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Association between baseline lipoprotein (a) levels and restenosis after coronary stenting: Meta-analysis of 9 cohort studies

Shan-yu Qin [a,1], Jie Liu [b,1], Hai-xing Jiang [a], Bang-li Hu [c], You Zhou [d,*], Vesa M. Olkkonen [d,**]

[a] First Affiliated Hospital of Guangxi Medical University, Nanning 530021, China
[b] People's Hospital of Guangxi Zhuang Autonomous Region, 530021, China
[c] Guangxi Medical Information Institute, Nanning 530021, China
[d] Minerva Foundation Institute for Medical Research, Biomedicum 2U, Tukholmankatu 8, FI-00290 Helsinki, Finland

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ABSTRACT

Background: Previous studies have shown inconsistent results on the association between baseline plasma Lipoprotein (a) [Lp(a)] levels and in-stent restenosis (ISR) after coronary stenting.
Objective: We conducted a meta-analysis of observational studies to assess the association between baseline Lp(a) levels and the restenosis after successful coronary stenting.
Methods: We searched for studies without language restriction in PubMed, Embase, Cochrane library, Ovid library database prior to October 2012. Random-effects method was applied to estimate the pooled standard mean difference (SMD). Heterogeneity, sensitivity and subgroup analysis were used to evaluate the results. Meta-regression analysis was employed to investigate sources of heterogeneity.
Results: 9 cohort studies including 1834 patients (600 ISR and 1234 no-ISR patients) were eligible for our analysis. Overall, we found significantly elevated baseline Lp(a) levels in ISR (in-stent restenosis) patients (SMD = 0.42, 95% CI: 0.14–0.71, $P = 0.003$). High heterogeneity existed between the individual studies ($P < 0.001$, $I^2 = 86.9\%$). The association was stronger in the Asian population than the overall association found. Further, similar observations were made in the subgroup with drug-eluting stent and the group in which Lp(a) was assayed by immunoturbidimetry. Multivariable regression analysis suggested that ethnicity was the major source of heterogeneity in the data ($P = 0.036$).
Conclusions: Our meta-analysis suggests that significantly elevated baseline plasma Lp(a) level is associated with ISR. The Lp(a) level appears to be a good predictor of ISR, especially in the Asian population or patients who received drug-eluting stent implantation. Further research is warranted to evaluate the association by taking the ethnicity and type of stent into account.

1. Introduction

Percutaneous coronary intervention (PCI) with stent implantation is a major and powerful strategy to treat coronary artery disease (CAD). Although drug-eluting stent (DES) has been gradually replacing the bare metal stent (BMS) in the recent clinical practice, the problem of in-stent restenosis, a serious complication after successful coronary stent implantation, remains unresolved [1–3]. The common pathogenic mechanism of ISR is neointimal hyperplasia and extracellular matrix synthesis at the site of stent implantation after PCI [4–6].

Lipoprotein (a) [Lp(a)] is a large low-density lipoprotein (LDL)-like particle, which contains apolipoprotein (a). It plays a role in lipid metabolism and the coagulation and fibrinolytic systems and takes part in the stimulation of smooth muscle cell proliferation [7,8]. Previous studies demonstrated that Lp(a) is a potential risk factor for atherosclerosis and thrombosis. Elevated plasma Lp(a) level has been identified as an independent risk factor causally associated with myocardial infarction [9].

A number of previous studies have explored the association between plasma Lp(a) levels and the risk of restenosis after PCI with stent implantation and found the baseline plasma Lp(a) level to be an independent predictor of stent restenosis. However, other

Abbreviations: Lp(a), lipoprotein (a); ISR, in-stent restenosis; PCI, percutaneous coronary intervention; DES, drug-eluting stent; BMS, bare metal stent; CAD, coronary artery disease; SMD, standard mean difference; 95% CI, 95% confidence interval; SD, standard deviation.

