Lipoprotein(a) as a Risk Factor for Venous Thromboembolism: A Systematic Review and Meta-analysis of the Literature

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Abstract

Elevated plasma levels of lipoprotein(a) (Lp(a)) are associated with increased cardiovascular risk in several clinical studies. However, there is a lack of data supporting a positive association between elevated Lp(a) levels and venous thromboembolism (VTE). Thus, we conducted a systematic review of the literature to better clarify its role as a risk factor for VTE. Medline and the Embase (up to May 2015) electronic databases were used to identify potentially eligible studies. Studies measuring Lp(a) values in adult patients with deep vein thrombosis and/or pulmonary embolism and in a population of patients without a VTE were selected. Studies on patients with major venous thromboembolic events occurring at other unusual site, case reports, and case series were excluded. The odds ratios (ORs) of the association between high values of Lp(a) and VTE and the weighted mean difference (WMD) in Lp(a) levels in cases and in controls were calculated using a random-effect model. Results were presented with 95% confidence interval (CI). Fourteen studies for a total of more than 14,000 patients were finally included in our analysis. Lp(a) was slightly but significantly associated with an increased risk of VTE (OR: 1.56, 95% CI: 1.36, 1.79; 10 studies, 13,541 patients). VTE patients had significantly higher Lp(a) values compared with controls (WMD: 14.46 mg/L, 95% CI: 12.14, 16.78; 4 studies, 470 patients). Lp(a) appeared to be significantly associated with increased risk of VTE. However, Lp(a) levels were only slightly increased in VTE patients compared with controls.

Keywords
- venous thromboembolism
- thrombosis
- lipoprotein(a)

Lipoprotein(a) (Lp(a)) is a complex serum lipoprotein consisting of a low-density lipoprotein core associated by a disulfide bond with apolipoprotein(a), a heterogenous glycoprotein that, due to its structural homology with plasminogen, competes for fibrin binding, inhibits tissue plasminogen activator, and ultimately impairs fibrinolysis.[1,2] It has been recognized that more than 90% of variation of plasma Lp(a) concentration is genetically regulated, with apolipoprotein(a) gene (*LPA*) being a major determinant. To date, several genetic variants in the *LPA* gene have been shown to influence Lp(a) plasma values, rs3798220 and rs10455872 polymorphisms accounting in particular for at least 40% of such variation.[3] Because of its dual nature (i.e., proatherosclerotic low-density lipoprotein-like and prothrombotic plasminogen-like), Lp(a) has been the subject of intense research over the past 20 years from both in vivo and in vitro studies that have analyzed its

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prothrombotic properties.[4–6] Elevated plasma levels of Lp(a) were found to be associated with an increased cardiovascular risk in several retrospective and prospective clinical studies.[1] Notably, a meta-analysis of almost 5,500 patients with coronary artery disease prospectively followed up for an average of 10 years reported that individuals with Lp(a) values in the top tertile had an approximately 70% increased risk of coronary artery disease events compared with individuals with values in the bottom tertile.[7] Although convincing epidemiological evidences were brought forward to propose a causal role of Lp(a) in the development, progression, and complication of occlusive arterial disease, data supporting a positive association between elevated Lp(a) values and venous thromboembolism (VTE) are less consistent. A previous systematic review and meta-analysis of the literature conducted a decade ago and including a limited number of studies found a statistically significant, albeit modest, association between high Lp(a) (>300 mg/L) and VTE (odds ratio [OR]: 1.87, 95% confidence interval [CI]: 1.51–2.30).[8] On the other hand, a more recent study reported an association between two variants of the *LPA* gene (rs10455872 and rs3798220 polymorphisms) and systemic and coronary atherosclerosis, but not with VTE.[9] Therefore, to better clarify the role of Lp(a) as a risk factor for VTE, we conducted an extensive systematic review of the literature updating the results of the previous meta-analysis.

Methods

A protocol for this review was prospectively developed, detailing specific objectives, criteria for study selection, approach to assess study quality, outcomes, and statistical methods.

