite: recurrent VTE and death due to CVTE	*n* = 1 (2.3%)	*n* = 2 (2.8%)	*n* = 3 (2.6%)
Recurrent thrombosis	*n* = 0	*n* = 2 (2.8%)	*n* = 2 (1.7%)
Death due to thrombosis	*n* = 1 (2.3%)	*n* = 0	*n* = 1 (0.9%)
All-cause mortality	*n* = 5 (11%)	*n* = 9 (12.7%)	*n* = 14 (12%)
Safety			
Major bleeding	*n* = 2 (4.5%)	*n* = 7 (9.9%)	*n* = 9 (7.8%)
CRNMB	*n* = 0	*n* = 1 (1.4%)	*n* = 1 (0.9%)
Minor bleeding	*n* = 0	*n* = 2 (2.8%)	*n* = 2 (1.7%)
Residual thrombosis			
Deteriorated	*n* = 0	*n* = 0	*n* = 0
Normalized	*n* = 21 (48%)	*n* = 33 (47%)	*n* = 54 (47%)
Improved	*n* = 20 (45%)	*n* = 23 (32%)	*n* = 43 (37%)
Unchanged	*n* = 0	*n* = 8 (11%)	*n* = 8 (7%)
Unknown	*n* = 3 (7%)	*n* = 7 (10%)	*n* = 10 (9%)

CRNMB, clinically relevant nonmajor bleeding; CVTE, catheter-related venous thromboembolism; VTE, venous thrombotic event.

thrombosis were present in 32 of the 55 patients managed with the wait-and-see policy. Six of the 55 infants did not undergo radiologic follow-up while the wait-and-see policy was being applied (bold in Figure 3). In 5 out of 26 (19%) and 7 out of 23 (30%) infants from the right-atrium and vein thrombosis groups, respectively, extension of thrombosis was observed using follow-up ultrasonography, after which anticoagulation was started. Children with signs and symptoms did have a higher risk for extension of thrombosis on follow-up ultrasonography scans (p = .42). Four of 61 (6.6%) children with LMWH and who underwent radiologic imaging showed extension on follow-up ultrasonography scans after 2 to 8 days and received thrombolysis. Two of them had anti-FXa values below the therapeutic range.

3.4 | Outcome

Table 2 shows the primary outcomes. All patients who received antithrombotic therapy were followed up until the end of treatment. One (0.9%) infant died because of a thrombotic event. The infant died because of pulmonary hypertension after embolization of right-atrium thrombosis to the left pulmonary artery during thrombolysis. Thirteen infants died because of other reasons; so, the all-cause mortality was 12%. Recurrent thrombosis during antithrombotic therapy occurred in 2 (1.7%) infants. One child developed a new catheter-related occluding thrombosis in the brachiocephalic vein on day 18 after the start of LMWH for the first thrombotic event in the right iliac vein. The anti-FXa level was 0.13 IU/mL at the time of diagnosis. The second patient was diagnosed with an asymptomatic nonoccluding thrombosis in the inferior caval vein during cardiac catheterization on day 14 of LMWH (anti-FXa level of 0.45 IU/mL) because of thrombosis in the brachiocephalic vein.

Major bleeding complications occurred in 9 (7.8%) infants. Two out of 7 (29%) infants treated with r-tPA developed intracranial and lung bleeding, respectively. Ten of 63 infants treated with LMWH had bleeding complications: major in 7 (11%) infants, CRNM bleeding in 1 (1.6%) infant, and minor bleedings in 2 (3.2%) infants. No bleeding complications occurred during the use of UFH (Table 3). Five of the 7 major LMWH bleeding complications were related to the use of subcutaneous catheters (Insuflon). Subcutaneous catheters were used in 43 of the 63 infants treated with LMWH. Seven of these 43 (16%) infants developed minor, CRNM, or major bleeding complications as a result of the use of subcutaneous catheters.

Follow-up ultrasonography or echocardiography was performed in 105 infants after a median follow-up duration of 46 days (IQR, 17.5-80) and a range of 1 to 240 days. In the entire group, complete and partial clot resolution of the index catheter-related thrombosis occurred in 54 (51.4%) and 43 (41%) infants, respectively. No relevant change in thrombotic burden was observed in 8 (7.6%) infants. After the wait-and-see policy alone, complete and partial clot resolution was achieved in 23 (54.8%) and 17 (40.5%) of 42 infants who underwent follow-up imaging, respectively. In 2 infants, no relevant change in thrombotic burden was observed. In addition, no difference in residual thrombosis was found between the infants managed with the wait-and-see policy (n = 42) and those receiving antithrombotic therapy (n = 63).