* Corresponding author. Tel.: +358 9 19125711; fax: +358 9 19125701.
** Corresponding author. Tel.: +358 9 19125706; fax: +358 9 19125701.
E-mail addresses: you.zhou@helsinki.fi, yoyo.biooo@gmail.com (Y. Zhou), vesa.olkkonen@helsinki.fi (V.M. Olkkonen).
[1] These authors contributed equally to this work.

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studies reported inconsistent results: Some of them failed to detect any association between Lp(a) levels and ISR after stent implantation [10,11]. The inconsistent results may be due to small sample size, the diverse ethnicities and the implanted stent types. Therefore, by using meta-analysis, we sought to evaluate the relationship between baseline Lp(a) levels and the ISR after PCI with stent implantation.

2. Material and methods

2.1. Search strategy and study selection

In order to find all the studies which examined the association between plasma Lp(a) levels and the ISR after PCI, we conducted a meta-analysis according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [12]. We searched Cochrane clinical trials database, Medline (PubMed), Embase, Chinese Biomedical Database (CBM) and Chinese National Knowledge Infrastructure (CNKI), Ovid library database for publications and conference abstracts prior to October 20th, 2012, using following search terms: "Lipoprotein a" or "Lp(a)" or "Lipoprotein(a)", "stent" and "restenosis". The search was not limited by language or publication status. We searched the references of all retrieved publications and conference proceedings again to trace additional relevant studies. In cases of multiple publications of the same or overlapping data, we selected the most recent ones with the largest number of subjects. Potentially relevant articles were then screened by at least two independent reviewers; disagreements were resolved by discussion or upon consensus from the third reviewer.

2.2. Inclusion and exclusion criteria

Studies that we identified should meet the following criteria: (1) the study design must be a cohort study in human beings [13]; (2) the study must have investigated the association between plasma Lp(a) at the base level and the ISR after stent implantation; (3) the study must have provided sufficient information about Lp(a) level in the patients with in-stent restenosis (ISR group) and without in-stent restenosis (no-ISR group). (4) The end point of the study should be angiographic restenosis which was defined as $\geq$50% diameter stenosis of the culprit lesion by quantitative coronary analysis. (5) The follow-up duration must be at least 6 months. The exclusion criteria were: laboratory studies, review articles, animal studies, studies which had not defined ISR clearly or provided insufficient information of ISR, studies which lacked of plasma Lp(a) level data and the follow-up period was shorter than 6 months.

2.3. Data extraction and quality determination

The extracted data included: (1) first author's last name, the publication year, origin of the studied population; (2) characteristics of the study population (age, diagnoses), methods of Lp(a) assay, stents types, period of follow-up); (3) endpoint evaluations (definitions of ISR and methods of ISR detection); (4) number of patients in ISR group and no ISR group; (5) average levels of Lp(a) at baseline (mean $\pm$ SD). Observational studies have varying quality scoring because of inherent biases and differences in study designs. Instead of providing aggregate scores, we assessed the quality of individual studies by reporting the key components of study designs in accordance with guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [14]. Two blinded reviewers independently performed data extraction. Disagreements between the reviewers were resolved through discussion or by the third reviewer.

2.4. Statistical analysis

Software STATA version 11.0 (Stata Corporation, College Station, TX, USA) was used for all analyses. To accommodate differences in the ways in which Lp(a) was measured and reported in various studies, the absolute Lp(a) levels were converted into a common unit by calculating weighted-effect sizes. These effect sizes or called standard mean differences (SMD) were derived by dividing the mean difference of Lp(a) levels in ISR and no-ISR groups of each study by their SD. We used SMD and corresponding 95% CI to evaluate the estimates of the association between Lp(a) levels and ISR. By assuming that studies are taken from populations with varying effect sizes, we used the random-effects method of DerSimonian and Laird [15].

