

Coexistence of High Fibrinogen and Low High-density Lipoprotein Cholesterol Levels Predicts Recurrent Cerebral Venous Thrombosis

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Abstract

Background: Cerebral venous thrombosis (CVT) may lead to serious neurological disorders; however, little is known about the risk factors for recurrent CVT. Our aim was to determine the association between elevated fibrinogen and decreased high-density lipoprotein cholesterol (HDL-C) levels with recurrent CVT.

Methods: This retrospective cohort study included participants if they had a first episode of objectively defined CVT and were admitted to Xuan Wu Hospital, Capital Medical University from August 2005 to September 2009. Demographic and clinical variables were collected, as well as laboratory parameters, including plasma fibrinogen and HDL-C. Patients with CVT were followed for recurrent symptomatic CVT. Follow-up was through the end of September 2010. Potential predictors of recurrence were analyzed using Cox survival analysis.

Results: At the end of the follow-up, 95 patients were eligible for the study. Twelve of 95 patients (12.6%) had recurrent CVT. The median time of recurrence was 7 months (range: 1–39 months). Eight of these 12 (66.7%) experienced recurrence within the first 12 months after their initial CVT. The recurrence rate of CVT was 2.76 per 100 patient-years. Multivariate Cox regression analysis demonstrated that the coexistence of high fibrinogen (>4.00 g/L) and low HDL-C (<1.08 mmol/L) levels at baseline was the only independent predictor for recurrent CVT (hazard ratio: 4.69; 95% confidence interval: 1.10–20.11; $P < 0.05$). Of the twelve patients with recurrent CVT in our study, 7 (58.3%) had high fibrinogen plus low HDL-C levels. All 7 of these patients took warfarin for 3–12 months, and 6 of 7 had recurrent CVT after the discontinuation of anticoagulant treatment.

Conclusions: Concomitant high fibrinogen and low HDL-C levels may be associated with recurrence of CVT. The effect of potential risk factors related to atherothrombosis on recurrent CVT should be closely monitored.

Key words: Cerebral Venous Thrombosis; Fibrinogen; High-density Lipoprotein Cholesterol; Recurrence; Risk Factor

INTRODUCTION

The venous system contains 70% of the cerebral blood volume and is of importance for normal cerebral circulation. Although cerebral venous thrombosis (CVT) only accounts for approximately 1% of all stroke cases,^[1] it may lead to serious consequences. In addition, CVT is usually noted in young individuals, including children. Of all CVT cases, 78% occur in patients <50 years of age.^[2] However, the amount of research on CVT has long been far less than that on cerebral artery thrombosis. Recently, a statement by the American Heart Association (AHA) and the American Stroke

Association (ASA), regarding the diagnosis and management of CVT, emphasized for the first time that more attention needs to be paid to CVT.^[2]

Cerebral venous thrombosis may cause serious neurological syndromes such as intracranial hypertension, seizures, motor defects, sensory loss, and loss of consciousness. The mortality ranges 5.5–30%.^[3] After a first CVT, there is an increased risk of further venous thromboembolic events (VTE),^[4] and 2–13% of all patients suffer CVT recurrence.^[1,5] CVT should be an important consideration because of its potential serious consequences and recurrence. However, very few studies have been done to assess CVT recurrence and determine predisposing risk factors for recurrence. Although CVT can be caused by a hypercoagulable condition (acquired

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or hereditary thrombophilias), an inflammatory state, or collagen vascular diseases,^[6] in 30% of cases no underlying etiology can be identified.^[7] Hence, the risk factors related to recurrent CVT remain unclear.

Anticoagulation is believed to be beneficial for the prevention of CVT recurrence. The duration of oral anticoagulation after the acute phase is uncertain.^[8] Identification of risk factors for recurrence after a first CVT would help to more accurately determine the best duration for anticoagulation treatment and for appropriate precautionary measures. In clinical practice, the authors have noticed that patients with CVT tended to have baseline high fibrinogen and/or low high-density lipoprotein cholesterol (HDL-C) levels. High fibrinogen or low HDL-C levels can increase arterial thrombosis and cardiovascular disease,^[9] hyperfibrinogenemia and low HDL-C levels may correlate with thrombophilia,^[10] but it is still unclear whether these two factors can increase the likelihood of recurrent CVT.

