Lipoprotein(a) and cardiovascular disease in diabetic patients

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Abstract

Lipoprotein(a) (Lp[a]) is a LDL-like particle consisting of an ApoA moiety linked to one molecule of ApoB$_{100}$. Recent data from large-scale prospective studies and genetic association studies provide highly suggestive evidence for a potentially causal role of Lp(a) in affecting risk of cardiovascular disease (CVD) in general populations. Patients with Type 2 diabetes display clustered metabolic abnormalities and elevated risk of CVD. Lower plasma Lp(a) levels were observed in diabetic patients in several recent studies. Epidemiology studies of Lp(a) and CVD risk in diabetic patients generated inconsistent results. We recently found that Lp(a)-related genetic markers did not predict CVD in two diabetic cohorts. The current data suggest that Lp(a) may differentially affect cardiovascular risk in diabetic patients and in the general population. More prospective studies, Mendelian randomization analysis and functional studies are needed to clarify the causal relationship of Lp(a) and CVD in diabetic patients.

Keywords

cardiovascular disease; diabetes; lipoprotein(a); Mendelian; randomization; prospective studies

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Since the discovery of lipoprotein(a) (Lp[a]) in 1963 by Berg [1], numerous studies have assessed its relationship with cardiovascular diseases (CVDs). Recent data from large-scale meta-analyses and genetic association studies using Mendelian randomization analyses provide highly suggestive evidence for a potentially causal role of Lp(a) in affecting CVD risk in general populations [2–5], promoting the discussion regarding utility of Lp(a) in clinical practice [6–8]. Patients with Type 2 diabetes are featured by clustered metabolic abnormalities and an approximately two- to four-fold increased risk of CVD compared with nondiabetics [9, 10]. It remains unclear as to whether Lp(a) causally affects increased CVD risk in diabetic patients. Interestingly, it was recently found that blood Lp(a) levels might be inversely related to risk of Type 2 diabetes [11, 12], making it more intriguing to understand the role of Lp(a) in the development of CVD, especially among diabetic patients. In this article, we focus on relationships of Lp(a), diabetes and CVD and, in particular, we discuss the issue of Lp(a) as a risk factor for CVD in diabetic patients.

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Lp(a) & genetic determinants

Lp(a) is a LDL-like particle that consists of an ApoA moiety linked to one molecule of apoB via a disulphide bond (Figure 1) [13, 14]. The LDL-like moiety is composed of a central core of cholesteryl esters and triglycerides surrounded by phospholipids, free cholesterol and a single molecule of apoB [13, 14]. Lp(a) is secreted by the liver [15] and circulates in blood, and plasma concentrations are highly heritable and mainly determined by the ApoA gene (*LPA*), which is located on chromosome 6q26–27 [16, 17]. It has been documented that a copy number variation, the kringle IV type 2 (KIV_2) size polymorphism [18], determines the differently sized isoforms of ApoA. A high number of KIV_2 repeats is correlated with low plasma levels of Lp(a), which is likely to be the result of the lower rate of production and secretion of the larger isoforms [19, 20]. In addition, several recent genome-wide association studies identified multiple single nucleotide polymorphisms (SNPs) in the chromosome 6q26–27 region associated with plasma Lp(a) levels in both general and diabetic populations [21–23].

Lp(a) as a cardiovascular risk factor in general populations

A larger number of studies have investigated the relationship between Lp(a) and CVD risk in general populations. A meta-analysis of 126,634 participants from 36 prospective studies, published in 2009, demonstrated that plasma Lp(a) level is continuously associated with an increased risk of coronary heart disease (CHD) and stoke [2]. Each 3.5-fold higher than usual Lp(a) level was associated with a 13% increased risk of CHD and a 10% increased risk of stroke after adjustment for age, sex, lipids and other conventional risk factors. In addition, a recent meta-analysis of 40 studies reported that smaller ApoA isoforms, which correlated with higher plasma Lp(a) levels, were associated with an approximately twofold increased risk of CVD in general populations [5]. These findings suggest that Lp(a) is an independent but moderate risk factor for CVD in general populations. Concurrently, a genetic-association study examined the association between genetically elevated levels of plasma Lp(a) and CHD risk by using the Mendelian randomization approach based on three pieces of data, including plasma Lp(a) levels, the *LPA* KIV_2 size polymorphism and myocardial infarction (MI) events [3]. It was found that elevated plasma Lp(a) levels were associated with an increased risk of MI, the number of KIV_2 repeats was inversely associated with Lp(a) levels (KIV_2 size polymorphism explained 20–30% of variation in Lp(a) levels) and a lower number of KIV_2 repeats was associated with increased risk of MI. In instrumental variable analysis, the risk ratio for MI for a doubling of genetically elevated Lp(a) levels was 1.22 (95% CI: 1.09–1.37). Later in the same year, a further important study on this topic identified two *LPA* SNPs in LD with the KIV_2 size polymorphism, rs3798220 and rs1045872, to be strongly associated with both an increased level of Lp(a) and an increased risk of CHD, and the association with CHD risk was abolished after adjustment for Lp(a) levels [4]. These associations were confirmed in a recent meta-analysis [24], in which each copy of the risk allele of rs3798220 (minor C-allele) and rs1045872 (minor G-allele) was associated with a 57% (risk ratio: 1.57 [95% CI: 1.38–1.79]) and 42% (risk ratio: 1.42 [95% CI: 1.22–1.65]) increased risk of CHD, respectively. These findings provide evidence of a potentially causal relationship between Lp(a) and CVD because genetic variants are generally independent of behavioral and environmental factors, thus yielding associations that are largely unaffected by confounding and reverse causation.