We assessed the heterogeneity between studies in meta-analysis by the Cochran Q test, and considered P values lower than 0.10 as an indicator of significant heterogeneity because of the low statistical power. We also calculated the inconsistency index I^2 to quantify heterogeneity. I^2 was documented for the percentage of the observed variation between studies which was caused by heterogeneity rather by chance. Generally, we considered I^2 values lower than 25% as an indicator of mild heterogeneity, I^2 values between 25% and 50% correspond to moderate heterogeneity, and I^2 values higher than 50% correspond to large heterogeneity [16].

In addition to exploring sources of heterogeneity, we performed sensitivity test and subgroup analyses. When unexpected heterogeneity was present, sensitivity analyses were performed to assess robustness and examine the results for possible bias. Subgroup analyses were carried out to look at more narrowly drawn subsets of the studies. Furthermore, we applied meta-regression analysis to estimate the extent to which one or more covariates explain heterogeneity. We used the method of moment-base to estimate the variance among studies in the regression analysis [17]. The meta-regression analysis was performed in two steps. First, all of the variables were examined in univariate regression. Second, variables which show statistical significance in the former step were further analyzed in multivariate regression.

To investigate whether publication bias might affect the validity of the estimates, funnel plots were constructed. An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test. It applies linear regression approach to measure funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision [18]. We employed Begg's test as well to assess the publication bias. This test used the rank correlation to investigate the relationship between standardized effect size and sample size or variance in effect size [19]. P values lower than 0.10 were considered to indicate significant publication bias due to a low statistical power caused by a limited number of studies.

3. Results

3.1. The studies included and overall analysis

The primary literature search retrieved 71 records; 12 records were excluded because of duplication. The remaining 59 records were screening by the titles and abstracts; 34 studies were excluded because they were laboratory studies, review articles, or studies which did not define ISR clearly. Among the remaining 25 eligible studies, nine studies did not report the value of plasma Lp(a) levels at the baseline in the ISR or no-ISR group; five studies were randomized control trials that evaluated the effect of drug interventions on ISR after PCI with stent implantation but did not present the value of plasma Lp(a) levels in ISR or no-ISR group; one

focused on the receptor of Lp(a) instead of Lp(a) itself [20]; Two studies [21,22] had overlapping study populations, and we excluded the older one with a smaller sample size. Finally, a total of 9 cohort studies including 1834 patients were eligible for our meta-analysis [9,21,23–29]. There were 600 patients in the ISR group and 1234 in the no-ISR group. Fig. 1 provides a flow summary of our selection process.

Table 1 summarizes the characteristics of the 9 eligible studies, and Table 2 presents the quality of the included studies. In order to measure Lp(a) levels, five studies used an ELISA assay [9,21,24–26], three studies employed immunoturbidimetry assay, and one study used a nephelometric assay [23]. Six studies focused on Asian ethnicity [9,24,25,27–29] and the remaining three on Caucasian ethnicity [21,23,26]. Two studies monitored the Lp(a) levels in patients after DES implantation [24,28], six studies [21,23–27] in BMS treated patients, and one study did not specify the stent type they used [9].

Overall, baseline plasma Lp(a) levels were significantly associated with ISR after stent implantation compared to the no-ISR group (SMD = 0.42, 95% CI: 0.14–0.71, $P = 0.003$). Plasma Lp(a) levels were significantly higher in patients with ISR compared to patients without ISR (Fig. 2). Cochran Q test showed high heterogeneity between the individual studies ($P < 0.001$, $I^2 = 86.9\%$).

4. Sensitivity and subgroup analysis

In the sensitivity analysis, the influence of each study on the pooled SMD was examined by repeating the meta-analysis while sequentially omitting each study. The summary estimates for the remaining studies were all statistically significant, in agreement with the main results (data not shown).