Therefore, we hypothesized that there is some association between baseline elevated fibrinogen or lowered HDL-C levels, or both in combination, with the recurrence of CVT. In this study, the clinical profiles and laboratory testing parameters at baseline (including fibrinogen and HDL-C) of patients with a first CVT were analyzed to ascertain this correlation, in order to explore potential CVT risk factors.

METHODS

Patients and follow-up

All patients with a first episode of CVT admitted to Xuan Wu Hospital, Capital Medical University, a tertiary care academic medical center, from August 2005 to September 2009, were included in this study. This study was approved by the Ethics Committee of the hospital. Patients were identified through a computerized search of discharge diagnosis codes (ICD-10: G08.X06, G08.X09, G08.X10, 167.651, 167.652) in the hospital discharge database. Diagnosis had been confirmed by cerebral digital angiography, or magnetic resonance imaging (MRI) plus magnetic resonance venography (MRV) in all patients.^[2] Exclusion criteria included medication for lipid-lowering or contraception, pregnancy, postpartum state, dehydration, trauma, heart failure, hepatic and renal diseases, or malignancy.

The data related to recurrence were obtained partly by reviewing clinical histories of patients who had revisited Xuan Wu hospital as outpatients or who were readmitted to the hospital as inpatients, and those of others from a telephone survey.

The endpoints of the study were recurrent symptomatic CVT, death from CVT, or end of the study (September 2010). Recurrent symptomatic CVT refers to the development of new neurological symptoms, with a new cerebral venous or sinus occlusion on repeated MRI tests, combined with MRV or cerebral digital angiography.^[2] Follow-up studies were conducted from discharge to September 2010. If the

patient had multiple recurrent CVT, only the first recurrence was included in the study. The data were collected by two trained residencies.

Parameters

Demographic and clinical variables were collected in a standardized file comprising clinical characteristics (age, gender, body weight, systolic blood pressure, diastolic blood pressure, history of smoking, hypertension, diabetes mellitus, cardiac disease, previous venous thrombosis, and the duration of anticoagulant therapy), and laboratory parameters (white blood cell count, red blood cell count, blood platelet count, hemoglobin, plasma fibrinogen, fasting blood glucose, serum total cholesterol, low-density lipoprotein cholesterol [LDL-C], HDL-C, triglycerides, apolipoprotein A1, and apolipoprotein B). All of the above testing parameters were determined based on the results of blood samples taken on day 1 of hospitalization, and all analyses were performed in our hospital laboratory. Plasma fibrinogen levels were measured using the STA automate (DE-STA-CO, Paris, France). Serum total cholesterol, LDL-C, HDL-C, triglycerides, apolipoprotein A1, and apolipoprotein B were analyzed with an automatic biochemical analyzer (Hitachi 7170, Tokyo, Japan). Normal ranges for fibrinogen and HDL-C were 2.00–4.00 g/L and 1.08–1.91 mmol/L, respectively. Warfarin was used to prevent CVT recurrence (target international normalized ratio, 2.0–3.0).

Statistical analysis

Basic demographic data and biochemical characteristics of patients were expressed as mean \pm standard deviation. Categorical data were given as counts and percentages. The relationship between high fibrinogen (>4.00 g/L) and low HDL-C (<1.08 mmol/L) was evaluated by Spearman's rank correlation coefficient. Factors that predicted time to total recurrent events were identified by univariate Cox regression analyses. The multivariate Cox proportional hazards model was used to evaluate the independent contribution of the risks to CVT recurrence, and to adjust for potential confounders. The risk factors, including those variables that had a $P < 0.05$ upon univariate Cox proportional hazard analysis, and some confounding factors, such as gender, venous thrombosis history, and duration of anticoagulation treatment, were introduced in a multivariate Cox regression model. The independent risk factors were assessed by Kaplan–Meier univariate analysis. The log-rank test was used for differences in recurrence. Differences were considered as statistically significant when the $P < 0.05$. Confidence intervals (CI) corresponded to the 95% level. All statistical analysis was performed with the use of SPSS version 16.0 software (SPSS, Inc.; Chicago, IL, USA) on a Windows XP platform.