On the basis of recent evidence from the large-scale epidemiological association studies and Mendelian randomization analyses, it has been widely considered that Lp(a) may causally affect CVD risk in general populations. The European Atherosclerosis Society Consensus Panel recommended screening for elevated Lp(a) in individuals at intermediated or high CVD risk, and a desirable level of below the 80th percentiles (<~50 mg/dl) as a cut-off for

global cardiovascular risk was decided on [7]. However, Gudnason and Dube *et al.* suggested that the clinical practice regarding Lp(a) might still be of limited use because of Lp(a)'s moderate effect on CVD risk and unknown functional mechanisms underlying the association [6, 8].

Lp(a) & diabetes

Results of studies investigating Lp(a) levels in patients with Type 1 diabetes are inconsistent. Several studies have reported that Lp(a) levels were increased in patients with Type 1 diabetes [25–28], while in others, a significant relationship was not observed [29–33]. It is also controversial as to whether Lp(a) levels are related to glycemic control in Type 1 diabetes. Although some studies suggested that Lp(a) levels decreased with improved metabolic and/or glycemic control [25, 26, 33, 34], others reported that improved metabolic control did not change plasma Lp(a) levels in patients with Type 1 diabetes [35, 36]. For example, in the Diabetes Control and Complications Trial [33], there was no difference in plasma Lp(a) levels between 1299 patients with Type 1 diabetes and 2158 nondiabetic controls at baseline. Patients receiving intensive insulin therapy showed lower Lp(a) levels compared with those receiving conventional insulin therapy, but Lp(a) levels was not correlated with glycemic control estimated by HbA1c levels [33].

Similarly, highly conflicting results were reported by studies examining the relationship between Lp(a) and Type 2 diabetes, in which unchanged [32, 37], increased [38] or decreased [39, 40] Lp(a) levels were observed in patients with Type 2 diabetes compared with healthy controls. The cross-sectional analysis of plasma Lp(a) levels from 36 studies showed that Lp(a) levels were 11% (95% CI: 4–17) lower in people with diabetes than in those without [2]. Although the type of diabetes was unknown, it is likely that most of these diabetic patients in the included populations (~90%) were affected by Type 2 diabetes. Lp(a) levels were also inversely associated with fasting insulin, and insulin and glucose levels measured by the 2-h glucose challenge test in both diabetic and nondiabetic subjects [41]. An *in vitro* study reported that insulin suppressed ApoA production in primary cynomolgus monkey hepatocytes [42]. These data may partly account for the decreased Lp(a) levels in patients with Type 2 diabetes (characterized by hyperinsulinemia and insulin resistance), and increased Lp(a) levels in patients with Type 1 diabetes (characterized by insulin deficiency). However, this hypothesis needs to be tested in further studies.

Recently, Mora *et al.* reported prospective data on plasma Lp(a) levels and incident Type 2 diabetes (n = 1670) in 26,746 women from the WHS trial, and replicated their findings in 9652 Danish men and women with prevalent diabetes (n = 419) from the CCHS trial [11]. In both the WHS and CCHS trials, Lp(a) levels were significantly lower in diabetes cases than in nondiabetics. In the WHS trial, Lp(a) levels were inversely associated with incident Type 2 diabetes, with fully adjusted hazard ratios (95% CIs) for quintiles 2–5 versus quintile 1 (the lowest) of 0.87 (95% CI: 0.75–1.01), 0.80 (95% CI: 0.68–0.93), 0.88 (95% CI: 0.76–1.02) and 0.78 (95% CI: 0.67–0.91), respectively; p = 0.002. These findings were replicated in a case–control analysis of the CCHS trial. Notably, the authors adjusted for correlates of insulin resistance, such as triglycerides, HDL-cholesterol, HbA1c and CRP, and results were not changed. This is the first prospective study yielding an inverse association between Lp(a) levels and risk of Type 2 diabetes. Of note, such an association is contrary to that with risk of CVD, although it has long been known that these two conditions may share a common soil in etiology [43]. Although it needs to be verified in further studies, this surprising finding suggests a more complicated role of Lp(a) in cardiometabolic diseases than we expected. Mendelian randomization studies using plasma Lp(a)-related genetic variants as instrumental variables (such as rs3798220 and rs1045872) would be useful in

testing whether there is a causal association between decreased Lp(a) levels and increased risk of Type 2 diabetes.

