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Lipoprotein(a), Polymorphisms in the *LPA* gene and Incident Venous Thromboembolism Among 21,483 Women

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Lipoprotein(a) (Lp(a)) is composed of a low density lipoprotein (LDL)-like particle with apoB-100 linked to the apolipoprotein(a) component. Elevated levels relate to increased risk of arterial disease.[1, 2] Lp(a) has structural homology to plasminogen,[3] may compete for binding to fibrin, inhibit tissue plasminogen activator, impair fibrinolysis and promote thrombosis by conveying a hypercoagulable state. Disparate data exist, however, in terms of whether Lp(a) relates to increased incidence of VTE, as some[4–6] but not all[7–9] studies have reported positive associations. To address whether circulating Lp(a) levels impact the development of VTE, we assessed its relationship to incident VTE. In addition, more than 90% of the variation in plasma lipoprotein concentrations may be attributable to the apolipoprotein(a) gene [10] and two common polymorphisms in the *LPA* gene, rs3798220 and rs10455872 may account for at least 40% of variation in Lp(a) levels[2]. Therefore, the relation of these polymorphisms to VTE was assessed.

We assessed these questions in the Women's Health Study.[11] In brief, this randomized trial evaluated the risks and benefits of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer.[11] During the run-in period, 28,345 women provided blood samples, plasma aliquots of which were stored in liquid nitrogen (−150 to −180°C) until biochemical analyses. Over a median follow-up of 14.4 years, VTE was collected and confirmed. Deep vein thrombosis was confirmed by a positive report of venous ultrasound or venography, and pulmonary embolism confirmed by positive angiogram, chest computed tomography scan or ventilation-perfusion scan with 2 mismatched defects. VTE was classified as unprovoked if it occurred in the absence of any recent trauma, hospitalization, surgery within 3 preceding months of the event and in the absence of a malignant condition that was diagnosed before or up to 3 months after the event, and as provoked if it occurred in a patient with cancer or if it occurred during or shortly after trauma, hospitalization, or surgery.

Lp(a) measurement was performed in a core laboratory certified by the NHLBI /CDC Prevention Lipid Standardization Program. We used the only commercially available assay, not affected by Kringle IV-Type 2 repeats, as assessed by a NHLBI and International Federation of Clinical Chemistry standardization group.[12] The turbidimetric assay used reagents and calibrators from Denka Seiken (Niigata, Japan) on the Hitachi 917 analyzer

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Conflict of Interest There are no additional conflicts to disclose.

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(Roche Diagnostics - Indianapolis, IN). The intraassay coefficients of variation at Lp(a) concentrations of 17.6 and 58.1 mg/dL were 3.6 and 1.5%, respectively. Genotyping of the two polymorphisms were performed as described previously for the rs3798220 polymorphism[13] and imputed for rs10455872 with a r^2 value of 0.52 (MaCH R^2>0.3). [14] The population reported in this evaluation is comprised of the Women's Health Study cohort who were Caucasian, and who were successfully assayed for Lp(a) and polymorphisms in Lp(a) (n=21,483).

To evaluate the association between plasma Lp(a) levels and VTE, we divided the population according to quintiles of Lp(a) levels and assessed the hazard ratios of future VTE in Cox proportional hazard models, comparing quintiles 2 through 5 to the lowest (referent) quintile. Hazard ratios were estimated in models adjusting for age only, and then in models adjusting for baseline covariates important to the development of venous thrombosis: age (years), smoking (current vs. other), body mass index (World Health Organization categories <25, 25–29.9, ≥30 kg/m^2), hormone therapy status (current vs. other at baseline), physical activity level (four categories of number of times exercise/week) and randomization treatment arms. Models were run both with and without BMI with similar results.

At study entry, the women were on average 54.2 years old (standard deviation 7.1), with body mass index of 25.9 (SD 5.0) kg/m^2. 2,499 women (11.6%) smoked, 538 women (2.5%) had history of diabetes, 5,271 women (24.5%) had history of hypertension. The median Lp(a) level was 10.4 mg/dL. 439 women developed venous thromboembolism (259 DVT, 115 pulmonary emboli; 65 women with both events), over a median follow-up time period of 14.4 years. Of these, 241 were provoked, 186 unprovoked and 12 of indeterminate type. For women with multiple events, time to development of the first was considered.

The table presents the age and multivariable-adjusted hazard ratios for future VTE according to quintiles of Lp(a). There was no relationship seen between quintiles of Lp(a) and development of total, unprovoked or provoked VTE (adjusted HR for total VTE was 1.04 [95% CI 0.77–1.41]; for unprovoked VTE 0.96 [95% CI 0.61–1.50]; and for provoked VTE 1.17 [95% CI 0.77–1.79] all comparing highest to lowest quintile of Lp(a)).

Additional analyses was performed to evaluate for evidence of threshold effects between increasing levels of Lp(a) and risk of future VTE, we utilized prespecified cutoffs at the 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th} and 99^{th} percentiles of baseline Lp(a) levels, calculating hazard risks for individuals with Lp(a) levels exceeding each of these thresholds. Only extremely high values (≥99^{th} percentile or 130.6 mg/dL) showed relationship to provoked VTE (adjusted HR 2.55 [95% CI 1.13–5.74]) compared to those with levels <99^{th} percentile, with marginal relationship to total VTE (adjusted HR 1.88 [95% CI 0.93– 3.78]).

