Vascular Medicine

High-Density Lipoprotein and the Risk of Recurrent Venous Thromboembolism

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Background—High-density lipoprotein (HDL) protects against arterial atherothrombosis, but it is unknown whether it protects against recurrent venous thromboembolism.

Methods and Results—We studied 772 patients after a first spontaneous venous thromboembolism (average follow-up 48 months) and recorded the end point of symptomatic recurrent venous thromboembolism, which developed in 100 of the 772 patients. The relationship between plasma lipoprotein parameters and recurrence was evaluated. Plasma apolipoproteins A1 and B were measured by immunoassays for all subjects. Compared with those without recurrence, patients with recurrence had lower mean (±SD) levels of apolipoprotein A1 (1.12±0.22 versus 1.23±0.27 mg/mL, P<0.001) but similar apolipoprotein B levels. The relative risk of recurrence was 0.87 (95% CI, 0.80 to 0.94) for each increase of 0.1 mg/mL in plasma apolipoprotein A1. Compared with patients with apolipoprotein A1 levels in the lowest tertile (<1.07 mg/mL), the relative risk of recurrence was 0.46 (95% CI, 0.27 to 0.77) for the highest-tertile patients (apolipoprotein A1 >1.30 mg/mL) and 0.78 (95% CI, 0.50 to 1.22) for midtertile patients (apolipoprotein A1 of 1.07 to 1.30 mg/mL). Using nuclear magnetic resonance, we determined the levels of 10 major lipoprotein subclasses and HDL cholesterol for 71 patients with recurrence and 142 matched patients without recurrence. We found a strong trend for association between recurrence and low levels of HDL particles and HDL cholesterol.

Conclusions—Patients with high levels of apolipoprotein A1 and HDL have a decreased risk of recurrent venous thromboembolism. (Circulation. 2007;115:1609-1614.)

Key Words: lipoproteins ■ thrombosis ■ risk factors ■ veins

Venous thromboembolism (VTE) is a frequent, multicausal, and potentially fatal disease.1 The risk of recurrence depends on the number and severity of risk factors in an individual patient. Important risk factors of recurrence include antithrombin deficiency, the lupus anticoagulant, high factor VIII, hyperhomocysteinemia, previous venous thrombosis, cancer, and male sex.1,2 Approximately 5% of patients with recurrence die of pulmonary embolism.3 In many patients with recurrent VTE, however, a thrombophilic risk factor cannot be detected, which suggests the existence of unknown risk factors.

Clinical Perspective p 1614

An association between VTE and risk factors for atherosclerotic vascular disease is emerging and may help identify significant new risk factors for venous thrombosis. Dyslipidemia and dyslipoproteinemia are well-established risk factors for arterial atherothrombosis,4–6 but little is known about dyslipoproteinemia in VTE disease. Elevated plasma cholesterol, elevated serum lipoprotein(a), and low levels of plasma glucosylceramide may be potential markers or risk factors of venous thrombosis.7–11 In men younger than 55 years of age, dyslipoproteinemia involving low levels of high-density lipoprotein (HDL) and high levels of low-density lipoprotein (LDL) was associated with a 5-fold increased risk of a first venous thrombosis.12 Interestingly, patients with deep vein thrombosis of the legs without symptomatic atherosclerosis had a 1.8-fold increased risk of carotid plaques compared with patients without thrombosis.13 Other circumstantial clinical evidence for a relationship between venous and arterial thrombotic diseases comes from the fact that the risk factors of age, male sex, body weight, lupus anticoagulant, and hyperhomocysteinemia are common to both types of thrombotic disease.1,2

There are multiple and distinct potential mechanisms both for pathogenic contributions of dyslipoproteinemia to venous thrombosis and for protective antithrombotic actions of HDL.14–16 The latter include the ability of HDL to enhance the anticoagulant activity of the protein C pathway.15 In patients who have significant risks for arterial atherothrombosis, low levels of HDL cholesterol merit attention in clinical practice, and the use of lifestyle modifications and of
medications to raise HDL to reduce risk was reviewed recently.\textsuperscript{17} Currently, it is unknown whether patients at increased risk for venous thrombosis, eg, for recurrent venous thrombosis events, are affected by low levels of potentially protective HDL. To test the hypothesis that elevated HDL levels may impart protection against venous thrombosis or, conversely, that HDL deficiency confers an increased risk of recurrent VTE, we monitored a large cohort of patients and investigated the relationships between HDL parameters and recurrent VTE.