Search Strategy

Using the Medline and the Embase (up to May 2015) electronic databases without any language restriction, we identified all published studies that evaluated the role of Lp(a) as a potential risk factor for VTE. We supplemented our search by manually reviewing abstract books from the Congress of the International Society on Thrombosis and Haemostasis (ISTH) (2011–2015), and the reference lists of all retrieved articles, manually searching recent issues of thrombosis and hemostasis journals. Search results were reported according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) reporting guidelines.[10]

Study Selection

Two reviewers (V.G. and M.G.) performed the study selection independently, with disagreements solved through discussion and by the opinion of a third reviewer (F.D.) if necessary. Studies were considered potentially eligible for this systematic review if they met the following criteria: they included a population of patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and a population of patients without a VTE (controls); Lp(a) values were measured in both patients with VTE and controls. Patients with major venous thromboembolic events at other unusual sites (e.g., splanchnic vein thrombosis and cerebral vein thrombosis) were not included in our systematic review. Furthermore, studies that only included patients with VTE recurrence were excluded. Finally, we did not include case reports, case series, and studies on patients younger than 18 years.

Data Extraction

Two reviewers (V.G. and M.G.) independently extracted data on study (year of publication, design) and population characteristics (number of patients, mean age, sex). Information on Lp(a) levels in VTE patients and in controls was also collected.

Statistical Analysis and Risk of Bias Assessment

Statistical analysis was performed using Review Manager (Version 5.2) provided by The Cochrane Collaboration (Copenhagen, Denmark). The ORs of the association between high values of Lp(a) and VTE and the weighted mean difference of Lp(a) values in case and in controls were calculated using a random-effect model.[11] The overall effect was tested using Z-scores, and significance was set at $p < 0.05$. Results were presented with 95% CI. Statistical heterogeneity was evaluated using the I^2 statistic and the chi-square Cochrane Q test, which assess the appropriateness of pooling the individual study results.[12] Heterogeneity was considered significant when $p < 0.10$. We also estimated the proportion of VTE in the population that could be attributed to elevated Lp(a) (population-attributable risk [PAR]) with the following formula:

$$\text{PAR} = 100 \times [\text{Prevalence (OR-1)}/\text{Prevalence (OR-1)} + 1]$$

For this calculation, we estimated the prevalence of exposure as frequency of elevated values of Lp(a) (> 300 mg/dL) among control subjects. Publication bias was graphically represented by funnel plots of the effect size versus the standard error.

Results

A total of 262 (90 Medline, 172 Embase) citations were identified by our systematic search (►**Fig. 1**). A total of 216 studies were excluded after title and abstract screening based on the predefined inclusion and exclusion criteria or because they were duplicates. Of the 32 studies retrieved in full text for more in-depth evaluation, 18 were excluded because they did not have a control group without VTE, did not provide information about the number of subjects with Lp(a) values above a pre-specified cut-off, they included children, or they considered patients with VTE other than DVT or PE (e.g., retinal vein occlusion). The interobserver for the study selection was perfect. Thus, 14 studies for a total number of 2,824 cases of VTE and 11,187 controls were included in our systematic review.[13–26] Baseline characteristics of the included studies are summarized in ►**Table 1**. Only one study provided separate data of patients with unprovoked VTE[22] and two studies also included patients with two or more episodes of VTE (15.5% in the study by Vormittag et al and 23% in the study by Marcucci et al).[18,22]

Association between Lp(a) value and the risk of VTE was evaluated in 10 studies[13–22] for a total of 2,607 VTE patients