In addition, we saw no relationship of the rs3798220 polymorphism in *LPA* with incident VTE (adjusted hazard ratios for overall VTE were 1.36 [95% CI 0.88–2.11]; unprovoked VTE 1.69 [95% CI 0.92–3.12]; and provoked VTE 1.18 [95% CI 0.62–2.22]). Similarly, there was no relationship of rs10455872 with incident VTE (adjusted hazard ratio was 1.04 [95% CI 0.72–1.50]; unprovoked VTE 1.12 [95% CI 0.64–1.94]; and provoked VTE 1.01 [95% CI 0.61–1.67]). For rs3798220, both additive and dominant models of inheritance were tested and Cox proportional hazard models were constructed using time to VTE and regressing on the *LPA* SNP. Rs10455872 was an imputed SNP that ranged from 0–2, with 2 indicating likely carriage of two minor variants; it was modeled as a continuous variable.

The data expand on varying evidence regarding plasma Lp(a) levels and VTE, as some [4–6, 15] but not all [7, 9, 16] studies have shown an association of Lp(a) with VTE. Our findings are concordant with those of the Longitudinal Investigation of Thromboembolism Etiology

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study (LITE) study that pooled the Atherosclerosis Risk in Communities Study (ARIC) and Cardiovascular Health Study (CHS) studies and found no relationship between Lp(a) levels (>30 mg/dL) and VTE[8].

Strengths of this study include its prospective nature and use of a reliable mass-based assay[12] to measure circulating levels of Lp(a). Some of the prior discrepant findings of studies regarding Lp(a) levels and VTE may be due in part to difficulty in measuring Lp(a). This study benefits from the well-characterized profiles of participants that allow adjustment for VTE risk factors such as smoking and hormone therapy. Limitations include the female-only nature of the cohort, that the cohort is comprised of health care workers which may limit its generalizability, and that there was single measurement of Lp(a) although levels are stable over time.[10]

This study shows that there is little evidence of relationship between quintiles of Lp(a) and total, unprovoked or provoked VTE. Analysis for threshold effects show only rare, extremely elevated values of Lp(a) (≥ 99th percentile, 130.6 mg/dL) may relate to VTE. In addition, the rs3798220 and rs10455872 polymorphisms in the *LPA* gene, while related to circulating Lp(a) levels, are not significantly related to venous disease. Unlike the reported relationships of Lp(a) with arterial disease, there was no evidence of relationship of circulating Lp(a) levels or Lp(a) polymorphisms with future venous thromboembolism in this large cohort.

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References

1. Danik JS, Rifai N, Buring JE, Ridker PM. Lipoprotein(a), measured with an assay independent of apolipoprotein(a) isoform size, and risk of future cardiovascular events among initially healthy women. JAMA. 2006; 296:1363–1370. [PubMed: 16985228]
2. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009; 361:2518–2528. [PubMed: 20032323]

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3. McLean JW, Tomlinson JE, Kuang WJ, Eaton DL, Chen EY, Fless GM, Scanu AM, Lawn RM. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. Nature. 1987; 330:132–137. [PubMed: 3670400]
4. Marcucci R, Liotta AA, Cellai AP, Rogolino A, Gori AM, Giusti B, Poli D, Fedi S, Abbate R, Prisco D. Increased plasma levels of lipoprotein(a) and the risk of idiopathic and recurrent venous thromboembolism. Am J Med. 2003; 115:601–605. [PubMed: 14656611]
5. von Depka M, Nowak-Gottl U, Eisert R, Dieterich C, Barthels M, Scharrer I, Ganser A, Ehrenforth S. Increased lipoprotein (a) levels as an independent risk factor for venous thromboembolism. Blood. 2000; 96:3364–3368. [PubMed: 11071628]
6. Sofi F, Marcucci R, Abbate R, Gensini GF, Prisco D. Lipoprotein (a) and venous thromboembolism in adults: a meta-analysis. Am J Med. 2007; 120:728–733. [PubMed: 17679133]
7. Lippi G, Bassi A, Brocco G, Manzato F, Marini M, Guidi G. Lipoprotein(a) concentration is not associated with venous thromboembolism in a case control study. Haematologica. 1999; 84:726–729. [PubMed: 10457409]
8. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med. 2002; 162:1182–1189. [PubMed: 12020191]
9. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Genetic Evidence That Lipoprotein(a) Associates With Atherosclerotic Stenosis Rather Than Venous Thrombosis. Arterioscler Thromb Vasc Biol. 2012; 32:1732–1741. 10.1161/ATVBAHA.112.248765. [PubMed: 22516069]
10. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest. 1992; 90:52–60. [PubMed: 1386087]
11. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005; 352:1293–1304. [PubMed: 15753114]
12. Marcovina SM, Albers JJ, Scanu AM, Kennedy H, Giaculli F, Berg K, Couderc R, Dati F, Rifai N, Sakurabayashi I, Tate JR, Steinmetz A. Use of a reference material proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to evaluate analytical methods for the determination of plasma lipoprotein(a). Clin Chem. 2000; 46:1956–1967. [PubMed: 11106328]
13. Shiffman D, O'Meara ES, Bare LA, Rowland CM, Louie JZ, Arellano AR, Lumley T, Rice K, Iakoubova O, Luke MM, Young BA, Malloy MJ, Kane JP, Ellis SG, Tracy RP, Devlin JJ, Psaty BM. Association of gene variants with incident myocardial infarction in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. 2008; 28:173–179. ATVBAHA.107.153981 [pii] 10.1161/ATVBAHA.107.153981. [PubMed: 17975119]
14. Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. Genetic epidemiology. 2010; 34:816–834. 10.1002/gepi.20533. [PubMed: 21058334]
15. Nowak-Gottl U, Junker R, Hartmeier M, Koch HG, Munchow N, Assmann G, von Eckardstein A. Increased lipoprotein(a) is an important risk factor for venous thromboembolism in childhood. Circulation. 1999; 100:743–748. [PubMed: 10449697]
16. Vormittag R, Vukovich T, Stain M, Lehr S, Minar E, Pabinger I. Lipoprotein (a) in patients with spontaneous venous thromboembolism. Thromb Res. 2007; 120:15–20. [PubMed: 16643992]