Methods

Study Population

Patients were participants in the previously reported Austrian Study on Recurrent Venous Thromboembolism (AUREC), an ongoing, prospective, multicenter cohort study in patients with VTE.\textsuperscript{2} Between July 1992 and November 2004, 3055 patients older than 18 years, who had been treated with vitamin K antagonists for at least 3 months after VTE, were eligible. Deep vein thrombosis was diagnosed by venography or color duplex sonography (in case of proximal deep vein thrombosis). Pulmonary embolism was diagnosed by ventilation perfusion scan or by multislice computed tomography.\textsuperscript{2} A total of 2283 patients were excluded because of previous thrombosis (n = 492); VTE secondary to surgery, trauma, or pregnancy (n = 471); antithrombin, protein C, or protein S deficiency (n = 71); the lupus anticoagulant (n = 67); cancer (n = 461); or requirement of long-term antithrombotic treatment for reasons other than VTE (n = 476); or because material for laboratory testing was not available (n = 122). Twenty-six patients with high factor VIII levels who participated in an interventional trial of long-term anticoagulation were excluded, as were 97 patients who used statins.

The present study was approved by the ethics committee of the Medical University of Vienna, Austria. Patients provided written informed consent and entered the present study at the time of their discontinuation of vitamin K antagonists. Subjects were seen at 3-month intervals during the first year and every 6 months thereafter. They received written information on VTE symptoms and were instructed to report when symptoms occurred.

Study End Point

The end point of the present study was recurrent, symptomatic deep vein thrombosis confirmed by venography or color duplex sonography (in case of proximal deep vein thrombosis of the contralateral leg) or symptomatic pulmonary embolism verified by perfusion lung scan and/or multislice computed tomography. Deep vein thrombosis was considered to have recurred if the patient had a thrombus in the leg or arm not affected by the previous thromboembolic event; a thrombus in another deep vein in the leg or arm not affected by the previous thromboembolic event; a thrombus in another deep vein in the leg or arm affected by the previous thromboembolic event; or a thrombus in the same venous system affected in the previous event, with proximal extension of the thrombus (if the upper limit of the original thrombus had been visible) or with a constant-filling defect surrounded by contrast medium (if the original thrombus had not been visible). Diagnosis was established by an adjudication committee that consisted of independent clinicians and radiologists.

Blood Sampling and Laboratory Analysis

Venous blood was collected with subjects in the fasting state after normalization of the prothrombin time (\textasciitilde3 weeks after vitamin K antagonist discontinuation), and plasma and genomic DNA were prepared as described previously.\textsuperscript{2} Levels of antithrombin, protein C, protein S, factor V Leiden, prothrombin 20210A, factor VIII, and the lupus anticoagulant were determined.\textsuperscript{2} Plasma levels of apolipoproteins AI and B were measured with immunoturbidimetric assays (DiaSorin; Stillwater, Minn).\textsuperscript{12}

Proton nuclear magnetic resonance (NMR) spectroscopy\textsuperscript{12,14,19} was used to determine levels of 10 lipoprotein subclasses (chylomicron/large very-low-density lipoprotein [VLDL], intermediate VLDL, small VLDL, intermediate-density lipoprotein, large LDL, small LDL also reported as medium small LDL and very small LDL, large HDL, medium HDL, and small HDL) and of lipids in citrated plasma. NMR-derived lipoprotein particle levels are based on the NMR signals that are characteristic of typical lipoprotein particles and are not actual lipid measurements. The NMR spectroscopy methodology was used to calculate HDL and LDL cholesterol levels because it exhibits a very strong correlation with conventional determinations for plasma lipids.\textsuperscript{19}