TABLE 3 Bleeding complications in 115 infants treated for catheter-related venous thrombosis.

Neonate	Drug	Age (d)	Bleeding type	Characteristics bleeding	Location	Last anti-Xa if applicable (U/mL)	Treatment
1	r-tPA	14	Major	Hb from 15.2 to 11.1 g/dL	ICH	–	Stop LMWH (r-tPA was already stopped 1 d earlier)
2	r-tPA	16	Major	Hb from 12.7 to 10.0 g/dL	Lung	–	Stop r-tPA, plasma, RBC, and platelet transfusions, fibrinogen concentrate, tranexamic acid
3	LMWH	52	Major	Hb from 10.0 to 6.3 g/dL	Leg (catheter)	0.62	Stop LMWH, RBC transfusion
4	LMWH	85	Major	Surgical intervention in operating room	Leg (catheter)	0.7	Stop LMWH, plasma, and RBC transfusion, protamin, surgery
5	LMWH	57	Major	Hb from 10.3 to 6.0 g/dL	Leg (catheter)	0.51	Stop LMWH, RBC transfusion, protamin
6	LMWH	66	Major	Hb from 12.65 to 9.0 g/dL	Leg (catheter)	0.72	Stop LMWH
7	LMWH	58	Major	Hb from 11.8 to 8.2 g/dL	Leg (catheter), rectum, bladder	0.5	Stop LMWH, RBC and platelet transfusion
8	LMWH	13	Major	Hb from 13.1 to 9.0 g/dL	Rectum	0.3	Stop LMWH, RBC transfusion
9	LMWH	49	Major	Hb from 11.9 to 8.9 g/dL	Intra-abdominal	NR	Stop LMWH, platelet (2×), plasma (2×) and RBC (2×) transfusions
10	LMWH	51	CRNM	Hb from 11.0 to 9.4 g/dL	Rectum	0.39	Stop LMWH, RBC transfusion
11	LMWH	100	Minor	Small hematoma	Leg (catheter)	1.1	LMWH dose decreased
12	LMWH	71	Minor	Small hematoma	Leg (catheter)	0.83	No specific treatment

CRNM, clinically relevant nonmajor; Hb, hemoglobin; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin; NR, not reported; RBC, red blood cell; r-tPA, recombinant tissue plasminogen activator.

4 | DISCUSSION

Neonatal thrombosis is a rare disease, and its management is hampered by lack of high-quality studies on the efficacy and safety of several therapeutic interventions. This is the first prospective multicenter study that evaluated a national guideline on the management of neonatal CVTE and did not include non-CVTE. Using this guideline, recurrent thrombosis and death due to thrombosis occurred in 1.7% and 0.9% of the infants, respectively. Major bleeding complications developed in 7.8% of the included patients.

In the NEOCLOT study, the rate of neonatal CVTE was 4.0 per 1000 NICU admissions, which is consistent with both old and recent reports [5,6,11,20]. The incidence of CVTE remained stable over the 6 study years. Nevertheless, this might be an underestimation because some centers may have not included all patients with CVTE in the registry. Unfortunately, we did not register the number of refusals of parents to participate. A retrospective study in a single Canadian NICU reported an incidence of neonatal arterial or venous thrombosis of 38 per 1000 NICU admissions [4,5,11,21]. Remarkably, 117 of 186 (63%) thrombi were located in the portal vein, whereas portal vein thrombosis occurred in only 9 (8%) patients in the NEOCLOT study. It is unclear whether patients were screened for CVTE in the Canadian intensive care unit. Screening may have increased the incidence of venous thrombosis because clinically silent portal vein thrombosis is often found in infants with umbilical vein catheters [22]. In the Netherlands, none of the NICUs screen for CVTE.

After the diagnosis of CVTE, the international guidelines advise removal of the catheter after 3 to 5 days of anticoagulant therapy [23]. In our cohort, the catheter was removed in 102 of the 115 infants shortly before or after the diagnosis of VTE without anticoagulation. No symptomatic PE occurred after catheter removal, confirming the findings of Jaffray et al. [24]. Catheter removal is not associated with symptomatic PE, irrespective of anticoagulation before catheter removal.