We next performed subgroup analysis according to the ethnicity, type of stent implantation, and methodology employed for the measurement of the Lp(a) levels. In the Asian population, baseline Lp(a) levels were significantly elevated in the ISR group (SMD = 0.68, 95% CI: 0.42–0.95, $P < 0.001$). We did not observe any significant association of Lp(a) levels with ISR in subjects of Caucasian ethnicity. In patients with DES, baseline Lp(a) levels were significantly higher in the ISR group compared to the controls (SMD = 0.72, 95% CI:0.48–0.95, $P < 0.001$). However, there was no remarkable difference of Lp(a) levels in the ISR vs. no ISR groups after treatment with BMS. In view of biochemical methodology, we found significantly elevated baseline Lp(a) levels in the ISR group of studies which used an immunoturbidimetry assay for Lp(a) levels. The subgroups analyzed with ELISA showed no significant elevation of Lp(a) levels in the ISR group (Table 3).

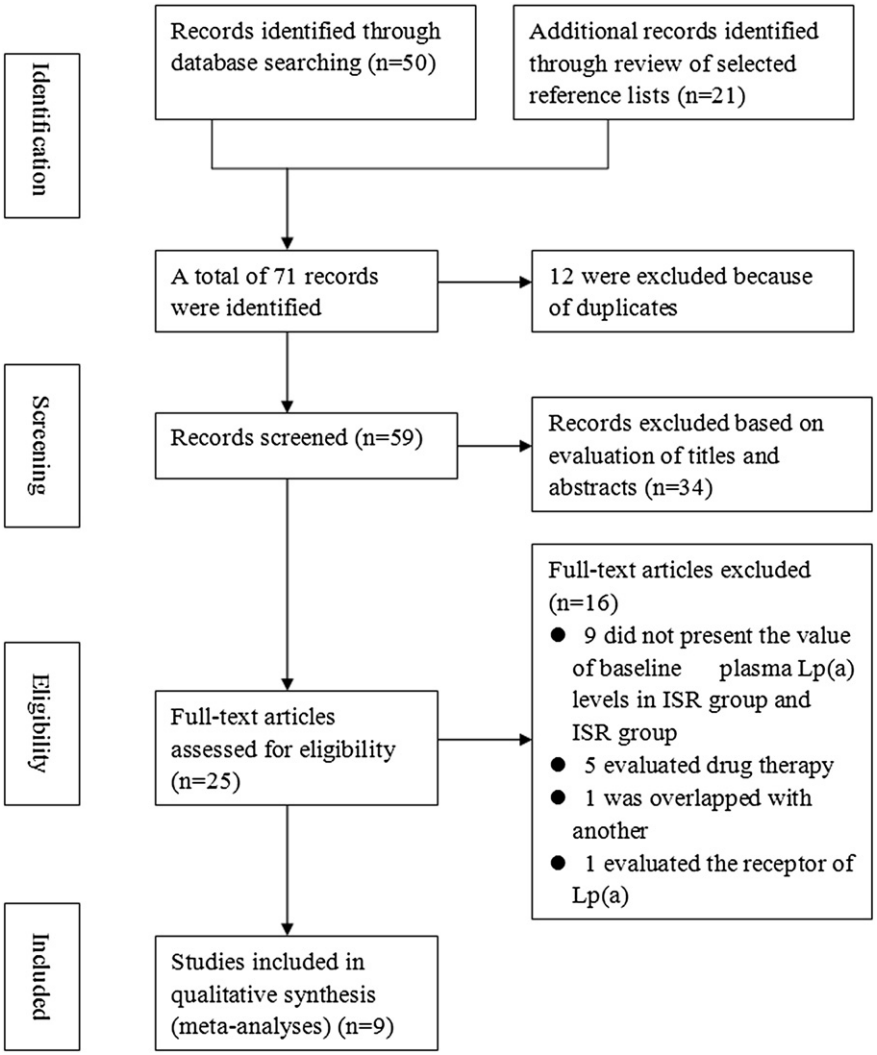

Fig. 1. Flow chart of study selection based on the inclusion and exclusion criteria.

Table 1
Characteristics of the 9 studies included in the meta-analysis.