Statistical Analysis

For numerical operations, SPSS 12.0 software (SPSS, Inc, Chicago, Ill) was used. To test for homogeneity between strata, we applied the log-rank and the generalized Wilcoxon test. Categorical data were checked for homogeneity with contingency table analyses (by the \( \chi^2 \) test), and continuous data (presented as mean \pm SD) were compared with the Mann-Whitney U test. Time to recurrence (possibly censored) was analyzed according to survival methods. Probability of recurrence was estimated according to Kaplan and Meier.\textsuperscript{20} Cox proportional hazards models were used to analyze the unadjusted and adjusted (for age and sex) effects between apolipoprotein AI and B levels and risk of recurrence. For a substudy of NMR-derived lipoprotein particle levels, 71 patients who had recurrent VTE within 3 years after study entry were compared with twice the number of patients without recurrence within 3 years after study entry (n = 142). Matching was based on sex and age (\textasciitilde3 years). In this substudy, apolipoprotein AI levels, HDL cholesterol, and large HDL particle concentrations were compared for sex and recurrence status by means of split-plot ANOVA, taking into account the matching as a random factor, the within-block factor of recurrence status, and the between-blocks factor of sex as a fixed factor.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

We studied 772 patients (440 women [57\%]) with a first spontaneous VTE, for whom the mean age was 47 \pm 16 years and median follow-up was 48 months. The baseline characteristics of these patients are shown in Table 1. A total of 192 patients eventually left the present study because of pregnancy (33 patients) or a diagnosis of cancer (15 patients) or because they required antithrombotic therapy for reasons other than VTE (112 patients); 15 patients were lost to follow-up; and 17 patients died, 2 of them due to recurrent

| TABLE 1. Baseline Characteristics of 772 Patients With First VTE |
|-----------------|-------------------|
| Characteristic   | Value             |
| Age at first VTE, y | 47 \pm 16 |
| Sex (male/female), n | 332/440 |
| Site of thrombosis, n (%) | Deep vein thrombosis: 344 (45) |
| Pulmonary embolism | 428 (55) |
| Factor V Leiden, n (%) | 220 (29) |
| Prothrombin G20210A, n (%) | 56 (7) |
| Factor VIII, IU/dL | 165 \pm 48 |
| Factor IX, IU/dL | 119 \pm 27 |
| Duration of oral anticoagulation, mo | 8 \pm 8 |
| Observation time, mo | 47 \pm 37 |
VTE. The patients were monitored until they left the study, when data were censored.

VTE recurred in 100 of 772 patients. The site of recurrence was deep vein thrombosis in 61 patients and pulmonary embolism in 39 patients. Patients with recurrence had significantly higher levels of factor VIII (179 ± 54 versus 163 ± 46 IU/dL, *P* = 0.02) and factor IX (129 ± 27 versus 118 ± 26 IU/dL, *P* < 0.001), had a shorter observation time (26 ± 24 versus 51 ± 38 months, *P* < 0.001), and were older (51 ± 15 versus 47 ± 17 years, *P* = 0.02) than those without recurrence. The proportion of heterozygous carriers of either factor V Leiden or prothrombin 20210A was not significantly different between patients with recurrence and those without recurrence (34% versus 24%, *P* = 0.2, and 11% versus 6%, *P* = 0.1, respectively).

### Recurrent VTE and Apolipoprotein AI

Patients with recurrent VTE had significantly lower levels of apolipoprotein AI than those without recurrence (1.12 ± 0.22 versus 1.23 ± 0.27 mg/mL, *P* = 0.001). When apolipoprotein AI was entered as a continuous variable in a Cox proportional hazard model, the relative risk of recurrence was 0.87 (95% CI, 0.80 to 0.94) for each 0.1-mg/mL increase in apolipoprotein AI level, and this remained unchanged after adjustment for age and sex (relative risk 0.87, 95% CI, 0.79 to 0.95).