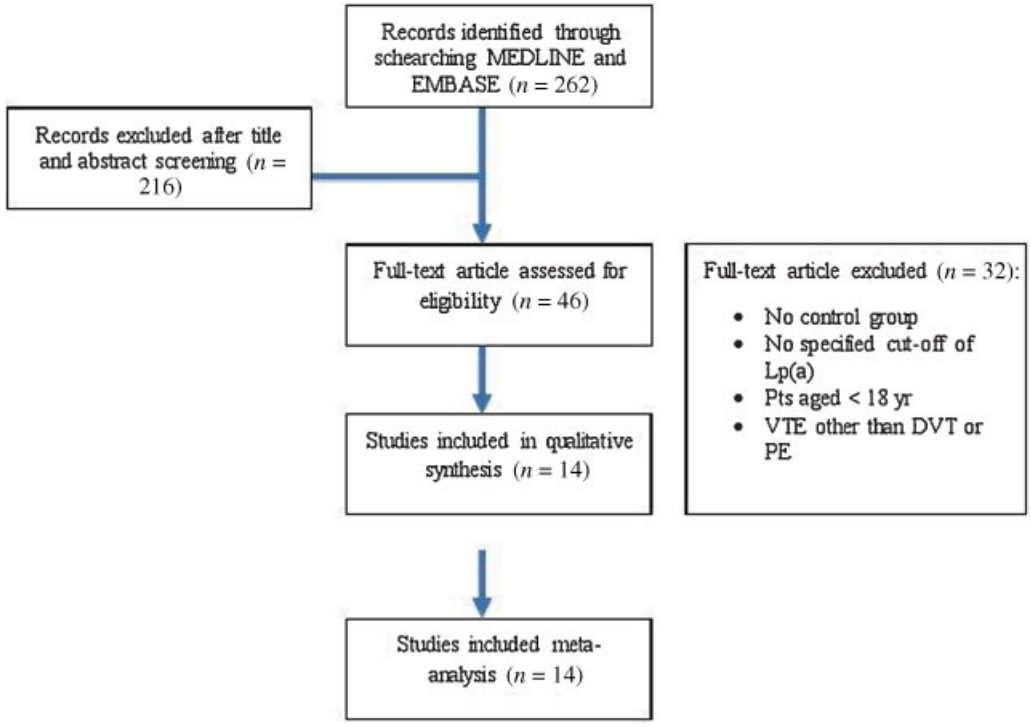

Fig. 1 Results of the systematic search.

and 10,934 controls. Lp(a) cut-off used for the analysis was the upper limit of the manufacturer's product reference range (usually 300 mg/L) in nine studies[13–16,18–22] and the 75th percentile of Lp(a) value in the control group in one study. [14] Lp(a) was significantly associated with an increased risk of VTE (OR: 1.56, 95% CI: 1.36, 1.79; ►**Fig. 2**). The estimated attributable risk of VTE conferred by elevated levels of Lp(a) was 19.8%. Heterogeneity among studies was significant (I^2: 77%, chi-square: 39.67; $p < 0.001$). Exclusion from the analysis of the study performed by Kamstrup et al significantly lowered the heterogeneity among the studies (I^2: 56%; $p = 0.02$).[16]

The funnel plots of effect size versus standard error appeared symmetrical, suggesting the absence of publication bias (►**Fig. 3**).

Mean value of Lp(a) in cases and in controls was compared in four studies[23–26] for a total of 470 patients (217 VTE patients and 253 controls). VTE patients had significantly higher Lp(a) levels compared with controls (WMD: 14.46 mg/L, 95% CI: 12.14, 16.78; ►**Fig. 4**). Heterogeneity among the studies was significant (I^2: 95%, chi-square: 62.44; $p < 0.001$). Exclusion from the analysis of the study performed by Ogunyemi et al significantly lowered the heterogeneity (I^2: 75%, $p = 0.02$).[25]

Discussion

Many observations have pointed out that Lp(a) levels may be a risk factor for arterial cardiovascular and cerebrovascular diseases, by inhibiting the activation of transforming growth factor and contributing to the growth of arterial atherosclerotic lesions by promoting proliferation of vascular smooth muscle cells and migration of smooth muscle cells to endothelial cells.[27] Furthermore, Lp(a) may act as a proinflammatory mediator, increasing the lesion formation in atherosclerotic plaques.[27] Due to structural homology with plasminogen, this lipoprotein may also compete with plasminogen for its receptors on endothelial cells, thus leading to diminished plasmin formation, thereby delaying clot lysis and favoring venous thrombosis.[28] However, evidence on its role as a risk factor for venous thromboembolic events remains controversial.[29]

Our meta-analysis, including data from 14 case–control studies for a total of 2,824 VTE patients and 11,187 healthy controls, showed a significant but only slight association between Lp(a) levels and VTE. The risk attributable to the presence of high levels of Lp(a) appeared globally modest (19.8%) and the WMD in Lp (a) values in cases and in controls was only 14.46 mg/L, a value that is likely composed of the analytical variability of the commercial immunoassays used for measuring Lp(a).[30]

In previous meta-analysis performed by Sofi et al,[8] the presence of high Lp(a) values was significantly associated with increased risk of VTE. However, their results were based on six studies for a total of 1,786 VTE patients and 1,024 controls only, and they did not calculate the risk of VTE attributable to the presence of high Lp(a) values, nor did they evaluate the WMD of this parameter in cases and in controls.

