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ORIGINAL RESEARCH

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Elevated FVIII levels in hereditary hemorrhagic telangiectasia: Implications for clinical management

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Abstract

Objectives: The objective of this study was twofold: to determine the prevalence of arterial and venous thromboembolic events in the Norwegian Hereditary Hemorrhagic Telangiectasia (HHT) population, and to explore potential factors linked to such events, with particular emphasis on FVIII.

Methods: Patients with an HHT diagnosis attending the Otorhinolaryngology Department at Oslo University Hospital—Rikshospitalet were included consecutively between April 2021 and November 2022. We recorded the participants' medical history with an emphasis on thromboembolic events. Measurements of blood constituents, including FVIII, FIX, vWF, hemoglobin, iron, ferritin, and CRP were performed.

Results: One hundred and thirty-four patients were included in the study. The total prevalence of thromboembolic events among the participants was 23.1%. FVIII levels were high (>150 IU/dL) in the majority of HHT patients ($n = 84$) (68.3%) and were significantly associated with thromboembolic events ($p < .001$), as was age. Of the patients with high FVIII levels, 28 (33%) had experienced a thromboembolic event. Furthermore, FVIII levels were measured consecutively in 51 patients and were found to fluctuate above or below 150 IU/dL in 25% of these cases.

Conclusion: Thromboembolic events are highly prevalent in the Norwegian HHT population and are significantly associated with FVIII levels. FVIII levels can fluctuate, and measurements should be repeated in HHT patients to assess the risk of thromboembolic events.

Level of Evidence: 4.

KEYWORDS
FVIII, hereditary hemorrhagic telangiectasia, HHT, Osler, thrombosis

1 | INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant inherited vascular dysplasia with an approximate prevalence of 1 in 6000 individuals.[1,2] It is characterized by mucocutaneous telangiectasias and arteriovenous malformations (AVMs) in internal organs. The telangiectasias in HHT increase in number and distribution with age, and characteristic locations are the face, fingers, and mucous

membranes of the oral cavity, nose, and gastrointestinal tract (GIT). AVMs most often occur in the pulmonary, cerebral, and hepatic circulations.[3]

Epistaxis is the most common and debilitating symptom for patients with HHT[4–6] and varies in frequency, intensity, and duration. Chronic blood loss from the GIT is also a prominent feature in HHT, as is iron deficiency anemia.[7] Most HHT cases are associated with genetic mutations in one of three genes—ENG, ACVRL1—and, more rarely, SMAD4.[8,9] The diagnosis of HHT is clinical and based on four criteria: (1) first-degree relative with a diagnosis of HHT, (2) mucocutaneous telangiectasias, (3) frequently recurring epistaxis, and (4) AVM(-s). Three or four positive criteria are conclusive, two positive criteria are suspected, and one or zero is unlikely.[4]

Although HHT causes chronic bleeding, it is not a coagulation disorder and does not protect against thromboembolism. On the contrary, patients with HHT may have an increased rate of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), compared to the general population.[10] Previous studies[10,11] have revealed that many patients with HHT have elevated coagulation factor VIII (FVIII) levels, especially if concurrent low iron levels are present. Elevated levels of FVIII are a significant predictor for first and recurrent VTE,[12,13] and the thromboembolic risk increases with higher levels of FVIII.[12–15] Causes of transient and sustained high levels of FVIII are shown in Table 1.[16–25]

The treatment for epistaxis in HHT is both surgical and non-surgical. Among the non-surgical options are: Tranexamic acid (TXA), Thalidomide, hormonal therapy such as anti-estrogens (e.g., Tamoxifen and Raloxifene), and Bevacizumab, a vascular endothelial growth factor inhibitor, all of which list thromboembolic risk as a possible side effect.[26–30]

The Second International Guidelines for Diagnosing and Managing HHT[31] recommends TXA (up to 1.5 g three times daily) as a second-line treatment for HHT-related epistaxis if topical moisturizing therapy is inadequate. The Guideline supplementary document cites absolute contraindications to this treatment[31] as recent VTE or arterial thrombosis, while atrial fibrillation, thrombophilia, or other pro-coagulant tendencies (e.g., elevated FVIII) are considered relative contraindications. In spite of elevated levels of FVIII being proposed as a relative contraindication to this treatment, no screening strategy for FVIII has been proposed.