RESULTS

Patients and disease characteristics

Of 151 patients screened, 48 were excluded according to the criteria. We identified a total of 103 patients with CVT as the

case group. Two patients died of other diseases (trauma or cardiac disease) during the follow-up period. An additional four patients were lost to follow-up, and two refused to participate in the study. The remaining 95 patients were eligible for the study, and their baseline demographic data and biochemical parameters are presented in Table 1. Of these 95 patients, 47 were men and 48 were women, with a median age of 35.3 years (range: 15–69 years). The duration of disease was 2 days to 1.3 years, with 13.7% (13/95) within 1-week after onset and hospitalization. Follow-up was conducted until September 30, 2010 (analysis cut-off date) with a duration ranging between 1 and 61 months (median of 27 months).

Recurrent cerebral venous thrombosis

At the end of the follow-up period, of the 95 included patients, 12 (12.6%) had recurrent CVT. The median time of recurrence was 7 months (range: 1–39 months). Eight of the CVT recurrences (66.7%) occurred within the 1st year. The recurrence rate of CVT was 2.76 per 100 patient-years (95% *CI*: 1.03–5.21).

Risk factors for recurrence

Elevated fibrinogen level was present in 41.1% of patients and lowered HDL-C level in 36.8% [Table 2] in the study. The risk factors affecting recurrence on univariate Cox proportional hazards analysis are shown in Table 2. CVT patients with a smoking habit had a higher recurrence rate (hazard ratio [*HR*]: 3.84; 95% *CI*: 1.25–12.08; *P* < 0.05). Many laboratory parameters were not related to the recurrence of CVT. Specifically, high fibrinogen or low HDL-C alone were not factors associated with recurrence (*P* > 0.05). Interestingly, only when high fibrinogen and low HDL-C occurred together did patients have a higher recurrence risk of CVT (*HR*: 4.93; 95% *CI*: 1.27–19.07; *P* < 0.05).

Multivariate Cox regression analysis [Table 3] was used to search for possible independent predictive risk factors for the recurrence of CVT, including smoking and the coexistence of high fibrinogen and low HDL-C, and confounding factors such as gender, venous thrombosis history, and

Table 1: Baseline characteristics of patients with first CVT and univariate Cox regression analysis of factors affecting recurrence

Characteristics	Value	<i>P</i>	<i>RR</i> (95% <i>CI</i>)
Age (years)	35.27 ± 12.18	0.368	1.021 (0.976–1.069)
Sex (male/female), <i>n</i>	47 (48)	0.199	0.454 (0.136–1.513)
Body weight (kg)	66.37 ± 11.01	0.441	1.021 (0.968–1.078)
Smoking habit, <i>n</i> (%) [*]	21 (22.1)	0.019 [†]	3.844 (1.249–12.078)
Hypertension, <i>n</i> (%) [*]	9 (9.5)	0.499	0.043 (0–39.281)
Heart disease, <i>n</i> (%) [*]	14 (14.7)	0.296	2.019 (0.541–7.526)
PVT, <i>n</i> (%) [*]	16 (16.8)	0.347	1.876 (0.506–6.964)
Systolic blood pressure (mmHg)	122.34 ± 16.46	0.833	0.996 (0.962–1.032)
Diastolic blood pressure (mmHg)	75.83 ± 10.33	0.893	0.996 (0.944–1.052)
Hemoglobin (g/L)	133.79 ± 25.33	0.349	1.012 (0.987–1.037)
White blood cell count (×10 ⁹ /L)	7.92 ± 2.86	0.464	1.074 (0.888–1.298)
Red blood cell count (×10 ¹² /L)	4.45 ± 0.70	0.929	0.965 (0.443–2.104)
Platelet count (×10 ⁹ /L)	263.58 ± 87.41	0.060	0.993 (0.985–1.000)
Blood glucose (mmol/L)	5.30 ± 1.53	0.622	1.083 (0.790–1.484)
Triglycerides (mmol/L)	1.95 ± 1.30	0.249	0.619 (0.273–1.400)
Total cholesterol (mmol/L)	4.54 ± 1.10	0.442	0.805 (0.463–1.400)
LDL-C (mmol/L)	2.48 ± 0.82	0.210	0.624 (0.299–1.303)
HDL-C (mmol/L)	1.17 ± 0.34	0.224	0.270 (0.033–2.230)
Apolipoprotein A1 (g/L)	1.09 ± 0.25	0.292	0.194 (0.009–4.089)
Apolipoprotein B (g/L)	0.87 ± 0.31	0.442	0.469 (0.068–3.229)
Fibrinogen (g/L)	3.76 ± 1.12	0.134	1.387 (0.905–2.126)

^{*}Percentage calculated on the total number of patients; [†]*P* < 0.05 indicates statistical significance. PVT: Previous venous thrombosis; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; CVT: Cerebral venous thrombosis; *RR*: Relative risk; *CI*: Confidence interval.