In a previous large prospective study performed by Tsai et al, high values of Lp(a) were not found to be significantly associated with increased risk of developing VTE.[31,32] The LITE study included 19,921 participants with no VTE history

Table 1 Baseline characteristics of the included studies

Reference	Cases/ controls, *n*	Cases, description	Lp(a) evaluation	Exclusion criteria	Controls, description	Exclusion criteria	Cut-off
März et al (1990)	203/115	Patients with DVT and/ or PE	Cut-off	Patients with prothrombotic disease and with vitamin K–dependent coagulation factors alterations	Healthy patients		Above the upper limit of the reference range (>300 mg/L)
Van Wersch (1994)	31/69	Patients with DVT (age range: 20–89 y)	Cut-off	Patients taking Lp(a)-lowering drugs. Patients with hypertension, renal, or liver diseases	Healthy volunteers (age range: 20–50 y)	Patients with known cardiovascular disease, cancer, or glucose intolerance	Above the upper limit of the reference range (>361 mg/L)
Császár et al (1995)	25/25	Consecutive patients with PE (age range: 21–77 y)	Mean concentrations ± SD		Consecutive healthy blood donors selected first by sex and then by age (age range: 26–64 y)		NA
Atsumi et al (1998)	31/22	Patients with venous thrombosis in APS	Cut-off		Healthy individuals (age range: 20–41 y)	History of autoimmune, infectious or thrombotic diseases	Above the upper limit of the reference range (>300 mg/L)
McColl et al (2000)	62/98	Women with previous episode of DVT or PE aged <50 y	Mean concentrations ± SD	VTE related to intravenous drug abuse or cancer. Patients taking lipid-lowering drugs or hormonal preparations. Diabetes mellitus, history of arterial disease	Healthy age-matched female individuals	Patients taking lipid-lowering drugs or hormonal preparations. Diabetes mellitus, history of arterial disease	Mean concentrations ± SD
von Depka et al (2000)	685/266	Consecutive patients with history of VTE	Cut-off	Arterial thromboembolism, cancer, laboratory evidence of AP antibodies	Healthy individuals matched for sex and age	History of thromboembolic events	Above the upper limit of the reference range (>300 mg/L)
Libourel et al (2002)	17/136	Factor V Leiden carriers with history of VTE aged >15 y	Cut-off		Factor V Leiden carriers without history of VTE		Levels of Lp(a) above the 75th percentile (216 mg/L) in factor V Leiden carrier's relatives
Marcucci et al (2003)	603/430	Consecutive patients with history of DVT of the limbs or PE who referred to the thrombosis center 6 mo to 1 y after the event	Cut-off	Patients with other types of venous thrombosis, history of arterial thromboembolism, known cancer, or known APS	Healthy subjects: blood donors, partners or friends of the patients in the same geographical areas	History of cardiovascular disease or venous thromboembolic events	Above the upper limit of the reference range (>300 mg/L) which coincides with the 90th percentile of the control group

Table 1 (*Continued*)