Lp(a) & CVD in diabetic patients

Plasma Lp(a) levels & CVD

A number of cross-sectional studies [44–52] and prospective studies [23, 40, 53–57] have investigated the relationship between plasma Lp(a) levels and CVD risk in diabetic patients and reported inconsistent results. Table 1 summarizes conflicting results from prospective studies in diabetic patients. Haffner *et al.* reported that plasma Lp(a) levels were not associated with CVD in a prospective nested case–control study of 22 patients with Type 1 diabetes and 48 patients with Type 2 diabetes (35 CVD cases and 35 controls) [53]. Similarly, in a prospective study in 449 patients with Type 2 diabetes after a mean of 13 years follow-up, the cumulative probability of CHD or stroke was not significantly different between patients with high Lp(a) levels and those with low Lp(a) levels [55]. By contrast, two prospective studies reported positive associations between Lp(a) levels and risk of CVD in patients with Type 2 diabetes, but the risk ratio for CVD by comparing high and low Lp(a) levels might be overestimated (relative risk [RR]: 7.67 [95% CI: 1.10–53.3] and 6.6 [95% CI: 1.6–26.8]) owing to the small number of cases (n = 8 and 23, respectively) [54, 55]. In 429 consecutive unrelated patients with Type 1 diabetes during the observation period of up to 10.7 years, Kollerits *et al.* reported Lp(a) levels of >30 mg/dl as a strong and independent predictor of CVD (RR: 2.23 [95% CI: 1.28–3.87]) [57].

The most recent prospective analysis was conducted in 926 women and 760 men with Type 2 diabetes from the NHS and HPFS trials [23]. In the two cohorts of women (16-year follow-up) and men (12-year follow-up) with Type 2 diabetes, there was a marginal association between plasma Lp(a) levels and CVD incidence and mortality in age-adjusted models (RRs per 1-standard deviation higher log-transformed Lp(a) levels for CHD, CVD and CVD death: 1.08 [95% CI: 0.98–1.19], 1.08 [95% CI: 0.98–1.18] and 1.17 [95% CI: 0.98–1.40], respectively). After further adjustment for lipids and other conventional risk factors, the RRs for CHD and CVD were reduced to 1.05 (95% CI: 0.95–1.15) and 1.05 (95% CI: 0.96–1.15), respectively, while the RR for CVD death slightly increased to 1.21 (95% CI: 0.99–1.47). This is the largest prospective study in diabetic patients to date, expanding a previous study by having longer follow-up and more CVD events [58]. Shai *et al.* previously reported a borderline association between Lp(a) levels and CHD (p = 0.035) in diabetic women from the NHS [58].

Several studies have compared the association between Lp(a) levels and CVD risk in diabetic and nondiabetic populations. In 587 consecutive patients undergoing coronary angiography (including 136 patients with Type 2 diabetes), Saely *et al.* found that Lp(a) was a strong and independent predictor of CVD events in nondiabetic individuals (RR per 1-standard deviation higher log-transformed Lp(a) levels: 1.461 [95% CI: 1.121–1.904]), but not in diabetic patients (RR: 0.812 [95% CI: 0.539–1.223]) [40], and there was a significant difference in the association of Lp(a) with CVD risk between nondiabetic individuals and diabetic patients (p = 0.008). However, a recent 10-year follow-up prospective study in a general population (n = 9330; 375 diabetics) reported that there was no significant difference in the association between Lp(a) and CHD stratified by diabetes (RR: 1.08 [95% CI: 1.01–1.16] in diabetic patients and 1.05 [95% CI: 1.03–1.07] in nondiabetic individuals; p = 0.25) [59]. In the earlier-mentioned meta-analysis data from general populations [2], the RRs for CHD also did not vary significantly due to diabetes status (p = 0.79), but the RR for CHD in people with diabetes was slightly smaller than that in those without diabetes (RR: 1.09 [95% CI: 1.01–1.18] vs 1.14 [95% CI: 1.09–1.19]).

In summary, most published prospective studies of plasma Lp(a) levels and CVD risk in diabetic patients are limited by their relatively small sample sizes, and the results are inconclusive. Although meta-analysis in general populations suggested that there was no significant difference in the association between Lp(a) and CHD stratified by diabetes status, larger prospective studies in clearly defined diabetic populations are required to evaluate the effect of Lp(a) on CVD risk in diabetic patients.