First author, Year	Location, Study period	Age	Follow-up (month)	Stent	Lp(a) assay	Lp(a) level of ISR	Lp(a) level of No-ISR	ISR/No-ISR number	Disease
Ribichini F [23], 1998	Italy, Dec.1993 –July.1997	61	6.3 ± 1.7	BMS	Nephelometric	37.81 ± 49.01	36.95 ± 40.65	67/245	CAD
Hu J [25], 2002	China, Jan.1996 –Oct.2001	61	6	BMS	ELISA	20 ± 20	10 ± 10	87/126	UA, MI
Gazzaruso C [21], 2003	Italy, not available	57	6	BMS	ELISA	29.5 ± 17.2	27.4 ± 20.2	52/121	T2DM with CAD
Kamitani T [9], 2005	Japan, Jan.1996 –Dec.2001	61	6	NA	ELISA	30.5 ± 23.9	16.9 ± 11.1	38/71	CAD
Li JX [27], 2008	China, Jan.2002 –Dec.2002	61	6–18	BMS	Immunotur-bidimetry	316 ± 128	196 ± 100	36/92	UA, SA
Qi DD [28], 2009	China, Jan.2004 –Aug.2008	63	6–24	DES	Immunotur-bidimetry	42 ± 28	26 ± 20	54/113	UA, SA
Yang XZ [29], 2010	China, Jan.2004 –Dec.2008	58	6.1	DES	ELISA	42.2 ± 27.5	25.7 ± 19.7	54/113	CAD
Gao J [24], 2011	China, Jan.2004 –May 2007	60	7.23 ± 2.71	BMS	ELISA	48 ± 36	40 ± 35	166/271	ACS, SA
Khosravi A [26], 2011	Iran, July.2003 –May 2005	53	6	BMS	ELISA	30.9 ± 26.4	51.6 ± 50.9	46/82	CAD

Lp(a): Lipoprotein (a); ISR: in-stent restenosis; BMS: bare metal stent; DES: drug-eluting stent; T2DM: type 2 diabetes mellitus; CAD: coronary artery disease; MI: myocardial infarction; SA: stable angina; UA: unstable angina; ACS: acute coronary syndrome; ELISA: enzyme-linked immunosorbent assay.

5. Meta-regression analysis

Exploring the possible causes of heterogeneity is crucial in meta-analysis. Therefore, we used a random meta-regression model to evaluate the extent to which modulators explained variation between the individual studies. Regarding the results from our subgroup analysis, we took the ethnicity and stent type into account in the random regression analysis. In the univariate regression, differences due to Lp(a) assay (Coef. = −0.138, $P = 0.701$) and stent type (Coef. = −0.372, $P = 0.377$) were found to be insignificant, while ethnicity (Coef. = 0.778, $P = 0.$ 0.008) was significant. In the multivariate regression of ethnicity, we found that ethnicity (Coef. = 0.773, $P = 0.036$) was the only significant source of the heterogeneity among the Lp(a) levels in the different studies.

6. Publication bias

Egger's test ($P = 0.368$) and Begg's test ($P = 0.348$) indicated negligible publication bias (Supplemental Fig. S1).

7. Discussion

The relationship between baseline plasma Lp(a) levels and restenosis after coronary artery stenting is controversial. Therefore, we conducted a systematic meta-analysis with 9 cohort studies including 1834 patients (634 ISR and 1234 no-ISR subjects). Our results suggest a significant association between baseline plasma Lp(a) levels and the risk of ISR, particularly in studies employing DES implantation, immunoturbidimetry assay for Lp(a) analysis, or in Asian populations. No statistical association was detected in groups in which BMS implantation or ELISA analysis of Lp(a) were applied, or in Caucasian populations. Meta-regression further confirmed that ethnicity was one major source of heterogeneity between the studies ($P = 0.036$), suggesting that genetic factors related to ethnicity may contribute to variation in the results.