Table 2: Univariate Cox regression analysis of predictors for recurrence after first CVT according to the main clinical parameters

Parameters	Value <i>n</i> (%) [*]	<i>P</i>	<i>RR</i> (95% <i>CI</i>)
High fibrinogen (≥4.0 g/L)	39 (41.1)	0.102	2.719 (0.818–9.034)
Low HDL-C (<1.08 mmol/L)	35 (36.8)	0.110	2.559 (0.809–8.091)
High fibrinogen and low HDL-C	19 (20.0)	0.021 [†]	4.928 (1.273–19.073)
Duration of oral anticoagulant (≥3 m)	79 (83.2)	0.721	1.271 (0.342–4.730)

^{*}Percentage calculated on the total number of patients; [†]*P* < 0.05. HDL-C: high-density lipoprotein cholesterol; CVT: Cerebral venous thrombosis; *RR*: Relative risk; *CI*: Confidence interval.

duration of anticoagulation. Surprisingly, the result was that coexisting high fibrinogen and low HDL-C levels is the only independent predictive variable for recurrent CVT (HR: 4.69; 95% CI: 1.10–20.11; $P < 0.05$). The cumulative recurrent risk affected by coexisting high-level fibrinogen and low-level HDL-C was calculated using Kaplan–Meier univariate analysis and log-rank test [Figure 1]. Patients with both high fibrinogen and low HDL-C levels had a cumulative risk of recurrent CVT, compared to that in patients with both normal fibrinogen and normal HDL-C, high fibrinogen alone, or low HDL-C alone ($\chi^2 = 6.61$, $P < 0.01$; $\chi^2 = 3.86$, $P < 0.01$; $\chi^2 = 5.61$, $P < 0.01$, respectively).

Within the group of patients with recurrent CVT, 7 of 12 (58.3%) had high fibrinogen and low HDL-C. All 7 took warfarin for a period from 3 to 12 months, and 6 patients (6/7, 85.7%) had recurrent CVT after discontinuation of anticoagulant treatment. One of 7 (14.3%) patients had a recurrence during anticoagulation therapy.

Two other patients with recurrent CVT who took warfarin for more than 3 months had high fibrinogen with normal HDL-C levels, and normal fibrinogen with normal HDL-C levels, respectively. The first patient had recurrent CVT during warfarin therapy, and the second had a CVT recurrence after

stopping warfarin treatment. One recurrent patient who had high fibrinogen level alone took warfarin for <3 months. Finally, two patients with normal fibrinogen and normal HDL-C levels experienced recurrence and had not taken any anticoagulant drugs.

Correlation between fibrinogen and high-density lipoprotein cholesterol

Spearman's correlation analysis was used to estimate the relationship between high fibrinogen and low HDL-C levels. The result showed that high fibrinogen levels were related to low HDL-C levels ($r = 0.205$, $P < 0.05$).

DISCUSSION

This study examined the risk factors for recurrent CVT. We found that the simultaneous presence of high fibrinogen and low HDL-C levels was a predictor of CVT recurrence compared to the presence of both normal fibrinogen and HDL-C levels, high fibrinogen level alone, or low HDL-C level alone. This study is the first to show an association between concurrent high fibrinogen and low HDL-C, and a risk for recurrent CVT.

Information on CVT recurrence is limited. Owing to the rarity of the disease, studies on CVT are mainly retrospective, with a small sample size and short follow-up. A larger retrospective cohort study from France included 77 CVT patients followed for 63 months. Of these, 11.7% had recurrence of CVT, with 10.4% occurring during the first 12 months.^[11] This study is similar to our current study, in which we found a 12.6% rate of CVT recurrence over a median period of 27 months. The recurrent risk of CVT in our study was 2.76 per 100 patient-years. Of these CVT recurrences, 66.7% occurred within the 1st year. However, in the International Study on Cerebral Vein and Dural Sinus Thrombosis, only 2.2% of patients studied had an episode of recurrent CVT after a median follow-up of 13.9 months. The rate of recurrence found was 1.5 per 100 patient-years. Of these CVT recurrences, 64.3% occurred within the 1st year.^[4] The lower recurrence rate of this study may be due to the shorter period of follow-up (13.9 months), as compared to 63 and 27 months in the studies mentioned above.