Genetic & Mendelian randomization analyses

Despite that a large body evidence has shown that Lp(a)-related genetic variants including KIV_2 size polymorphism and SNPs are associated with CVD risk in general populations [3, 4, 22, 24, 60, 61], evidence of associations between Lp(a)-related genetic variants and CVD risk in diabetic patients is sparse. Recently, the authors conducted a genome-wide association study for plasma Lp(a) levels in 2308 patients with Type 2 diabetes and identified six SNPs in a region encompassing *LPA, PLG, SLC22A3* and *LPAL2* genes on chromosome 6q26–27 that were independently associated with Lp(a) levels [23]. Consistent with the results in the general populations [4], the SNP rs10455872 in *LPA* showed the strongest association with Lp(a), with a similar effect size (1.28 vs 1.08 for 1-standard deviation log-transformed Lp[a]) on plasma Lp(a) levels in the diabetic and general populations (Table 2). However, this SNP was not associated with risk of CHD, CVD or CVD death in diabetic patients [23]. The association between SNP rs10455872 and CHD risk showed significant heterogeneity (p = 0.006) between the diabetic patients (odds ratio: 0.94; 95% CI: 0.69–1.28) [23] and general populations (odds ratio: 1.47; 95% CI: 1.35–1.60) [4]. It should be noted that the SNP rs10455872 accounted for a much smaller proportion of the variation in plasma Lp(a) levels in diabetic patients (~3–4%) compared with the general populations (~25%) [4, 23]. In order to test whether the relatively small proportion of the variation in plasma Lp(a) levels explained by this SNP may account for the null association with CVD risk in the diabetic population, a genotype score calculated based on the six SNPs that jointly explained approximately 20% variation of plasma Lp(a) levels was used. Similarly, the genotype score was not associated with CVD risk in diabetic patients [23]. These data regarding Lp(a)-related genetic variants, together with inconsistent results of plasma Lp(a) and CVD risk, from the diabetic patients suggest that Lp(a) may contribute less to cardiovascular risk in diabetic patients than in the general population. However, given the moderate size of the genetic effect, studies with larger sample sizes are needed to provide further verification.

Mendelian randomization is a recent development in genetic epidemiology [62–65], and its principle originates from 'The Law of Independent Assortment', also known as 'Mendel's second law', which states that assortments of alleles/genotypes are randomly transferred from parent to offspring at the time of gamete formation and the inheritance of one trait is independent of other traits. The independent distribution of alleles/genotypes means that a study relating health outcome to genetic variation would not be affected by confounders that often distort the interpretation of findings. In addition, because the random assignment to genotype takes place at conception, the association between a genetic variant and disease is free of reverse causation. Thus, Mendelian randomization is particularly intended to address these two major biases affecting observational associations. Mendelian randomization analysis mimics a randomized controlled trial (Figure 2A) [62, 66]. The method of using the genetic markers related to the exposure of interest as instrumental variables (robust proxies for modifiable exposures) is a formal test of Mendelian randomization [63, 67, 68]. This method estimates the predicted effect of genetically determined levels of exposure on outcome, based on the observed associations between genotype and exposure and between genotype and outcome.

In the case of Lp(a) and CVD risk in diabetic patients, using Mendelian randomization analysis may avoid the influence of some diabetes-specific metabolic changes (such as hyperinsulinemia and insulin resistance) on the plasma levels of Lp(a) as well as the potential reverse causation of CVD onset. Moreover, because plasma levels of Lp(a) are largely determined by genetic factors, genetic variants strongly associated with Lp(a) levels, for example, SNP rs10455872 and a genotype score combining all the independently associated SNPs, could be robust proxies in Mendelian randomization analysis. The application of Mendelian randomization, using an instrumental variable method in this case, requires three observed relationships and a fourth predictive relationship to be estimated:

- ■   A relationship between a genetic marker and plasma Lp(a) levels;

- ■   Association between the selected genetic marker and CVD risk;

- ■   Association between plasma Lp(a) levels and CVD risk;

- ■   The predicted relationship between genetically elevated Lp(a) levels and CVD risk (derived from the first two estimates), which is then compared with the third estimate (Figure 2B).

Since the predicted association between genetically elevated Lp(a) levels and CVD risk is unbiased and nonconfounded, if the association between plasma Lp(a) and CVD risk is true (causal effect), the observed and predicted Lp(a)–CVD associations will be similar.

Since the effect size of most associations between genetic variants and diseases is small–modest, a very large sample size (>10,000 individuals) is usually required to estimate reliable genetic associations for adequately powered Mendelian randomization studies, and most of the individual studies are underpowered [64, 65]. Although the study conducted by Qi *et al.* simultaneously investigated the relationships among plasma Lp(a) levels, genetic variants and CVD risk in diabetic patients, the sample size was inadequate for performing Mendelian randomization analysis [23]. Since the association data among Lp(a)-related genetic variants, plasma Lp(a) and CVD risk can be obtained from different study samples for Mendelian randomization analysis [65, 69, 70], a meta-analysis based on large-scale collaboration of multiple studies with related data would be a promising next step to investigate causal inference for Lp(a) and CVD risk in diabetic patients in the future.