TABLE 1 Causes of transient and sustained high levels of FVIII.

- High body mass index
- Higher levels of glucose, insulin, fibrinogen, and triglycerides
- Exercise
- Age
- Pregnancy
- Surgery
- Chronic inflammation
- Malignancy
- Liver disease
- Hyperthyroidism
- Intravascular hemolysis
- Renal disease
- Non-O blood group

The objective of this study was twofold: to determine the prevalence of arterial and venous thromboembolic events in the Norwegian HHT population, and to explore potential factors linked to such events, with particular emphasis on FVIII.

2 | METHODS AND STUDY PARTICIPANTS

Patients with an HHT diagnosis attending the Otorhinolaryngology Department at Oslo University Hospital—Rikshospitalet were included consecutively between April 1, 2021, and November 30, 2022. This Department forms part of the national HHT Center of Excellence in Norway, receiving referrals from the whole country. The inclusion criterion was a diagnosis of HHT according to the diagnostic criteria.[4] Genetic testing was performed. Patients suspected of having HHT (two positive criteria) in addition to a pathogenic gene variant were included.

The participant's medical history was recorded and included previous or active thromboembolic disease and smoking. Patients were asked explicitly about DVT and PE, myocardial infarction (MI), and thromboembolic stroke. Thromboembolic disorders other than these were recorded as "other." The participants' recollection of the time of disease was noted, and their medical record was reviewed for accuracy. Thus, the patient's electronic medical record confirmed all recorded thromboembolic events. Recent events that could be a risk factor for thrombosis or high FVIII were stressed.

The epistaxis grade was evaluated using the Epistaxis Severity Score (ESS)[32] and the Epistaxis Intensity, Frequency, and Need for Blood Transfusion Score (IFT).[33,34]

Blood tests were collected with each consultation or treatment and screened for coagulation factors VIII and IX, vWF antigen and activity, hemoglobin, ferritin, iron, and C-reactive protein (CRP). However, the measurements of FIX and vWF were not performed for all patients. Hospital laboratory blood testing and analysis were not set to a specific time during the day as patients travel from all parts of the country, and compliance would not have been feasible. Testing and analysis were therefore performed whenever possible but not more than 2 days after the consultation or treatment. Measurements of consecutive blood samples from the same participants were included in the study material if obtained within the study period. Screening for pro-coagulant factors other than those mentioned above was not performed.

The participant's medical prescription history was reviewed through the national prescription database, and prescriptions for TXA and iron supplements were noted if prescribed within the last 3 years.

2.1 | Laboratory methods

Samples were analyzed for ferritin and iron concentrations on the Cobas 8000 instrument platform (Roche Diagnostics, Basel, Switzerland). The ferritin assay was traceable to the 1st International Standard, with agreement with the 3rd International Standard, according to the assay manufacturer. The iron assay was traceable to the

reference material SRM 937. The hemoglobin assay was performed on the Sysmex XN-1000 hematology analyzer (Sysmex, Kobe, Japan). The factor IX activity was determined with a one-stage clotting assay, using SynthASil reagent and factor IX deficient plasma, performed on an ACL TOP instrument (IL/Werfen, Barcelona, Spain). The assay was calibrated using the Hemosil calibration plasma (IL/Werfen) traceable to the WHO 09/172 International Standard for factor IX in human plasma. The factor VIII activity was measured using the chromogenic Coatest SP FVIII (IL/Werfen) and the one-stage clotting assay, using SynthASil reagent and factor VIII deficient plasma, both on the ACL TOP instrument (IL/Werfen). There were no significant biases between the one-stage and the chromogenic FVIII assays. Von Willebrand factor (VWF) antigen and activity were measured using automated chemiluminescent-based assays on an AcuStar instrument (IL/Werfen). FVIII assays and the VWF antigen and activity assays were calibrated with materials that were traceable to the WHO 6th International Standard for FVIII and von Willebrand in human plasma (07/316).

2.2 | Statistical methods

SPSS V26.0 software was utilized for statistical analyses. Pearson's correlation coefficient was used to quantify the correlation between numerical values and the chi-square test to analyze categorical variables. A logistic regression model was used for the significant risk factors. A p-value <.05 was considered statistically significant.