The common risk factors for CVT in previous studies were prothrombotic conditions; however, in the past, high fibrinogen or low HDL-C levels have not been described with regard to CVT. These two factors were also not included in the AHA/ASA statement about diagnosis and management of CVT.^[2] Only a few studies have shown a correlation between high fibrinogen or low HDL-C with risk of VTE or recurrent VTE,^[12,13] but these findings were not consistent with other studies that suggested no correlation.^[14,15] Until this study, there has been little attention paid to the prognostic importance of fibrinogen and HDL-C levels at baseline in CVT patients. However, there have been many reports about high fibrinogen and low HDL-C as prothrombotic factors promoting atherothrombotic diseases.^[16,17] Fibrinogen is a circulating protein synthesized in the liver and is

Table 3: Multivariate Cox proportional hazards regression analysis for CVT recurrence

Variables	RR (95% CI)	P
Sex	1.828 (0.188–17.732)	0.603
Smoking habit	6.636 (0.745–59.085)	0.090
Previous venous thrombosis	0.709 (0.084–5.977)	0.752
Duration of oral anticoagulant (≥ 3 m)	0.659 (0.145–3.002)	0.590
High fibrinogen and low HDL-C	4.693 (1.095–20.114)	0.037*

* $P < 0.05$. HDL-C: High-density lipoprotein cholesterol; CVT: Cerebral venous thrombosis; RR: Relative risk; CI: Confidence interval.

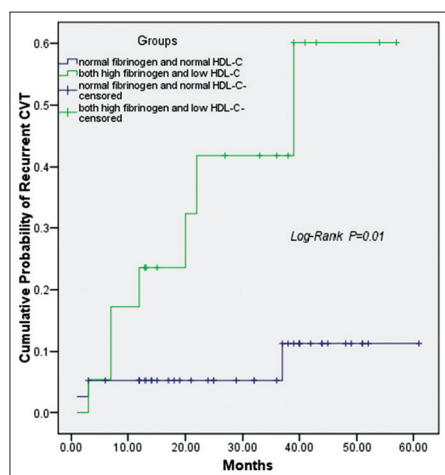


Figure 1: Kaplan–Meier analysis for cumulative risk of recurrent CVT (log-rank test): The cumulative risk of recurrent CVT in patients with both high fibrinogen and low HDL-C was significant difference from patients with both normal fibrinogen and normal HDL-C. The P value of the log-rank test for the difference is 0.01. HDL-C: High-density lipoprotein cholesterol, CVT: Cerebral venous thrombosis.

converted to fibrin by the action of thrombin. Previous studies have demonstrated that fibrinogen was directly involved in a variety of mechanisms that mediate thrombotic processes. Fibrinogen contributes to blood viscosity, platelet aggregation, and fibrin formation.^[18,19] Elevated fibrinogen levels can lead to increased intravascular fibrin deposition and thrombosis,^[19] and make clots more resistant to lysis.^[20] HDL-C participates in the process of reverse transport of cholesterol. Past studies have shown that HDL-C contributes an antithrombotic effect that may be a result of a reduction in viscosity, an inhibition of platelet aggregation, a decrease in inflammation, or the protection of endothelial cell function. Low HDL-C level is associated with endothelial damage and the hypercoagulable state.^[21,22] In this study, 41.1% patients had elevated fibrinogen levels, and 36.8% had lowered HDL-C levels. These proportions are much higher than the 2% and 11.1–26.4%, respectively, in healthy subjects found in two previous studies.^[23,24] Notably, although fibrinogen is an acute phase reactant,^[18] only 13.7% patients in our study were within 1-week after onset, while most other patients were in the subacute or chronic stage in the hospital; therefore, we think that the effect of the acute phase response was not significant for the observations in the study. However, it was notable that elevated fibrinogen or lowered HDL-C alone had no significant correlation with the recurrence of CVT in this study. Therefore, this implied that initial high fibrinogen or low HDL-C alone may not be independent risk factors for recurrent CVT. This is consistent with the viewpoint that thrombophilia alone is not sufficient to trigger recurrent CVT when it is not associated with other synergistic risk factors.^[25]