Influence of pharmacologic agents on Lp(a) levels

Several pharmacologic agents have been demonstrated to influence plasma Lp(a) levels. For example, it has been found that niacin (nicotinic acid or vitamin B3), a drug with a CVD-reducing effect [71], lowered Lp(a) levels by up to 30–40% in a dose-dependent manner [7, 72]. Regular aspirin use has also been reported to lower CVD risk and ApoA mRNA expression by up to 85% [73]. Two kinds of well-known CVD agents, statins and fibrates, were reported to influence Lp(a) levels but with minimal effects [7, 72, 74, 75]. Very recently, the *LPA* SNP rs10455872 was reported to be associated with a LDL-cholesterol response to atorvastatin therapy [76]. Other agents have been reported to lower Lp(a) levels, including l-carnitine, ascorbic acid combined with l-lysine, calcium antagonists, angiotensin-converting enzyme inhibitors, androgens, estrogen and its replacements (e.g., tibolone), antiestrogens (e.g., tamoxifen) and thyroxine replacement [7, 8, 72, 77]. It is unknown whether reduction of Lp(a) levels by pharmacologic agents directly reduce CVD risk, as most Lp(a)-lowering drugs also modulate other lipoproteins. For example, in addition to lowering Lp(a), niacin has apparently beneficial effects on LDL-cholesterol, total cholesterol, HDLcholesterol, triglycerides, apoB-containing lipoprotein particles and remnant cholesterol levels [7, 8, 72]. Thus, the benefit of niacin on CVD might not be solely attributed to Lp(a) reduction.

In patients with Type 2 diabetes, treatment of insulin led to higher plasma Lp(a) levels than that with diet or oral hypoglycemic agents [30]. Similarly, insulin administration resulted in a significant increase in Lp(a) levels in patients with Type 1 diabetes [78]. Metformin, an antihyperglycemic drug, has been reported to lower Lp(a) levels in nondiabetic individuals, while a study in patients with Type 2 diabetes found that Lp(a) levels were not influenced by metformin administration. In addition, troglitazone, a withdrawal antidiabetic drug owing to its adverse side effects, has been reported to increase Lp(a) levels in patients with Type 2 diabetes and obese subjects with insulin resistance [79–81]. It seems that some antidiabetic treatments may increase Lp(a) levels, although more studies are needed to confirm these observations and elucidate the underlying mechanisms. This raises a critical question as to whether elevated Lp(a) levels by pharmacologic agents increase risk of cardiovascular complications in diabetic patients. If this is true, an evaluation of the effect of diabetes management and treatment on Lp(a) levels will be necessary in the future.

Conclusion & future perspective

During past decades, great efforts have been devoted to clarifying the relationship between Lp(a) and CVD, and recent advances in large epidemiological studies and genetic-association studies has materially expanded our knowledge in this area. Lp(a) has been established to be an independent risk factor for CVD in general populations, raising a number of discussions on the potential usefulness of Lp(a) in clinical practice. Since diabetic patients have a significantly increased risk of CVD compared with nondiabetic individuals, it is of particular interest to investigate the role of Lp(a) in the development of CVD in diabetic patients. Current data suggest that the roles of Lp(a) in affecting CVD risk among diabetic patients are more complicated owing to the presence of various metabolic abnormalities, and a clear role of Lp(a) in diabetic patients is yet to be demonstrated. Several issues need to be further clarified in future studies prior to evaluation of the use of Lp(a) in clinical practice in diabetic patients.

More prospective studies of plasma Lp(a) levels and CVD risk with larger samples of diabetic patients are needed. A large-scale meta-analysis based on individual data would be useful to clarify the relationship between Lp(a) levels and CVD risk in diabetic patients. The question of whether Lp(a) has a linear or threshold effect on CVD risk in diabetic patients will be particularly motivating, as it is possible that only extreme levels of Lp(a) may exert adverse effects – either highly increased levels (in the case of CVD) or very low levels (in the case of diabetes) [11, 12]. Whether the association is the same in diabetic patients remains unknown. Studies in diabetic patients among different ethnic groups will provide additional useful information because plasma Lp(a) levels vary with two- to three-fold differences among various ethnic groups [7, 82].

Large-scale Mendelian randomization studies of Lp(a) and CVD risk in diabetic patients will help to clarify the casual relationship between them, in which Lp(a)-related genetic makers, such as KIV_2 size polymorphism, individual SNPs (e.g., rs10455872) and a genotype score [23, 83, 84] could be analyzed as instrumental variables. In addition, randomized controlled intervention trials as the gold standard of evidence may be ultimately required to demonstrate that a reduction in Lp(a) levels leads to reduced CVD in causal inference. Despite this, functional studies have implicated various mechanisms underlying the association between elevated Lp(a) and increased CVD risk, such as through promoting thrombosis, atherogenesis, inflammation, endothelial dysfunction and foam cell formation [85–88]. However, little is known in the setting of the diabetic condition, and the related data are urgently needed.

In conclusion, the current evidence does not support Lp(a) as a causal factor for CVD in diabetic patients. It remains elusive regarding whether Lp(a) is a useful maker in the practice of medicine and public health in relation to cardiometabolic diseases. Such discussions will continue until the relationships between Lp(a), diabetes and CVD are fully understood.

Acknowledgments

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Executive summary

Background

- Lipoprotein(a) (Lp[a]) is a LDL-like particle consisting of an ApoA moiety linked to one molecule of $ApoB_{100}$.