Because the present study was a hypothesis-generating study, we did not predefine cutoff values for apolipoprotein AI levels but rather investigated the strength and linearity of an association between apolipoprotein AI and risk of recurrence by calculating relative risks for various apolipoprotein AI levels. The strongest association between apolipoprotein AI and recurrent VTE was found at a cutoff level of 1.30 mg/mL, which corresponds to the lower limit of the third tertile of the present study cohort (Table 2). Compared with patients with apolipoprotein AI levels in the lowest tertile (<1.07 mg/mL), the relative risk of recurrence was lower (0.78 [95% CI, 0.50 to 1.22]) for midtertile patients (apolipoprotein AI of 1.07 to 1.30 mg/mL) and much lower (0.46 [95% CI, 0.27 to 0.77]) for patients in the highest tertile (apolipoprotein AI ≥ 1.30 mg/mL). Adjustment for age and sex did not substantially influence these findings (Table 2).

According to Kaplan-Meier analysis, the cumulative probability of recurrence after 4 years was 8.8% (95% CI, 4.6% to 12.9%) among patients with apolipoprotein AI levels >1.3 mg/mL, compared with 13% (95% CI, 8.3% to 17.7%) among those with apolipoprotein AI levels of 1.07 to 1.30 mg/mL and 18.7% (95% CI, 13.1% to 24.3%) among patients with apolipoprotein AI levels <1.07 mg/mL (Figure 1). A significant divergence was found between patients with apolipoprotein AI levels >1.3 mg/mL and the other 2 groups (*P* = 0.002 compared with patients with apolipoprotein AI levels <1.07 mg/mL and *P* = 0.05 compared with patients with apolipoprotein AI levels of 1.07 to 1.30 mg/mL). Patients with lower apolipoprotein AI levels were younger and had slightly higher body mass index.

### Table 2. Relative Risks of Recurrent VTE According to Tertiles of Apolipoprotein AI Plasma Concentrations

<table>
<thead>
<tr>
<th>Apolipoprotein AI</th>
<th>No. of Patients</th>
<th>No. of Recurrences</th>
<th>Unadjusted Relative Risk (95% CI)</th>
<th>Adjusted* Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.07 mg/mL</td>
<td>243</td>
<td>43</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>1.07 to 1.30 mg/mL</td>
<td>267</td>
<td>36</td>
<td>0.78 (0.50–1.22)</td>
<td>0.76 (0.48–1.21)</td>
</tr>
<tr>
<td>&gt;1.30 mg/mL</td>
<td>262</td>
<td>21</td>
<td>0.46 (0.27–0.77)</td>
<td>0.50 (0.28–0.88)</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex.

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**Figure 1.** Kaplan-Meier estimates of the probability of recurrent VTE according to tertiles of apolipoprotein (Apo) AI levels.
Apolipoprotein AI levels were significantly lower among men than among women (1.15±0.23 versus 1.26±0.28 mg/mL, P<0.001). Men with recurrence had the lowest apolipoprotein AI levels, whereas women without recurrence had the highest levels (Figure 2). Both men and women without recurrence had higher apolipoprotein AI levels than those with recurrence (P=0.02 and 0.07, respectively; Figure 2).

Apolipoprotein B and Risk of Recurrent VTE
Apolipoprotein B levels were higher among patients with recurrence than among those without recurrence (1.01±0.27 versus 0.96±0.28 mg/mL, P=0.03). Relative risk of recurrence was 1.06 (95% CI, 1.01 to 1.12) for each 0.1-mg/mL increase in apolipoprotein B level and 1.02 (95% CI, 0.96 to 1.09) after adjustment for age and sex. Compared with patients with apolipoprotein B levels lower than 0.84 mg/mL (which corresponds to the lowest tertile), relative risk of recurrence was higher (1.4 [95% CI, 0.8 to 2.3]) among patients with apolipoprotein B levels between 0.84 and 1.04 mg/mL (midtertile) and highest (1.9 [95% CI, 1.1 to 3.1]) among those with the highest levels (≥1.05 mg/mL, upper tertile). After adjustment, the significant increase in risk of recurrence associated with apolipoprotein B levels disappeared (1.0 [95% CI, 0.6 to 1.7] and 1.2 [95% CI, 0.7 to 2.1], respectively).