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Table

Hazard ratios of future venous thromboembolic events among initially healthy women according to Lp(a) quintiles at study entry

Lp(a) median (range), mg/dL	**Quintile 1 1.90 (0.10–3.40)**	**Quintile 2 5.40 (3.50–7.40)**	**Quintile 3 10.40 (7.50–14.90)**	**Quintile 4 23.80 (15.00–43.50)**	**Quintile 5 65.20 (43.60–229.40)**	***P* trend[‡]**
All VTE (n=439)						
Number of VTE events (% with events in quintile)	84 (1.9%)	91 (2.2%)	85 (2.0%)	92 (2.2%)	87 (2.0%)	
Person-years of follow-up	59,656	57,455	58,358	58,011	57,999	
Incidence Rate (95% CI)[*]	1.41 (1.18, 1.74)	1.58 (1.33, 1.95)	1.46 (1.22, 1.80)	1.59 (1.34, 1.95)	1.50 (1.26, 1.85)	
Age-adjusted HR (95% CI)	1	1.14 (0.85, 1.53)	1.02 (0.75, 1.38)	1.10 (0.82, 1.48)	1.03 (0.77, 1.40)	0.92
Fully-adjusted[†] HR (95% CI)	1	1.13 (0.84, 1.53	1.06 (0.78, 1.44	1.13 (0.84, 1.52)	1.04 (0.77, 1.41)	0.89
Unprovoked VTE (n=186)[§]						
Number of Unprovoked Venous Thromboembolic Events	39 (0.9%)	32 (0.8%)	41 (1.0%)	37 (0.9%)	37 (0.9%)	
Incidence Rate (95% CI)[*]	0.65 (0.50, 0.89)	0.56 (0.42, 0.79)	0.70 (0.54, 0.95)	0.63 (0.49, 0.88)	0.64 (0.49, 0.88)	
Age-adjusted HR (95% CI)	1	0.86 (0.54, 1.37	1.06 (0.69, 1.65)	0.96 (0.61, 1.50	0.95 (0.61, 1.49)	0.93
Fully-adjusted[†] HR (95% CI)	1	0.84 (0.53, 1.35)	1.09 (0.70, 1.70)	1.00 (0.63, 1.56)	0.96 (0.61, 1.50)	0.95
Provoked VTE (n=241)						
Number of Unprovoked Venous Thromboembolic Events	41 (0.9%)	58 (1.4%)	42 (1.0%)	52 (1.2%)	48 (1.1%)	
Incidence Rate (95% CI)[*]	0.69 (0.53, 0.93)	1.01 (0.81, 1.31)	0.72 (0.56, 0.97)	0.90 (0.71, 1.18)	0.83 (0.65, 1.10)	
Age-adjusted HR (95% CI)	1	1.49 (1.00, 2.22)	1.03 (0.67, 1.58)	1.27 (0.84, 1.91)	1.16 (0.77, 1.76)	0.99
Fully-adjusted[†] HR (95% CI)	1	1.51 (1.01, 2.26)	1.09 (0.71, 1.68)	1.30 (0.86, 1.96)	1.17 (0.77, 1.79)	0.95

[*] Incident events per 1000 person-years.

[†] Fully-adjusted models refer to covariates of age, smoking, body mass index, hormone therapy status, exercise level and randomization treatment arms.

[‡] Tests for trends across quintiles of Lp(a) were addressed by entering a single ordinal term for each quintile based on the median value for Lp(a) within each quintile.

[§] Type of VTE was not assigned in 12 individuals who developed VTE.

In sensitivity analyses, additional models were run without adjustment for BMI and with and without adjustment for alcohol use, without significant change.