- Plasma Lp(a) concentrations are highly heritable and mainly determined by the *LPA* gene.

Lp(a) & cardiovascular disease in general populations

- Large-scale prospective studies demonstrate that Lp(a) is an independent but moderate risk factor for cardiovascular disease (CVD) in general populations.

- Mendelian randomization studies suggest that Lp(a) may causally affect CVD risk in general populations.

Lp(a) & diabetes

- Plasma Lp(a) levels are decreased in patients with Type 2 diabetes compared with nondiabetics in a cross-sectional analysis.

- Plasma Lp(a) levels are inversely associated with risk of Type 2 diabetes in a prospective study.

Lp(a) & CVD in diabetic patients

- Most published prospective studies of Lp(a) levels and CVD risk in diabetic patients are limited by their relatively small sample size and the results are inconclusive.

- Plasma Lp(a) levels and related genetic variants are not significantly associated with CVD risk in the largest prospective study in diabetic patients to date.

Treatments on Lp(a)

- Several pharmacologic agents (e.g., niacin) have been demonstrated to lower plasma Lp(a) levels, but it is unknown whether reduction of Lp(a) levels by pharmacologic agents directly reduces CVD risk.

- Some antidiabetic treatments (e.g., insulin) may increase Lp(a) levels in diabetic patients.

Conclusion & future perspective

- Current evidence does not support Lp(a) as a causal factor for CVD in diabetic patients.

