Lipoprotein(a) [Lp(a)] \(^2\) is a structurally and functionally unique lipoprotein consisting of the glycoprotein apolipoprotein(a) [Apo(a)] covalently linked to LDL (1). Soon after its discovery in 1963 by Berg, Lp(a) was shown in case-control studies to be associated with coronary heart disease (CHD) (2). Since then, it has received widespread interest, and a large database has been accumulated concerning its potential role as a predictor of cardiovascular risk. Recently, a metaanalysis, summarizing results of 36 prospective long-term studies with a total of 126 634 participants, was reported by the Emerging Risk Factors Collaboration (3). It confirmed a significant and independent association between increased Lp(a) concentrations and risk of CHD, resulting in a summary odds ratio (OR) of 1.13 (95% CI 1.09–1.18) for each SD increase after adjustment for conventional cardiovascular risk factors. The corresponding adjusted risk ratio for ischemic stroke was 1.10 (95% CI 1.02–1.18).

In this issue of Clinical Chemistry, Mora et al. (4) report prospective data from healthy US women [Women’s Health Study (WHS)] on Lp(a) concentration and risk of type 2 diabetes and replicate their findings in a cohort of Danish men and women [Copenhagen City Heart Study (CCHS)] with prevalent diabetes. In WHS participants, incident type 2 diabetes was ascertained primarily by self-report on annual follow-up questionnaires but was extensively validated by supplemental questionnaires and review of medical records. In the CCHS, prevalent type 2 diabetes was ascertained by self-report, the use of hypoglycemic drugs, or a nonfasting plasma glucose >200 mg/dL. Surprisingly, Lp(a) concentrations in the WHS and CCHS were significantly lower in diabetes cases compared with noncases, although the medians differed clearly by study population (WHS 9.5 vs 10.7 mg/dL, \(P = 0.001\); CCHS 15.7 vs 17.4 mg/dL, \(P = 0.006\)). Pearson correlation coefficients showed a low correlation of Lp(a) with other risk factors for diabetes in the WHS (all coefficients <0.02). In the WHS, the incidence rates for diabetes were significantly lower in quintiles 2–5 compared with quintile 1. In fasting participants, there was a threshold effect of approximately 20% lower relative risk in quintiles 2–5 compared with quintile 1. In nonfasting participants, there was a more linear effect, with an up to 50% lower relative risk in quintile 5 compared with quintile 1. Notably, the inverse association of Lp(a) with diabetes remained significant and was only minimally attenuated after full adjustment for covariates, including LDL cholesterol, triglycerides, and HbA1c. Overall, nonfasting low Lp(a) concentrations were more strongly associated with risk of incident diabetes (\(P\) for interaction 0.002) compared with fasting concentrations. Almost identical results were obtained when participants were stratified by LDL cholesterol (below or above the median of 121 mg/dL) or when initially excluded women with baseline HbA1c \(\geq 6.0%\) were included into analysis. These findings were replicated in 2 settings. First, in a case-control analysis of WHS, women with baseline prevalent diabetes or HbA1c \(\geq 6.5%\) served as cases, whereas women free of diabetes during follow-up served as controls. In this setting, an Lp(a) value <1 vs \(\geq 1\) mg/dL was significantly associated with diabetes with an adjusted OR of 2.29 (95% CI 1.59–3.28). Second, in the CCHS, a Lp(a) value <1 vs \(\geq 1\) mg/dL was associated with an adjusted OR of 1.54 (95% CI 1.14–2.08).

Two aspects of the current study are noteworthy. First, the association of Lp(a) with diabetes was stratified for hormone use, and similar results were obtained for both groups. This is of special interest, since Lp(a) concentrations have been repeatedly reported to be influenced by hormones (5). Second, because it has been hypothesized that Lp(a) may be a marker of insulin resistance, the authors adjusted for correlates of insulin resistance, such as lipids, HbA1c, and high-sensitivity C-reactive protein (CRP), but results were not altered (6).

This is the first prospective analysis revealing an inverse association between Lp(a) and type 2 diabetes, contrary to what one might have expected, given the fact that type 2 diabetes and CHD share at least several risk factors. Based on this, Stern in 1995 postulated the

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Received May 20, 2010; accepted May 21, 2010.
Previously published online at DOI: 10.1373/clinchem.2010.150953

2 Nonstandard abbreviations: Lp(a), lipoprotein(a); Apo, apolipoprotein; CHD, coronary heart disease; OR, odds ratio; WHS, Women’s Health Study; CCHS, Copenhagen City Heart Study; CRP, C-reactive protein; HR, hazard ratio.
common soil hypothesis (7). This surprising finding, based on solid epidemiological data, clearly deserves further investigation, but by definition cannot prove causal relationship, and several issues need further clarification.