Reference	Cases/ controls, *n*	Cases, description	Lp(a) evaluation	Exclusion criteria	Controls, description	Exclusion criteria	Cut-off
Ogunyemi et al (2003)	30/30	Pregnant women with DVT or PE	Mean concentrations ± SD		Pregnant woman matched by age and race without VTE		Mean concentrations ± SD
Aito et al (2007)	43/46	Patients with spinal cord lesion with history of DVT during the acute stage (first 30 d). Age range: 13–78 y	Mean concentrations ± SD	Patients who underwent pneumatic compression to the lower extremities	Patients admitted in the Spinal Unit in the same period, with no history of DVT. Age range: 21–82 y)	Patients who underwent pneumatic compression to the lower extremities	Mean concentrations ± SD
Vormittag et al (2007)	233/122	Consecutive patients with spontaneous symptomatic DVT and/or PE	Cut-off	Pregnancy; cancer; diabetes mellitus; chronic renal, liver, or pancreatic disease; or delivery	Healthy individuals from the same geographic region	History of venous thromboembolism or arterial thrombosis	Above the upper limit of the reference range (> 300 mg/L)
Todorovska et al (2010)	100/100	Patients with confirmed DVT	Mean concentrations ± SD		Voluntary blood donors (age range: 45–50 y)		Mean concentrations ± SD
Grifoni et al (2012)	443/304	Consecutive patients with first episode of DVT and/or PE (age range: 18–88 y)	Cut-off	Patients with known active cancer or known APS	Blood donors or friend in the same geographical area (age range: 19–75 y)	History of cardiovascular disease or VTE patients	Above the upper limit of the reference range (>300 mg/L)
Kamstrup et al (2012)	318/9,424	Patients included in the CGPS and in CCHS study who developed a VTE	Cut-off		Patients included in the CGPS and in CCHS study who did not develop a VTE		Tertiles (highest tertile vs. lowest tertile)

Abbreviations: APS, antiphospholipid syndrome; DVT, deep vein thrombosis; Lp(a), lipoprotein(a); PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

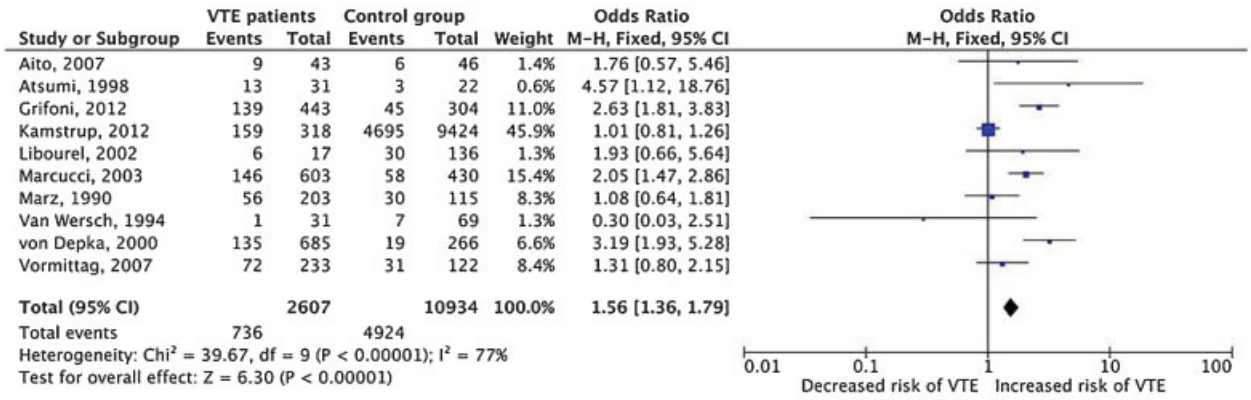

Fig. 2 Forrest plot evaluating the association between elevated levels of Lp(a) and the risk of VTE. CI, confidence interval.

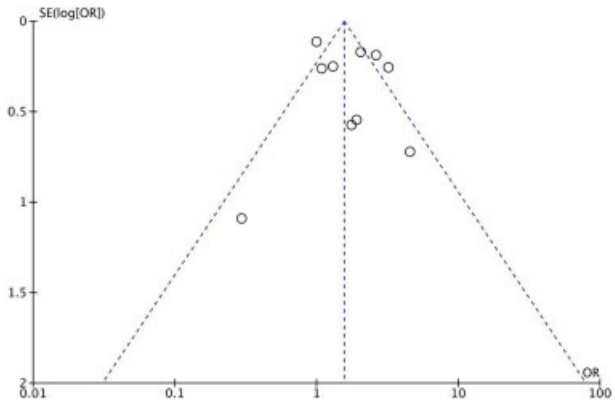

Fig. 3 Funnel plots of effect size versus standard error evaluating the presence of publication bias.

at baseline, were not taking warfarin, and had Lp(a) measured. The age and sex-adjusted hazard ratio for Lp(a) >300 mg/L versus ≤300 mg/L was 1.12 (95% CI: 0.55–2.27) for whites and 1.31 (95% CI: 0.69–2.47) for blacks, thus suggesting that the association between elevated Lp(a) and VTE was likely modest, if any.