To further explore a cooperative effect between fibrinogen and HDL-C, we examined CVT recurrence in patients with concurrent high fibrinogen and low HDL-C. Surprisingly, we found that concurrent high fibrinogen and low HDL-C could increase the risk of recurrent CVT. We speculate that this is partially because of their similar or overlapping actions, such as their effect on blood viscosity, platelet aggregation, and inflammation, in promoting thrombosis. Apart from that, the interplay of their respective prominent actions may also contribute to thrombosis. Low HDL-C levels can lead to endothelial damage,^[26] which produces a more thrombogenic surface.^[27] Elevated fibrinogen can then elicit augmented fibrin deposition at the vascular wall.^[19] Therefore, elevated fibrinogen and low HDL-C could accelerate thrombosis, possibly by promoting and augmenting endothelial injury and fibrin deposition.^[28] This may help to explain the etiologic link between the additive effect of fibrinogen and HDL-C, which may predispose to recurrent CVT events.

In addition, we found that high fibrinogen was also related to low HDL-C ($r = 0.205$, $P < 0.05$). The levels of HDL-C dipped slightly when the concentration of fibrinogen rose above physiologic levels. This result was in accord with other studies.^[9]

In the present study, smoking was associated with recurrent CVT in univariate regression analysis. However, this

association was no longer retained in the multivariate analysis models. It is likely that the impact of other parameters was more pronounced, and smoking was not an independent risk factor for CVT recurrence. Although smoking is well-established as an important risk factor for atherosclerosis,^[29] a previous study found no association of smoking with VTE.^[12] This study was in accordance with our findings.

Anticoagulant treatment is essential for the prevention of thrombosis extension and recurrence of the disease.^[30] The proper duration for administering oral anticoagulation after CVT has not been adequately studied,^[31] and the optimal time period of administration remains uncertain.^[7] Guidelines have suggested a continuation of anticoagulation for a period between 3 and 12 months to prevent CVT recurrence.^[32,33] In our study, 75% (9/12) of recurrent patients were taking an anticoagulant (warfarin) for 3–12 months. However, we found no significant association between prolonging anticoagulant administration beyond 3 months and the recurrence of CVT. Previous studies have also shown that the risk of venous thrombotic recurrence was not influenced by anticoagulant therapy or duration of anticoagulation.^[4,34] There have even been suggestions that routine use of long-term anticoagulant therapy or life-long secondary prevention is unnecessary for preventing venous thrombotic recurrence.^[8] However, this does not imply that prolonged anticoagulation is unnecessary for preventing recurrence of CVT in some patients with multiple risk factors. A total 58.3% (7/12) of recurrent patients had both high fibrinogen and low HDL-C in our study. Of these, 85.7% (6/7) recurred after discontinuation of anticoagulant treatment. Prolonged administration of oral anticoagulation may be helpful for preventing recurrent CVT in these patients. Besides, it is questionable whether prevention targeted at high fibrinogen and low HDL-C is as useful in reducing the recurrence of CVT as dietary modification, smoking cessation, weight loss, physical exercise, and even avoidance of potential air pollution exposure. Recent epidemiological studies have demonstrated that air pollution is associated with elevated fibrinogen and low HDL-C.^[35-37] Further research is required to explore the effect, pathogenesis, and preventive measures of the potential risk factors, including concomitant factors, related to atherothrombosis in CVT recurrence.

There were some limitations in this study, including the small sample size, and data derived from only one center. In particular, inherited thrombophilia could not be completely assessed because of the retrospective nature of the study. In addition, because oral contraceptives, pregnancy, and the postpartum state may lead to a temporary increase in the risk for initial venous thrombosis or recurrence,^[38,39] we did not include such patients in our study. The limitations mentioned above may cause some bias.

In conclusion, we found that initial high fibrinogen level alone or low HDL-C level alone is not an independent risk factor for recurrent CVT; however, concurrent high fibrinogen and low HDL-C levels at baseline may be associated with recurrence.

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