1. The WHS was initially designed to evaluate the effect of aspirin in primary prevention of cardiovascular disease and type 2 diabetes but failed to show a significant beneficial effect of 100 mg after 10 years of treatment (8, 9). Of note, it has been shown previously, in vitro and in vivo, that aspirin reduces Lp(a) production in human hepatocytes up to 80% by suppression of Apo(a) gene transcription (10, 11). The magnitude of the decrease was found to be larger in patients with high concentrations of Lp(a), which has been suggested to result from a greater reduction of Apo(a) gene transcription by aspirin in patients with high baseline transcriptional activity of the gene. If Lp(a) plays a causal role in the pathogenesis of diabetes and cardiovascular disease, one might have expected a significant benefit on outcome in the verum group. However, pursuing this hypothesis in the WHS is hampered by the lack of plasma samples after randomization to aspirin or placebo. Nevertheless, it would be of particular interest to see the predictive value of Lp(a) on diabetes in the analysis by Mora et al. (4) after stratification for aspirin intake.  

2. It has been reported that a minor allele variant of Apo(a) (rs3798220) is associated with both increased Lp(a) plasma concentrations and increased cardiovascular risk (12). In WHS, 3.7% of the study population carried the minor allele (13). Median concentrations of Lp(a) at baseline were 10.0, 79.5, and 153.9 mg/dL for major allele homozygotes, minor allele heterozygotes, and minor allele homozygotes, respectively. Among carriers, cardiovascular risk was reduced more than 2-fold by aspirin [hazard ratio (HR) 0.44; 95% CI 0.20–0.94], whereas the risk was not reduced among noncarriers (HR 0.91; 95% CI 1.39–3.52). Although the study was not powered to test if the cardiovascular risk associated with the polymorphism is explained by functional differences between gene variants, it might be possible that the differences in cardiovascular (or diabetes) risk are attributed to and fully explained by differences in Lp(a) concentrations. Moreover, one may hypothesize that only extreme values of Lp(a) concentrations may exert adverse biological effects—either very low (in the case of diabetes) or highly increased (in the case of cardiovascular disease), suggesting a threshold effect, and potentially an optimal range of individual concentrations. This hypothesis is supported by the fact that in the present study in fasting participants (nearly 80% of all participants) a lower relative risk was seen for incident diabetes throughout quintiles 2–5 compared to the lowest quintile of Lp(a). Likewise, as previously reported, participants in the WHS in the highest quintile of Lp(a) had an approximately 50% increased risk (HR 1.47; 95% CI 1.21–1.79) of developing cardiovascular events than women in the lowest quintile, and this association was almost entirely confined to the top quintile, again suggesting a threshold effect (14). So it might be interesting to see if carriers of the minor allele of this polymorphism show an even lower incidence of diabetes, since they demonstrate extremely increased Lp(a) concentrations.

3. The size of the Apo(a) isoform and Lp(a) plasma concentrations are inversely correlated, which is caused by a variable rate of degradation before the Apo(a) protein has matured for Lp(a) assembly (15). Various studies in healthy populations have suggested that assessing Apo(a) isoforms carries predictive utility beyond the information provided by Lp(a) concentrations alone (16). Recently Erqou et al. (16) presented a systematic review of 40 studies involving 58 000 participants, showing that subjects with smaller Apo(a) isoforms have an approximately 2-fold higher risk of CHD or ischemic stroke than those with larger isoforms. In the present study, baseline Lp(a) was measured using an immunoturbidimetric assay that is not affected by the number of kringle IV type 2 repeats, thereby not allowing to distinguish between Apo(a) isoforms. Thus, it would be interesting to see how measurement of isoforms would affect the presented data.

In primary prevention of cardiovascular disease and diabetes, Lp(a) seems to add predictive value to lipid screening and enhances risk prediction based on established risk variables; however, the effect is only modest in several studies. The controversial discussion on whether to use Lp(a) to identify at-risk, otherwise healthy individuals will continue with this intriguing study providing thought-provoking results, until the mechanisms of this opposite predictive effect of Lp(a) in these 2 common diseases, which seem to share a common soil, are elucidated. Intervention studies with a specific Lp(a) antagonist might provide more insight; however, no such drug is available to date. In conclusion, the present study opens the door to a possibly more precise assessment of diabetes risk, but further insights are needed to understand the pathogenic role of Lp(a) in diabetes and cardiovascular disease.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting
or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

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