The natural history of catheter-related venous thrombosis in infants is unknown. Spontaneous resolution may occur, especially in small thrombi, and more in nonocclusive than in occlusive CVTE [25–27]. Therefore, the national guideline advises to execute the wait-and-see policy for nonobstructive vein thrombosis and small right-atrium thrombosis instead of prompt administration of LMWH, independent of the presence of signs or symptoms of thrombosis. This policy seems justified because thrombosis did not extend in 37 of 47 (76%) infants who underwent follow-up ultrasonography and were managed with the wait-and-see policy alone. In addition, no acute complications, including embolism, occurred. Thrombosis even disappeared totally or partially in 36 (97%) of 37 infants without treatment. However, follow-up for infants with nonobstructive vein thrombosis and small right-atrium thrombosis managed with the wait-and-see policy is needed because 12 of 49 (24%) infants showed extension of thrombosis on follow-up ultrasonography or echocardiography scans, especially in infants with signs and symptoms. Radiologic follow-up after the start of LMWH was also indicated because CVTE was enlarged in 6.6% of the infants treated with LMWH, as detected using ultrasonography, after 2 to 8 days. LMWH treatment might be a challenge in infants. In a study by Sol et al. [28], only 32 of 64 (premature) infants treated with nadroparin twice daily reached the therapeutic target range from 0.5 to 1.0 U/mL. The median time to reach the target range was 3.5 days (range, 1-21 days). For dalteparin, the median time was 3.0 days (IQR, 1-5 days) [29]. Delay in reaching the target range may be the cause of extension of CVTE. Higher starting dosages of LMWH are needed in infants.

In contrast to spontaneous resolution, some neonatal CVTE may enlarge quickly and become life or limb threatening. Yang et al. [30] tried to define high-risk features of neonatal right-atrium thrombosis on echocardiograms, which included large size, >2 cm in any dimension, pedunculated, mobile, or snake shaped, and mobile. Thrombolysis is advised in the national guideline for high-risk right-atrium thrombosis, whose definition was partly based on Yang et al. [30]. Nevertheless, 5 of 9 patients with high-risk thrombosis were successfully treated without thrombolysis. Bearing in mind the high risk of bleeding with thrombolytic therapy, starting with LMWH in high-risk right-atrium thrombosis instead of thrombolysis may be considered. High starting dosages of LMWH and prompt radiologic follow-up are extremely important to switch to thrombolysis in case of extension of thrombosis with LMWH.

The frequency of major bleeding complications in the NEOCLOT study was relatively high, especially in infants treated with LMWH. A pooled analysis of a recent literature review showed a bleeding rate for infants aged <3 months treated with LMWH to be 4.1%. In the included studies, the bleeding rates varied from 0% to 30% because of various definitions of bleeding, sample size, and study population [31]. In the NEOCLOT study, most bleeding complications were caused by the use of a subcutaneous catheter for the administration of LMWH. Without these complications the major bleeding rate would be 4.3%, resembling previous studies. While using subcutaneous catheters for the administration of LMWH, frequent inspection of the catheter injection site is important to prevent bleeding complications.

This study has limitations. The efficacy and safety of the proposed management of CVTE were not studied in a randomized controlled manner. Unfortunately, because of the rarity of neonatal CVTE and the low frequency of the endpoints, a randomized controlled trial is challenging to execute in this age group. The NEOCLOT study shows that a prospective observational cohort study might be a useful alternative, which can also be applied to investigate management strategies in other rare neonatal thrombotic events such as neonatal renal vein thrombosis or catheter-related arterial thrombosis. The International Pediatric Thrombosis Network enables international collaboration to execute these studies using the THROM-Ped registry, allowing greater and faster patient inclusion [32]. Another limitation is the lack of long-time follow-up. The wait-and-see policy seems justified for small right-atrium thrombosis and nonoccluding vein thrombosis; however, the long-term consequences, including postthrombotic symptoms, have not been studied yet. Nevertheless, complete or partial clot resolution occurred in >90% of the investigated infants, as detected using follow-up

ultrasonography, making the development of severe postthrombotic symptoms unlikely. Finally, follow-up ultrasonography or echocardiography was not performed in 8 patients managed with the wait-and-see policy, as advised by the guideline. Therefore, it is unknown whether the progression of thrombosis occurred without antithrombotic treatment in these patients.

In conclusion, this study showed that with the use of the Dutch national guideline on the management of neonatal CVTE, the incidence of recurrent thrombosis and death due to thrombosis was low. The incorporation of LMWH at high initial doses as potential first-choice treatment option for high-risk right-atrium thrombosis and frequent inspection or even avoidance of subcutaneous catheters for LMWH in the next management protocol might increase safety. In addition, strict follow-up using radiologic imaging is important in all patients.

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AUTHORS CONTRIBUTIONS

All authors contributed to the study concept and design, analysis and/or interpretation of data, and writing or critical revision of the manuscript. All authors approved the final version of the manuscript for publication.

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