Recurrent VTE and Lipoprotein Particle Subclass Levels
For a subgroup study of levels of 10 different lipoprotein particles determined by NMR spectroscopy, 71 patients with recurrence were compared with 142 age- and sex-matched patients without recurrence. In this cohort of 213 subjects, the well-known correlation between apolipoprotein AI and HDL cholesterol levels was observed (r=0.93, P<0.001; data not shown). In this subgroup of 213 patients, higher apolipoprotein AI levels conferred a significant decrease in relative risk of recurrence (relative risk 0.86 [95% CI, 0.75 to 0.99] for each 0.1-mg/dL decrease). HDL cholesterol was significantly lower in patients with recurrence than in those without recurrence (P=0.04; Figure 3A). When HDL particle subclasses were analyzed, patients with recurrent VTE had lower levels of large HDL particles than patients without recurrence (P=0.07; Figure 3B). Medium and small HDL particle concentrations did not show an association with recurrence (data not shown). Analysis for VLDL and LDL subclass particle concentrations showed they did not differ significantly for patients with or without recurrence.

Discussion
Significant risk factors for recurrence of venous thrombosis include elevated factor VIII, male sex, antiphospholipid antibodies, and a previous episode of venous thrombosis.\(^1,2\) The present study is prospective in nature and provides strong evidence that apolipoprotein AI levels differ by sex and are an important predictor of recurrent VTE. These findings suggest that apolipoprotein AI levels may provide useful information regarding the risk of recurrence.
Evidence for an association of protection against risk of recurrent venous thrombosis with elevated levels of apolipoprotein AI, the major protein component of HDL. In consecutive patients with a single episode of unprovoked VTE, the risk of recurrence was reduced by half in those with apolipoprotein AI levels greater than the 67th percentile (1.30 mg/mL) compared with those with lower levels. Statistical analyses showed a continuous relationship between risk reduction and elevations in this HDL component. Furthermore, using proton NMR analysis of plasma samples to measure HDL subclasses in a subgroup of patients, we found markedly reduced concentrations of HDL cholesterol, or of large HDL particles or all HDL particles, in patients with recurrent venous thrombosis. Thus, deficiency of HDL, and notably, deficiency of large HDL particles, is associated with recurrent venous thrombosis. These various findings are consistent with the hypothesis that HDL is protective against venous thrombosis.

Male sex is an independent risk factor for venous thrombosis recurrence and conveys a 4-fold greater risk than does female sex, yet an explanation for this sex difference remains elusive. Could the antithrombotic protective activities of HDL provide a clue to this puzzle? Compared with males, females have higher levels of HDL, and sex-linked differences in lipoprotein particle patterns and concentrations are well documented in the Framingham Offspring Study, with females notably having on average a 2-fold higher concentration of large HDL particles. One might therefore speculate that the elevated levels of HDL particles, especially large particles, may contribute, at least in part, to the lower risk of recurrence in females because the elevated levels of protective HDL particles in females afford a greater degree of protection for females against venous thrombosis recurrence.

Whether any particular clinical association is causal or only incidental to another causative factor often requires substantial examination. Both clinical observations and basic laboratory experimentation support the hypothesis that HDL is antithrombotic, at least in the arterial setting, as reviewed recently. HDL can exert multiple antithrombotic direct and indirect actions. In addition to downregulation of thrombin generation via promotion of the anticoagulant action of the protein C pathway, HDL acts directly on the endothelium to minimize prothrombotic reactions via enhancement of endothelial nitric oxide synthase activity and via reduction of leukocyte adhesion to endothelium. Coagulation and inflammation are intimately linked in the body’s host-defense system, and inflammation may contribute to procoagulant processes and thus to both arterial and venous thrombosis.

The metabolism of HDL is remarkably complex. Much effort is currently aimed at increasing HDL cholesterol levels, because decreasing the “bad cholesterol,” ie, LDL, is at best only partially successful in reducing cardiovascular events, and a low level of HDL is an independent risk factor for atherosclerosis and arterial thrombosis. Current efforts are intended to determine whether increasing plasma levels of HDL will decrease atherosclerosis and arterial thrombotic events. Nonpharmacological strategies to increase HDL include regular aerobic exercise, diet, moderate alcohol consumption, and smoking cessation, whereas pharmacological approaches to raise HDL levels include niacin, fibrates, and statins. New drugs that are most advanced include 2 inhibitors of cholesteryl ester transfer protein that markedly raise the levels of large HDL particles by altering lipoprotein metabolism. Assuming that further investigation provides additional support for our novel concept that HDL is protective against venous thrombosis, it may become germane to assess whether various established and novel experimental strategies that raise HDL, such as cholesteryl ester transfer protein inhibitors, have the ability to reduce the risk for first or recurrent venous thrombotic events.