To our best knowledge, this is the first meta-analysis to investigate the association between baseline plasma Lp(a) levels and the risk of ISR. Comparing to the individual reports, our meta-analysis of 9 studies involving a larger sample size has greater power to detect the significant association and to provide reliable estimates. In addition, this is the first study to reveal the impact of ethnicity on the relationship between the levels of Lp(a) and ISR, as a confounding factor. Concerning the rapid increase of reports on ISR in the medical literature and the inconsistency of the published results, our findings are particularly meaningful.

PCI with stent implantation can successfully enlarge the stenotic lumen of the coronary artery; however, this technique has significant limitations, a major one of which is ISR. During the stent implantation process, the stent acts as a stimulator that causes local vessel inflammation and leads to platelet activation and formation of mural thrombus. This process results in the stimulation of smooth muscle cell growth and finally leads to the occurrence of

Table 2
Qualitative evaluation of the included studies.

Author	Clear definition of study population	Clear definition of outcome and out assessment	Independent assessment of outcome parameters	Sufficient duration of follow-up	No selective loss during follow-up	Important confounders and prognostic factors identified
Ribichini F	Yes	Yes	Yes	Yes	Yes	No
Gazzaruso C	Yes	Yes	Not clear	Yes	Yes	No
Kamitani T	Yes	Yes	Yes	Yes	Yes	No
Li JX	Yes	Yes	Yes	Yes	Yes	No
Yang XZ	Yes	Yes	Not clear	Yes	Yes	No
Gao J	Yes	Yes	No	Yes	Yes	No
Khosravi A	Yes	Yes	Yes	Yes	Yes	No
Qi DD	Yes	Yes	Yes	Yes	Not clear	No
Hu J	Yes	Yes	Not clear	Yes	Yes	No

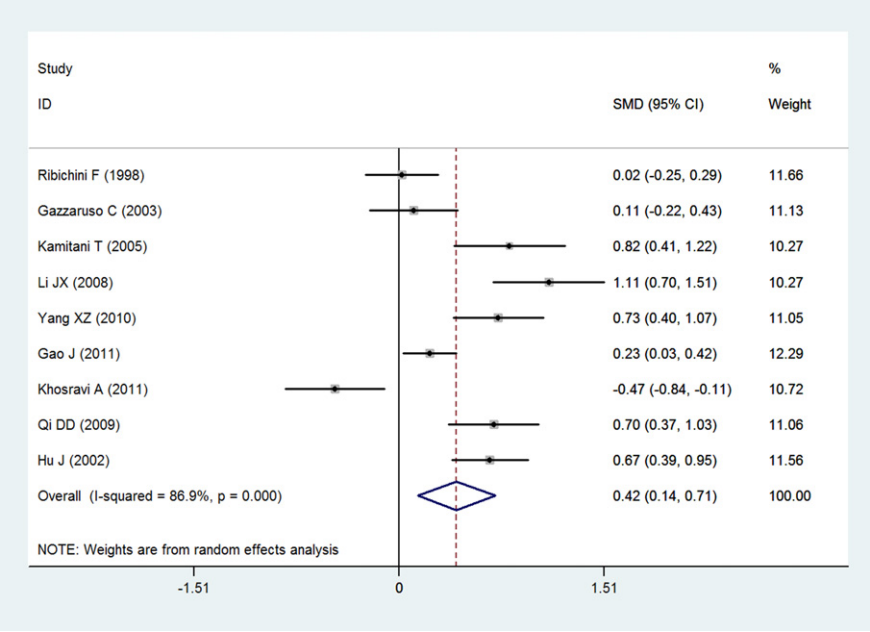

Fig. 2. Random-effects meta-analysis of 9 cohort studies. The squares and horizontal lines correspond to the study-specific SMD and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamonds represent the summary SMD and 95% CI.