- More prospective studies, Mendelian randomization analyses and functional studies are needed in order to clarify the relationships between Lp(a), diabetes and CVD.
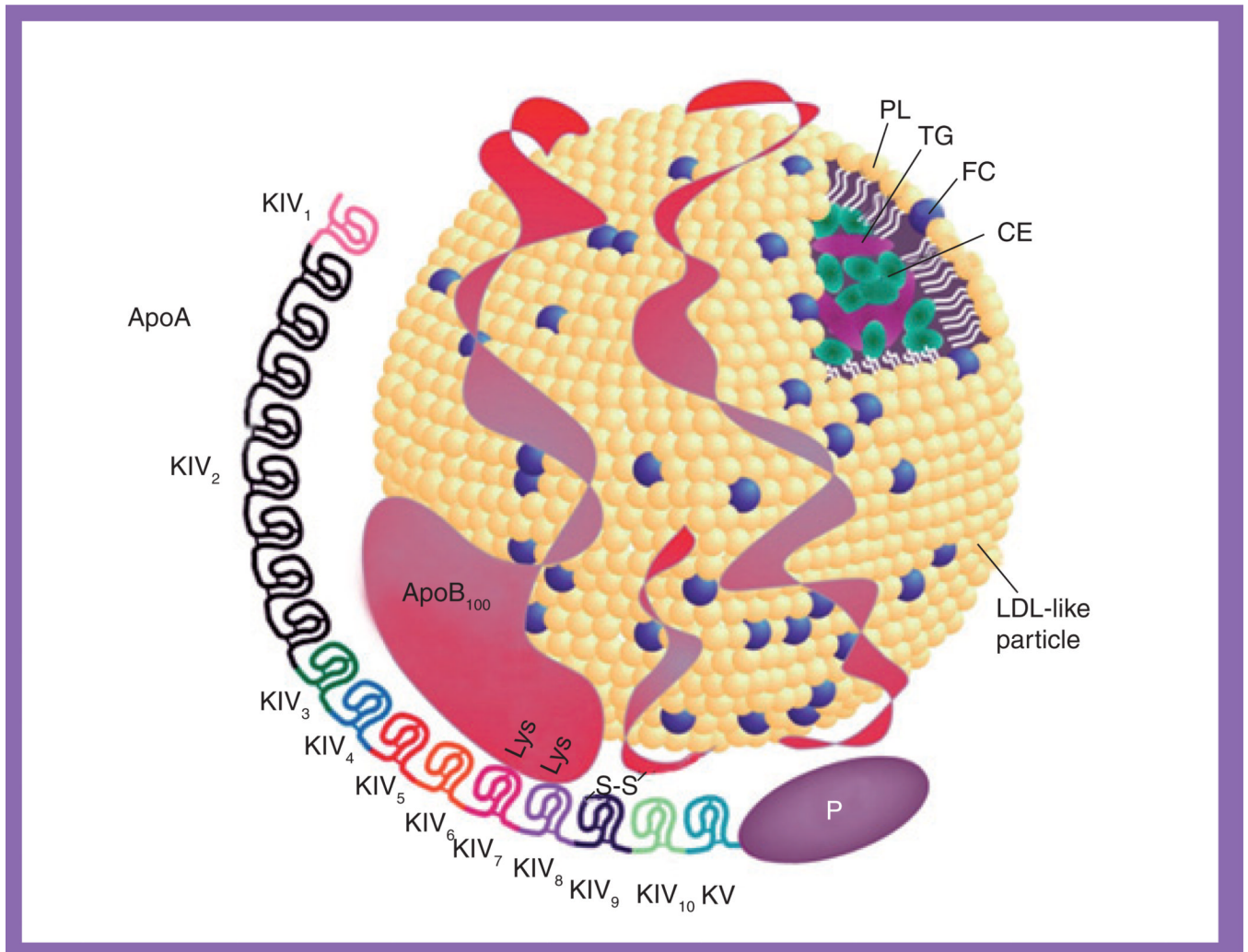
Figure 1. Structure of lipoprotein(a)
Lipoprotein(a) is a LDL-like particle that consists of an ApoA moiety linked to one molecule of ApoB$_{100}$.
CE: Cholesteryl ester; FC: Free cholesterol; KIV: Kringle IV domain; KV: Kringle V domain; PL: Phospholipid; TG: Triglyceride.
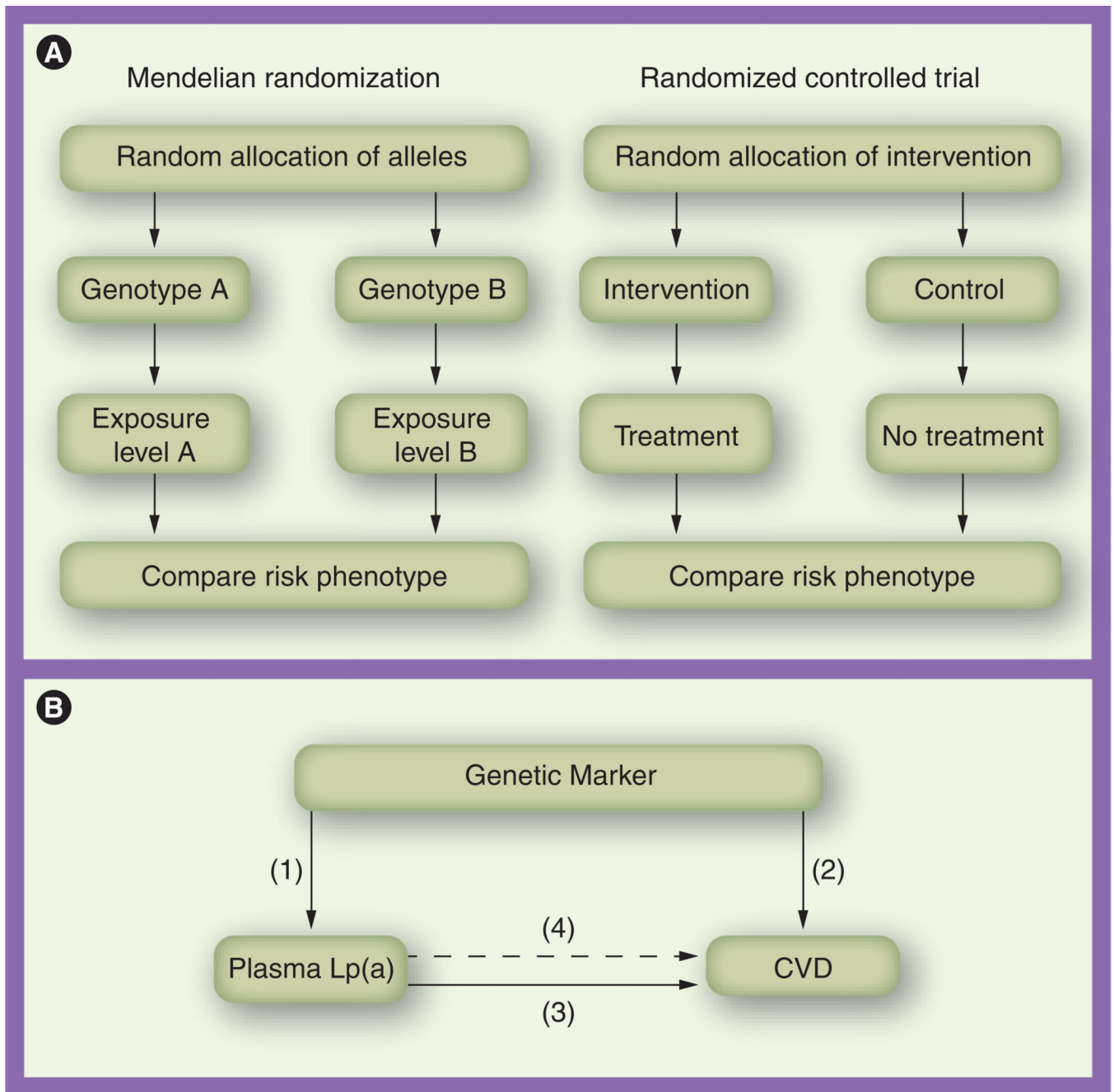Modified with permission from [14].