Some specific issues regarding the design and analysis of the present study should be noted. The observed risk of recurrent VTE was lower here than in other trials because we included patients with a low risk of recurrence (ie, patients with distal deep vein thrombosis only) and excluded patients with a known high risk of recurrence, such as those with previous thrombosis; deficiency of antithrombin, protein C, or protein S; the lupus anticoagulant; cancer; or high factor VIII. AUREC is a hypothesis-generating cohort study, which precludes predefinition of certain cutoff values of continuous plasma analytic levels. The strength and linearity of an association between apolipoprotein AI or apolipoprotein B levels and risk of recurrence were investigated by calculating relative risks for arbitrary apolipoprotein AI and apolipoprotein B cutoff levels, with the results reported here. These results merit further study, including replication in other patient populations. Additional studies are needed to determine whether 1 or more HDL parameters (eg, apolipoprotein AI or HDL cholesterol) might be of value to clinicians for risk assessment of individual patients.

In summary, patients with high levels of apolipoprotein AI, HDL cholesterol, and large HDL particles have a decreased risk of recurrent VTE. This finding may justify further clinical studies to assess whether strategies to elevate HDL using lifestyle changes or medications will reduce risk for venous thrombosis.

Sources of Funding
This work was supported in part by grants from the National Institutes of Health (HL52246, HL07195, and HL21544) and by grants from the Jubilaeumsfonds of the Österreichische Nationalbank and the Medizinisch-Wissenschaftlicher Fonds des Bürgermeisters der Bundeshauptstadt Wien.

Disclosures
The Scripps Research Institute owns rights to a pending patent application that is concerned with HDL as a risk factor for venous thrombosis. Drs Eichinger and Kyrlle have received research grants from Jubilaeumsfonds of the Österreichische Nationalbank and Medizinisch-Wissenschaftlicher Fonds des Bürgermeisters der Bundeshauptstadt Wien. Dr Pecheniuk is employed by the Scripps Research Institute. Dr Deguchi has received a research grant from the National Institutes of Health (HL07195) and is employed by the Scripps Research Institute. Dr Griffin has received a research grant from the National Institutes of Health (HL52246 and HL21544), honoraria from Pfizer, served as a consultant/advisory board member of Pfizer, and is employed by the Scripps Research Institute. The remaining authors report no conflicts.
Dyslipidemia and dyslipoproteinemia are established risk factors of arterial thrombosis, and lipid-lowering drugs are a cornerstone in preventing arterial ischemic events. There is evidence that arterial and venous thrombotic disease share some risk factors, including age, male sex, elevated body weight, lupus anticoagulant, and hyperhomocysteinemia. The relevance of dyslipoproteinemia for occurrence of venous thrombosis is unclear. To investigate the association between high-density lipoprotein (HDL) and recurrent venous thrombosis, we conducted the present prospective cohort study and monitored 772 patients with first unprovoked venous thrombosis for a mean of 4 years. The principal finding was that HDL parameters (apolipoprotein A-I, HDL cholesterol, and large HDL particles) are protective against recurrence. The risk of recurrent venous thrombosis was reduced by half in patients with apolipoprotein AI levels >1.30 mg/mL compared with those with lower levels. As in arterial disease, women with venous thrombosis had higher levels of HDL parameters than men. This observation can partially explain our previous finding that men have a higher risk of recurrent venous thrombosis than women. Our present study may inspire researchers to conduct clinical trials to assess whether strategies to elevate HDL using lifestyle changes or medications will reduce risk for venous thrombosis.
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Circulation. 2007;115:1609-1614; originally published online March 19, 2007; doi: 10.1161/CIRCULATIONAHA.106.649954

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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