ISR [5,30]. Previously, Hou et al. [31] found that lipid-rich, thin fibrous cap plaques were detectable in the stent region after a follow-up period that averaged 6.5 years. Kamitani et al. [9] showed that plasma plasma Lp(a) levels was higher in ISR patients compared with non-ISR patients. After stent implantation, the Lp(a) accumulates in the vessel walls at sites of injury and inhibits cell surface plasminogen activation, which significantly reduces generation of plasmin and a smooth muscle cell proliferation preventer, TGF-β [32,33]. Furthermore, Caplice et al. [34] showed that the inhibition of plasmin generation by Lp(a) could induce the proliferation of smooth muscle cells. In addition, Lp(a) binds directly to the extracellular matrix and is ingested by macrophages, resulting in the accumulation of lipids and thus promoting atherosclerosis [35]. Hence, the association between plasma Lp(a) levels and ISR detected in our study, is most likely to be accounted for by a direct effect on thrombosis and smooth muscle cells proliferation, which potentially contribute to the development of ISR. Further studies are needed to clarify the precise mechanism.

A few studies conducted in the Asian populations [9,24,25,27–29] showed the significant association between Lp(a) and ISR, which was consistent with our results. Although Ribichini et al. [23] failed to identify the Lp(a) levels as a predicting factor of restenosis after elective high-pressure coronary stenting in Caucasians, they excluded patients with long coronary lesions. To be noted, restenosis was more frequently found in longer lesions and smaller vessels [9]. Moreover, Kamitani et al. [9] found that lowering Lp(a) concentration by LDL apheresis effectively prevented restenosis after PCI in Japanese patients. Igarashi et al. [36] reported that an elevated Lp(a) concentration was an independent predictor of adverse long-term outcome in patients with acute myocardial infarction treated by PCI. Lp(a) plasma levels are reported to vary across different ethnicities. Banerjee et al. [37] found that Lp(a) levels in Asian Indians and Non-Hispanic Whites were markedly higher than in Chinese population ($P \leq 0.001$ and $P = 0.003$). Schmidt et al. [38] reported that plasma Lp(a) levels largely differ among European, Asian and African populations. The Lp(a) levels in Africans were on average two to three fold higher than in Europeans. Furthermore, Lanktree and coworkers analyzed multiethnic samples and demonstrated that both single-nucleotide polymorphisms (SNPs) and kringle IV type 2 (KIV-2) copy number coordinately contribute to a larger proportion of variation in plasma Lp(a) concentrations in European population (36%) than in Chinese (27%) or South Asians (21%) [39]. The variation of Lp(a) levels across different ethnicities might cause the heterogeneous results in identifying the correlation between Lp(a) and ISR in the samples. In the present study, we found positive association in Asian ethnicity but not in Caucasians, indicating the profound effect of genetic factors on the correlation between Lp(a) and ISR, especially in the

Table 3
Results of subgroup analysis.

Variables	Studies number	ISR/No-ISR number	*P*	SMD (95% CI)	I^2 (%)	*P* heterogeneity	*P* interaction
Stent type							
BMS	6	454/937	0.135	0.27(−0.08,0.62)	88.7	<0.001	0.202
DES	2	108/226	<0.001	0.72(0.48, 0.95)	0.0	0.888	
Assay							
ELISA	5	239/442	0.113	0.36(−0.09,0.82)	88.8	<0.001	0.812
Immunoturbidimetry	3	256/476	0.013	0.67(0.14, 1.19)	88.7	<0.001	
Ethnicity							
Asian	6	435/768	<0.001	0.68(0.42, 0.95)	77.3	<0.001	0.008
Caucasian	3	165/448	0.546	−0.10(−0.43,0.22)	68.8	0.044	

BMS: bare metal stent; DES: drug-eluting stent; ELISA: enzyme-linked immunosorbent assay.

Asian populations. Our regression result further confirmed that ethnicity is a critical source of heterogeneity. Further studies are needed to clarify the precise mechanism underlying this finding.