2.3 | Ethical considerations and informed consent

The study adhered to ethical guidelines on informed consent in accordance with the Helsinki Declaration. All participants provided written consent after receiving comprehensive information about the study and its implications for participation. Moreover, the study underwent review by the Regional Ethics Committee for Medical and Health Research Ethics South-East Norway, which concluded that it fell outside the scope of the Health Research Act and could therefore be conducted without their approval. Additionally, the data protection officer at Oslo University Hospital raised no objections to the study.

3 | RESULTS

3.1 | Study demographics

The study included 134 patients with an HHT diagnosis. The mean age, gender distribution, and gene variants are listed in Table 2.

3.2 | Thromboembolic events

Thirty-one of the 134 patients (23.1%) reported a previous thromboembolic event. Eleven patients reported having two or more thromboembolic events (Table 2).

TABLE 2 Study participant demographics.

Total number patients	134	
Age	Mean: 56.37 (± 15.11 years)	
Gender		
Female	68 (50.7%)	
Male	66 (49.3%)	
Gene		
ENG	46 (34.3%)	
ACVRL1	74 (55.2%)	
No mutation detected	7 (5.2%)	
Not tested	4 (3.0%)	
SMAD4	0	
Variant of uncertain significance	3 (2.2%)	
Patients with thromboembolic events		
Yes	31 (23.1%)	
No	103 (76.9%)	
Types of thromboembolic events		
VTE	17 (12.7%)	
DVT + PE	6 (4.4%)	
Only DVT	7 (5.2%)	
Only PE	4 (3.0%)	
Cerebral thromboembolism	12 (9.0%)	
Myocardial infarction	4 (3.0%)	
Other thromboembolic events[a]	6 (4.5%)	
Epistaxis		
	IFT	8.39 ± 4.12 (range 0–24)
	ESS	5.09 ± 1.92 (range 1.01–9.09)
Other HHT manifestations		
	PAVM	42 (31.3%)
	CAVM	3 (2.2%)
	HAVM	10 (7.5%)
	GI bleeding	14 (10.4%)
Smoking	13	9.7%

Abbreviations: CAVM, cerebral arteriovenous malformation; ESS, Epistaxis Severity Score; GI, gastrointestinal; HAVM, hepatic arteriovenous malformation; IFT, Epistaxis Intensity, Frequency, and Need for Blood Transfusion Score; PAVM, pulmonary arteriovenous malformation; VTE, venous thromboembolism.

[a]The other thromboembolic events were intramural aortic thrombosis with simultaneous splenic thrombosis, transient ischemic attack (two cases), popliteal artery thrombosis (two cases), and one case with proximal and peripheral arterial thrombosis in one leg.

3.3 | Thromboembolic events and iron metabolism

Low iron levels (<9 μmol/L) were significantly associated with thromboembolic events ($p = .017$). No significant association was found between thromboembolic events and hemoglobin or ferritin (Table 3).

TABLE 3 Association between thromboembolic events and coagulation factors, vWF, hemoglobin, ferritin, and iron.

		Thromboembolic event			
		Yes	No	Total	*p*-value
Hemoglobin	Low	17	36	53	.128
	Normal	14	66	80	
	Total	31	102	133	
Ferritin	Low	7	20	27	.601
	Normal	23	82	105	
	Total	30	102	132	
Iron	Low	19	34	53	.017
	Normal	12	68	80	
	Total	31	102	133	
VIII	High	28	56	84	.001
	Normal	2	37	39	
	Total	30	93	123	
IX	High	2	4	6	.142
	Normal	3	27	30	
	Total	5	31	36	
vWF antigen	High	2	3	4	.173
	Normal	4	29	34	
	Total	6	32	38	
vWF activity	High	2	3	5	.200
	Normal	4	28	32	
	Total	6	31	37	

3.4 | Coagulation factors, vWF antigen, vWF activity, and thromboembolic events

FVIII was measured in 123 of the 134 patients. The FVIII level was high (>150 IU/dL) in 84 patients (68.3%). FVIII levels were measured in 30 out of the 31 patients with a reported thromboembolic event. The average period between the last thromboembolic event and FVIII measurement was 7 years (range 5 months-26 years). Twenty-eight (93.3%) had high levels of FVIII; only two had normal levels. FVIII was significantly associated with thromboembolic events ($p = .001$) (Table 3).