Figure 2. Mendelian randomization and randomized controlled trial in the case of lipoprotein(a) and cardiovascular disease
(A) Parallel relationship between Mendelian randomization and randomized controlled trial.
(B) Application of Mendelian randomization to the case of Lp(a) and CVD. Relationships include (1) genetic marker and plasma Lp(a) levels; (2) genetic marker and CVD risk; (3) plasma Lp(a) levels and CVD risk; and (4) the predicted relationship between genetically elevated Lp(a) levels and CVD risk (derived from the first two estimates), which is then compared with the observed estimate (3).
CVD: Cardiovascular disease; Lp(a): Lipoprotein(a).
Modified with permission from [65].

Table 1

Summary of prospective studies addressing the association between circulating lipoprotein(a) levels and cardiovascular disease risk in diabetic patients.

Study (year)	Country	Participants (n)	Outcomes	Results	Comments	Ref.
Cohorts with only diabetic patients						
Haffner *et al.* (1992)	USA	70	35 CHD deaths	No significant difference in the distribution (p = 0.70) and mean levels (p = 0.78) of Lp(a) between cases and controls; RR not provided	No association	[53]
Hiraga *et al.* (1995)	Japan	215	Eight CVD events	For high Lp(a) vs low Lp(a) levels (difference 20 mg/dl), the RR of CVD was 7.67 (95% CI: 1.10–53.3; p = 0.0395)	Positive association	[54]
Abu-Lebdeh *et al.* (2001)	USA	449	216 CHD and 115 stroke events	For high Lp(a) vs low Lp(a) levels, there was no significant difference in the cumulative probability of CHD (p = 0.19) or stroke (p = 0.44); RR not provided	No association	[55]
Hernández *et al.* (2005)	Spain	100	23 CVD deaths	For Lp(a) 20 vs <20 mg/dl, the RR of CVD death was 6.6 (95% CI: 1.6–26.8; p = 0.008)	Positive association	[56]
Kollerits *et al.* (2006)	Austria	429	60 CVD events	For Lp(a) >30 vs 30 mg/dl, the RR of CVD was 2.23 (95% CI: 1.28–3.87; p = 0.004)	Positive association	[57]
Qi *et al.* (2012)[†]	USA	1686	561 CVD events	For 1-SD higher log-transformed Lp(a), the RRs of CHD, CVD and CVD death were 1.05 (95% CI: 0.95–1.15; p = 0.35), 1.05 (95% CI: 0.96–1.15; p = 0.32) and 1.21 (95% CI: 0.99–1.47; p = 0.06), respectively	No association	[23]
Cohorts or general populations with both diabetic & nondiabetic individuals						
Saely et al. (2006)	Austria	136 diabetics; 451 nondiabetics	42 CVD events in diabetics	For 1-SD higher log-transformed Lp(a), the RRs of CVD were 0.81 (95% CI: 0.54–1.22; p = 0.32) in diabetic patients and 1.46 (95% CI: 1.12–1.90; p = 0.005) in nondiabetic individuals (p = 0.008)	No association	[40]
Kamstrup et al. (2008)	Denmark	375 diabetics (4% of overall population)	103 CHD events in diabetics	For 10 mg/dl-higher Lp(a), the RRs of CHD were 1.08 (95% CI: 1.01–1.16) in diabetic patients and 1.05 (95% CI: 1.03–1.07) in nondiabetic individuals (p = 0.25)	Positive association	[59]
Erqou et al. (2009)	Meta-analysis in general populations	6372 diabetics (6% of overall population)	942 CHD events in diabetics	For 1-SD higher log-transformed Lp(a), the RRs of CHD were 1.09 (95% CI: 1.01–1.18) in diabetic patients and 1.14 (95% CI: 1.09–1.19) in nondiabetic individuals (p = 0.79)	Positive association	[2]

[†]This is an updated analysis expanding a previous study conducted by Shai et al. [57], which is not included in this table.

CHD: Coronary heart disease; CVD: Cardiovascular disease; Lp(a): Lipoprotein(a); RR: Relative risk; SD: Standard deviation.

Table 2

Single nucleotide polymorphism rs10455872, plasma lipoprotein(a) levels and risk of coronary heart disease in the diabetic and general populations.

Populations	Risk allele frequency	Plasma Lp(a) levels (mg/dl)		Variance explained (%)	Risk of CHD		Ref.
		β (95% CI)[†]	*p-value*		*Odds ratio (95% CI)*	*p-value*	
Diabetic patients	0.07	1.28 (1.08–1.48)	4.6×10^{-39}	3–4	0.94 (0.69–1.28)	0.36	[23]
General populations	0.07	1.08 (1.02–1.13)	3.6×10^{-166}	25	1.47 (1.35–1.60)	3.6×10^{-15}	[4]
[‡]p-value for heterogeneity	–	–	0.06	–	–	0.006	–

[†]Regression coefficients were estimated as each one copy effect of a risk allele (G-allele) for 1-standard deviation log-transformed Lp(a).

[‡]The p-value was tested for heterogeneity in the association of single nucleotide polymorphism rs10455872 with plasma Lp(a) levels and risk of CHD between the diabetic and general populations.

CHD: Coronary heart disease; Lp(a): Lipoprotein(a).