DES, also called drug-coated stent, represents a breakthrough technology which is widely used for PCI. It potently reduces restenosis of patients, by inhibiting leukocyte infiltration and smooth muscle cell activation and proliferation [40,41]. The first generation of DES was reported to be positively associated with the risk of late stent thrombosis [42]. Recently, one study [43] including 1015 patients with DES implantation, reported that Lp(a) level in patients undergoing PCI with DES was closely associated with worse clinical outcomes, including target vessel and lesion revascularization. Zairis et al. [11] showed that a high plasma level of Lp(a) may be associated with a higher incidence of late adverse events for 483 patients after successful coronary stenting, including ISR and progression of atherosclerosis to a significant lesion. The data by Gibson et al. [44] showed that patients undergoing DES implantation achieved more reductions in periprocedural markers of inflammation than patients receiving BMS. As a natural regulator of the inflammatory response [45], the effect of Lp(a) might become more prominent after DES implantation, at a situation in which the vascular wall inflammation is suppressed by the eluting drugs, while a higher inflammatory activity in the BMS recipients could mask the Lp(a) effect. However, one should be cautious in drawing conclusions from this because a potential bias might be present due to the limited study numbers on DES. Large, long-term clinical studies are hence warranted.

Lp(a) levels can be measured by a wide variety of immunochemical methods such as ELISA and immunoturbidimetric assay. It has been reported that the Lp(a) levels are heavily affected by the size of the attached apo(a) protein. Isoform-insensitive immunoreactivity to apo(a), the choice of apo(a) size as the calibrator, and appropriate standard are three main factors responsible for the variation of immunochemical measurements [46]. The accuracy of ELISA measurement varies largely according to the different commercial kits used. Furthermore, Levine and coworkers demonstrated that immunoturbidimetric analysis, compared with commercial ELISA applications, is a rapid, accurate and precise method to screen plasma Lp(a) [47]. Although we observed the positive association in the subgroup of immunoturbidimetric assay rather than ELISA, the regression analysis did not show any statistical significance between these two methods concerning the heterogeneous result. Hence, this subgroup result should be considered with caution.

Individual studies designed to assess the correlation between levels of lp(a) and ISR after stenting have been limited to sole ethnicity and small sample size. Hence, it has not been possible to measure the effect of ethnicity on the basis of limited information and statistical power in the previous studies. Meta-analysis is a powerful tool for aggregating information from multiple studies and confirming the associations which were unclear from individual independent studies [48]. Nowadays the use of meta-analysis is more and more popular in genome-wide association studies (GWAS) to identify associations that have not been revealed in the individual studies [49]. After combining all the eligible studies with populations from different ethnicities, we were able to test the confounding effect of "ethnicity" variable in a regression model with relatively robust statistical power. It is most likely that our analysis provided more credible estimate than the individual studies.

Some potential limitations of the present study should be considered. First, our analyses are based on observational studies which may be burdened by potential biases, because of the limited information available. Second, the presence of heterogeneity in our meta-analysis raises concerns of possible biases. However, we were able to identify ethnicity as a major source of heterogeneity. This is a pivotal point to be considered when designing future clinical studies. Third, due to insufficient data from the eligible studies, we could not define the appropriate cut-off value of Lp(a) which best predicts the risk of ISR. Fourth, the associations between plasma Lp(a) levels and the risk of ISR might vary according to different disease profiles of the patients [9,20]. We could not examine the possibility that the disease profiles might confound the association since the profiles had not been depicted or categorized clearly in most of the eligible studies. These variables, such as diabetes mellitus, have the potential to affect the result and cause the bias. Further research including disease profile analysis should be warranted. This would be highly interesting for clinical cardiologists. Fifth, because of the limited data available and small groups of patients in some of the studies, we could not exempt the possibility of a selection bias in the populations. A possible publication bias should not be totally neglected even though the Egger's analysis and Begg's test indicated no such bias in our study.

8. Conclusions

We suggest that elevated baseline plasma Lp(a) levels are associated with increased risk of ISR after successful PCI with stent implantation. However, our results need to be confirmed by larger and well-designed randomized prospective studies.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2013.01.014.

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