Of the patients with a reported thromboembolic event, one had a heterozygous factor V Leiden mutation, and another had a homozygous factor V Leiden mutation and protein C deficiency. One patient experienced PE postoperatively 5 months before the measurement of FVIII.

Coagulation factor IX was measured in 36 patients, and vWF antigen and activity were measured in 38 and 37 patients, respectively. No significant association was found between coagulation factor IX, vWF activity, vWF antigen, and thromboembolic events (Table 3).

3.5 | Correlation between hemoglobin, ferritin, iron, CRP, age and smoking and FVIII

Hemoglobin, iron, age, and smoking were significantly correlated with FVIII levels (data for smoking not shown; $p = .002$). The acute phase reactants CRP and ferritin were not correlated with FVIII levels (Table 4).

3.6 | FVIII variation over time

The level of FVIII was measured more than once in 51 patients (twice in 51 patients, three times in 18 patients, and four times in 3 patients) during the study period. The median time interval between measurements was 6 months. FVIII levels remained high in 27 patients and normal in 13 patients. Eleven patients had FVIII levels fluctuating between high and normal (over and under 150 IU/dL). Of the patients with sustained high levels of FVIII, 9 of the 27 patients (33%) reported previous thromboembolic events; 2 of the 11 patients (18%) with fluctuating levels of FVIII reported previous thromboembolic events, but none of the 13 patients with sustained normal levels of FVIII had experienced a thromboembolic event (Table 5). This gives an odds ratio of 5.50 (95% CI: 1.05–28.75) for a thromboembolic event in the patients with sustained high FVIII levels compared to those with fluctuating and sustained normal levels of FVIII.

3.7 | Other parameters

The prevalence of AVMs and GI bleed among our patients is shown in Table 2. Of the patients with thromboembolic stroke, 66% (8/12) had PAVM ($p = .005$).

Fifty-eight patients (43.3%) had prescriptions for TXA, while 29 (21.6%) had been prescribed iron supplements. Twelve of the 31 patients with a recorded thromboembolic event had TXA

TABLE 4 Correlation between coagulation factor VIII, markers of iron metabolism, CRP, and age.

	Pearson's correlation coefficient	*p*-value	95% CI
FVIII-Hemoglobin	−0.302	<.001	−0.454 to 0.133
FVIII-Ferritin	0.171	.059	−0.006 to 0.338
FVIII-Iron	0.188	.037	0.012 to 0.353
FVIII-Age	0.266	.003	0.094 to 0.422
FVIII-CRP	−0.005	.948	−0.135 to 0.143

Abbreviations: CI, confidence interval; CRP, C-reactive protein.

TABLE 5 FVIII variation over time.

	Thromboembolic event	No thromboembolic event	Total
FVIII levels remained high	9	18	27
Fluctuating FVIII levels[a]	2	9	11
FVIII levels remained normal	0	13	13
Total	11	40	51

Note: Consecutive measurements of FVIII with a median interval of 6 months between the measurements.
[a]Over and under 150 IU/dL.

prescriptions, and 10 had prescriptions for iron supplements. However, obtaining complete information on treatment with iron supplements was impossible because patients are treated at different hospitals, and some used over-the-counter iron supplements.

Age was significantly associated with thromboembolic events. Gender and gene variants were without significant association with FVIII or thromboembolic events. The same was true for pulmonary arteriovenous malformation (PAVM) (other than thromboembolic stroke), cerebral arteriovenous malformation, hepatic arteriovenous malformation, and GI bleed (Table 6). The mean epistaxis grading with the ESS and IFT was 5.09 ± 1.92 (1.01–9.09) and 8.39 ± 4.12 (0–24) (Table 2). The ESS and IFT scores had no significant association with thromboembolic events or FVIII levels (data not shown).

3.8 | Regression analysis

Logistic regression analysis, including age, FVIII, and iron in relation to thromboembolic events, showed that FVIII and age significantly influenced the development of thromboembolic events. In contrast, iron showed no such influence (Table 7).