Furthermore, Lp(a) appeared to have a limited role in identifying patients at high risk of VTE recurrence. In a quite large prospective study, elevated Lp(a) levels do not appear to be associated with recurrent VTE in patients with history of unprovoked VTE,[33] and no study has demonstrated that Lp (a)-lowering therapy might be beneficial in reducing the incidence of VTE recurrence, at least in some subgroups of patients with high Lp(a) levels.

Therefore, the results of our meta-analysis confirm the questionable role of Lp(a) as a risk factor for VTE. Overall, Lp (a) appeared a weak risk factor for venous thrombosis, so that its extensive evaluation outside the context of clinical research in patients with a previous VTE does not appear justified, also considering that the current methods available on the market are quite expensive.

Our meta-analysis has several potential limitations. First, the application of formal meta-analytic methods to observational studies is controversial, because inherent bias in the study design may misrepresent the strength of associations within data.[10] To minimize this potential bias, we included only studies in which the diagnosis of venous thromboembolic event was objectively confirmed. Second, studies included in our meta-analysis have different inclusion and exclusion criteria, and to combine results across studies may be inappropriate. Furthermore, the heterogeneity among the studies was significant, suggesting caution in the interpretation of the results. Different study design and difference in the population evaluated (e.g., pregnant patients) may explain heterogeneity among the studies. Another important drawback is the use of different methods for measuring Lp(a), each of which displays different performance due to the heterogeneity of the molecule being measured. Due to the lack of universal standard and reference antibodies, the size effects of larger or different isoforms may lead to conflicting conclusions when pooling data.[34] However, we decided to combine our results using the random-effect model, an approach that takes into account the variance among the studies. Third, due to the limits of a study-level meta-analysis, we were not able to

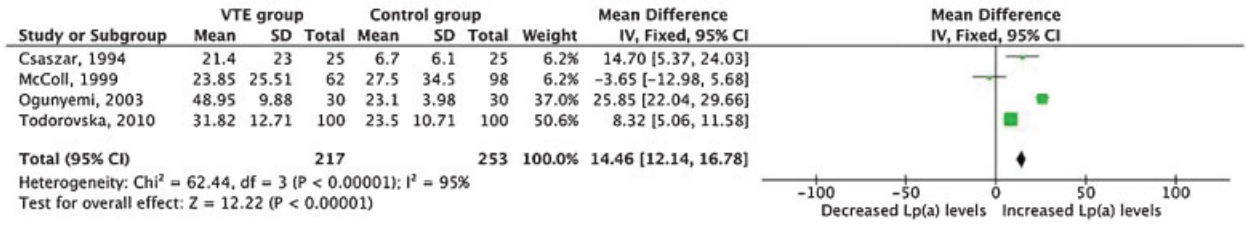

Fig. 4 Forrest plot evaluating the weighted mean difference in Lp(a) levels in VTE cases and in controls. CI, confidence interval.

adjust our results for these potential risk factors; therefore, we could not analyze the association with specific subgroup of patients (e.g., patients with unprovoked VTE). Finally, although an extensive research of the literature was performed and the funnel plots of effect size versus standard error appeared symmetrical, the presence of publication bias, albeit extremely unlikely, could not be definitively excluded.

In conclusion, Lp(a) appeared to be significantly associated with increased risk of VTE. However, Lp(a) levels were only slightly increased in VTE patients compared with controls and the heterogeneity of the analytical techniques is still a cause for large bias. Thus, an extensive evaluation of this parameter in all the patients with a previous VTE does not appear justified. Other prospective studies evaluating the role of Lp(a)-specific subgroups of patients with VTE (e.g., patients with an unprovoked event) are still warranted.

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