4 | DISCUSSION

Epistaxis is the most common and debilitating aspect of HHT. The challenge for an otolaryngologist is in providing the most optimal treatment for epistaxis after considering the severity of the episodes, quality of life, blood work, and ongoing treatment for co-existing illnesses. The high prevalence of thromboembolic events in HHT patients raises concern about treatment safety, keeping in mind that most medications used to treat epistaxis in HHT may give thrombosis as a potential side effect. The Second International Guidelines for Diagnosing and Managing HHT patients recommend treatment with TXA at high dosages for epistaxis after excluding the risk of thromboembolic disease, including high FVIII levels[31] (see Guideline supplement).

TXA is an antifibrinolytic agent that stabilizes and prevents premature dissolution of the fibrin clot. TXA is a competitive inhibitor to the lysine receptor found on plasminogen, reducing the conversion of plasminogen into plasmin. Plasmin degrades fibrin clots, fibrinogen, and other plasma proteins, including the pro-coagulant factors V and VIII.[35]

Two randomized controlled trials[36,37] have demonstrated a significant decrease in the severity and frequency of epistaxis episodes in HHT patients treated with TXA. No increased risk of thromboembolic events using TXA was reported. However, the trial period of both clinical studies was limited to 3 months. Information about the long-term use of TXA in HHT patients is lacking. However, a recent study involving 24 patients treated with TXA or aminocaproic acid (an antifibrinolytic agent) for 13 months did not report any thromboembolic events.[38] A retrospective study[39] involving 29 patients using TXA reported no difference in the thrombosis rate before and during treatment. Although none of these studies measured FVIII, there is no indication that elevated FVIII levels, TXA use, and thromboembolic events are correlated. In addition, TXA is shown neither to increase thrombin generation nor to lead to hypercoagulability.[40,41]

Despite the evidence that TXA is a safe treatment for epistaxis in HHT patients, skepticism about its possible side effects remains.[31,42] Although absolute and relative contraindications to this treatment are suggested, an individual assessment of thromboembolic risk before initiating treatment is not explicitly required or recommended. Many patients with HHT have elevated levels of FVIII, a known risk factor for thromboembolic disease, especially VTE.[12,13] The higher the level of FVIII, the higher the risk of developing VTE.[14–17] We aimed in this study to identify factors associated with increased risk of thromboembolic events in HHT patients, including FVIII.

		Thromboembolic event			
		Yes	No	Total	*p*-value
Gene	ENG	13	33	46	.787
	ACVRL1	14	60	74	
	No mutation detected	2	5	7	
	Variant of uncertain significance	1	2	3	
	Total	30	100	130	
PAVM	Yes	13	29	42	.421
	No	17	66	83	
	Total	30	95	125	
HAVM	Yes	3	7	10	.577
	No	14	39	53	
	Total	17	46	63	
CAVM	Yes	1	2	3	.706
	No	15	48	63	
	Total	16	50	66	
GI bleeding	Yes	6	8	14	.196
	No	13	42	55	
	Total	19	50	69	
Gender	Female	18	50	68	.353
	Male	13	53	66	
	Total	31	103	134	
Age	15–29 years old	0	5	5	.033
	30–39 years old	1	12	13	
	40–49 years old	4	23	27	
	50–59 years old	8	29	37	
	60–69 years old	4	15	19	
	70–79 years old	9	16	25	
	80–87 years old	5	3	8	
	Total	31	103	134	

TABLE 6 Association between thromboembolic events and gene variant, arteriovenous malformation (AVM), gender, age, and smoking.

Abbreviations: CAVM, cerebral arteriovenous malformation; GI, gastrointestinal; HAVM, hepatic arteriovenous malformation; PAVM, pulmonary arteriovenous malformation.

TABLE 7 Binary logistic regression of thromboembolic events.

	Regression coefficient	OR (95% CI)	*p*-value
Factor VIII	0.016	1.016 (1.007–1.026)	<.001
Iron	−0.045	0.956 (0.909–1.006)	.081
Age	0.047	1.049 (1.013–1.085)	.007

Abbreviations: CI, confidence interval; OR, odds ratio.

The risk of VTE in HHT patients has been comprehensively described by Shovlin et al.[11] However, the total prevalence of thromboembolic events (both arterial and venous) in HHT patients has not been previously investigated. Our study showed that the prevalence of VTE events among our HHT population was 12.7%, while 16.5% were arterial events. These prevalence numbers are much higher than in the general population, which for VTE in Norway, is estimated to be 0.24%.[43] Of the registered thromboembolic events in our study, 9.0% were thromboembolic strokes, and 3.0% were MI. The period prevalence of stroke (including hemorrhagic stroke) and MI in the general population in Norway between 2012 and 2020 was 0.26% (95% CI: 0.26–0.26) and 0.30% (95% CI: 0.30–0.30), respectively.[44] These observations confirm that thromboembolic events are a significant complication in HHT and that arterial thromboembolic events are an important concern.

Over two-thirds (68.3%) of our patients had high levels of FVIII, and most HHT patients with a history of thromboembolic events had high levels of FVIII (93.3%). A previous study by Livesey et al.[10] showed that low serum iron levels correlate with high FVIII levels and VTE. Elevation of FVIII to promote thrombosis in the setting of iron deficiency was proposed as a plausible mechanism.[10] Although our

data initially suggested a correlation between low iron levels and thromboembolic events, this was not reflected in the regression analysis. Rather, FVIII and age were the factors that significantly associated with thromboembolic events. However, it should be borne in mind that iron levels are influenced by iron supplementation as well as diurnal changes. An alternative explanation for elevated levels of FVIII in HHT patients could be that chronic vascular inflammation causes endothelial cell activation. This is because Pentraxin 3 is shown to be significantly elevated in HHT patients, reflecting systemic inflammation and, at least partly, vascular inflammation.[45]

HHT patients with PAVM are known to be at a higher risk of thromboembolic stroke due to the lack of first-pass filtration by the lungs,[46] and our results are in line with this concept.

The level of FVIII can fluctuate over time. However, high levels of FVIII are known to persist in patients with thrombosis and are generally not caused by acute-phase reactions.[14,15,47,48] The acute phase reactants CRP and ferritin were not correlated with the FVIII level in our study. Among our patients whose FVIII levels were measured at regular intervals, 75% had consistently high or normal levels of FVIII. The remaining 25% had fluctuating levels of FVIII. Of those with consistently high levels, 33% had experienced thromboembolic events, while 18% of those with fluctuating levels had experienced the same. No patients with consistently normal levels of FVIII reported having a thromboembolic event. This suggests that relying on a single measurement of FVIII in individuals with HHT may not be sufficient and that the test should be repeated consecutively. The intention of this study was not to prove causality, and the study design would not be sufficient for this purpose. However, we see a clear tendency where the patients with previously reported thromboembolic event(s) also had sustained high FVIII levels.

Among the limitations of our study, screening for other pro-thrombotic factors beyond those already mentioned was not performed. Thus, whether co-existing pro-thrombotic factors influenced the recorded thromboembolic events in those included remains unknown. Two patients with Factor V Leiden mutation were included in this study. This decision to include these was made to reflect the general population in which this mutation is estimated to be present in 3%–8% of caucasians.[49] The only potentially pro-thrombotic medications our subjects used were TXA and intranasal Avastin (Bevacizumab). Intranasal Avastin is not known to cause thrombosis mainly due to the low concentration used and the longer intervals between treatments.[50,51] The retrospective nature of the assessment of thromboembolic events is a potential weak point. ABO typing is relevant to FVIII measurements as non-O blood group patients have higher levels of FVIII than those with type O.[23–25] Blood typing was not performed in this study and, therefore, not adjusted for. The timing of blood sampling was not standardized, which is a limit because iron levels vary during the day. Our overview of the participants' prescription history for TXA and iron supplements was insufficient due to limited access to the patient's medical and prescription history.

5 | CONCLUSION

Both arterial and venous thromboembolic events are highly prevalent in the Norwegian HHT population. High FVIII levels and age are important risk factors for thromboembolic events in HHT. Hemoglobin, iron, and ferritin are unreliable indicators for the level of FVIII and the thromboembolic risk. FVIII levels can fluctuate over time. Therefore, repeated measurements of FVIII are important to assess present levels accurately. However, it is unclear whether the FVIII level should be taken into consideration when considering the use of medications that carry a potential risk of thrombosis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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