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EDITORIAL COMMENT

Lipoprotein(a) and Cardiovascular Disease in Heterozygous Familial Hypercholesterolemia

Should We Also Blame the LDL Receptor?*

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Heterozygous familial hypercholesterolemia (FH) is associated with an elevated lifetime burden of cardiovascular disease (CVD) (1). However, despite early exposure to elevated plasma low-density lipoprotein cholesterol (LDL-C) levels, there is heterogeneity at the onset of CVD in this population. In addition to the presence of traditional risk factors such as hypertension, smoking, and low plasma high-density lipoprotein cholesterol levels, elevated lipoprotein(a) [Lp(a)] levels have been associated in some (2,3), but not all (4,5), studies with a greater prevalence of clinical and subclinical CVD in patients with FH. However, these studies have been limited by their cross-sectional or retrospective design and also, with exception of 1 study (3), by the small number of included subjects.

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A recent patient-level meta-analysis of prospective studies, as well as a large Mendelian randomization evaluation (6,7), have established an independent association between Lp(a) levels and the risk of CVD in the general population. This might occur because Lp(a) is an LDL-like lipoprotein. Nonetheless, Lp(a) carries an additional apolipoprotein, apo(a) (8), that inhibits fibrinolysis and may be the link between lipid transport and coagulation systems in the atherogenic process (8). In addition to its high cholesterol content and antifibrinolytic action, Lp(a) should also induce atherosclerosis by its pro-inflammatory action secondary to increased binding and transport of oxidized phospholipids (9). Plasma Lp(a) levels are strongly determined genetically, and production rates predominate over catabolism as their main determinants (10,11).

In this issue of the *Journal*, Alonso et al. (12) elegantly report on the association between Lp(a) levels as a predictor of CVD and the interaction with the severity of *LDLR* mutations in a well-characterized Spanish cohort of patients with FH in SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study). The investigators initially found that Lp(a) levels were higher in patients with FH than in their nonaffected normolipidemic relatives. The investigators then showed that patients with FH and CVD had higher Lp(a) levels than either unrelated subjects with FH, but without CVD, or normolipidemic relatives without CVD. When subjects carrying the most frequent null and defective *LDLR* mutations were compared, those with null mutations had higher Lp(a) levels and a greater incidence of CVD. Moreover, for those with *LDLR* null mutations, who are in theory those with the highest risk of CVD due to more elevated LDL-C levels from birth (1), Lp(a) levels were higher in those with CVD. Also, subjects with null mutations and Lp(a) levels >50 mg/dl, a value associated with an elevated risk of CVD in the general population (13), had the shortest free survival time from onset of CVD. Finally, Lp(a) levels were independently associated with CVD in the whole FH cohort.

This is a well-performed proof-of-concept study with a large number of study subjects and is carefully analyzed. All subjects with FH had a molecular diagnosis, and the nonaffected control subjects were their relatives. Of course, the cross-sectional nature of the study precludes the final conclusion that an elevated Lp(a) level is indeed an independent risk factor for CVD in patients with FH, as it is for the general population (6,7). However, this study advances the knowledge in the field and adds important information regarding a possible interaction between more severe *LDLR* mutations and higher Lp(a) levels with a greater risk of CVD.

The lack of a role of LDLR in catabolism of Lp(a) is intriguing, because this lipoprotein encloses apoB-100, the natural binder of LDLR within its particle. Studies in both subjects with homozygous FH (10) and transgenic mice (11) failed to show reduced clearance from plasma of Lp(a) in the absence of the LDLR. Indeed, statins that increase hepatic *LDLR* expression do not show a significant effect on Lp(a) plasma levels (13). However, the role of a putative influence of the LDLR on Lp(a) catabolism cannot be discarded because subjects with homozygous FH present with higher Lp(a) levels than both subjects with heterozygous FH and normolipidemic subjects (14). The finding of the current study (12) of higher Lp(a) levels in those with more frequent *LDLR* null mutations suggests that this association might not be attributable to chance only. However, one cannot discard that those with more severe *LDLR* mutations can also inherit greater apo(a) production capacity and therefore have higher Lp(a) plasma levels.

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Recent evidence showing that antibodies that block PCSK9 (proprotein convertase subtilisin/kexin type 9), a protein that facilitates the degradation of LDLR in the liver, reduce, not only LDL-C and apoB-100, but also Lp(a) (15) plasma levels in patients with FH adds more controversy to the matter. Should we also blame LDLR for higher Lp(a) plasma levels and possibly a greater risk of CVD in subjects with FH?

Notwithstanding biological controversies, the study by Alonso et al. (12) suggests an interaction between the more severe *LDLR* mutations and Lp(a) as a cause of CVD in patients with FH. The prospective phase of SAFEHEART is needed to confirm the findings of the current evaluation.

Despite the strong evidence between increased Lp(a) plasma levels and a greater risk of CVD in the general population (6,7) and the suggested elevated risk of CVD shown in the study by Alonso et al. (12) and studies from others in subjects with FH (2,3), there is very little evidence that a reduction in Lp(a) level prevents CVD (16). It is important to show that newer therapies that reduce Lp(a) levels in addition to LDL-C levels (15,17) will prevent CVD.

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REFERENCES

1. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478–90.
2. Seed M, Hoppichler F, Reaveley D, et al. Relation of serum lipoprotein(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. N Engl J Med 1990;322:1494–9.
3. Jansen AC, van Aalst-Cohen ES, Tanck MW, et al. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: data in 2400 patients. J Intern Med 2004;256:482–90.
4. Hopkins PN, Stephenson S, Wu LL, Riley WA, Xin Y, Hunt SC. Evaluation of coronary risk factors in patients with heterozygous familial hypercholesterolemia. Am J Cardiol 2001;87:547–53.
5. Miname MH, Ribeiro MS II, Parga Filho J, et al. Evaluation of subclinical atherosclerosis by computed tomography coronary angiography and its association with risk factors in familial hypercholesterolemia. Atherosclerosis 2010;213:486–91.
6. Emerging Risk Factors Collaboration. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009;302:412–23.
7. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 2009;301:2331–9.
8. Hancock MA, Boffa MB, Marcovina SM, Nesheim ME, Koschinsky ML. Inhibition of plasminogen activation by lipoprotein(a): critical domains in apolipoprotein(a) and mechanism of inhibition on fibrin and degraded fibrin surfaces. J Biol Chem 2003;278:23260–9.
9. Tsimikas S, Witztum JL. The role of oxidized phospholipids in mediating lipoprotein(a) atherogenicity. Curr Opin Lipidol 2008;19:369–77.
10. Rader DJ, Cain W, Ikewaki K, et al. The inverse association of plasma lipoprotein(a) concentrations with apolipoprotein(a) isoform size is not due to differences in Lp(a) catabolism but to differences in production rate. J Clin Invest 1994;93:2758–63.
11. Cain WJ, Millar JS, Himebauch AS, et al. Lipoprotein [a] is cleared from the plasma primarily by the liver in a process mediated by apolipoprotein [a]. J Lipid Res 2005;46:2681–91.
12. Alonso R, Andres E, Mata N, et al., for the SAFEHEART Investigators. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. J Am Coll Cardiol 2014;63:1982–9.
13. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J 2010;31:2844–53.
14. Kraft HG, Lingenhel A, Raal FJ, Hohenegger M, Utermann G. Lipoprotein(a) in homozygous familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2000;20:522–8.
15. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. Circulation 2012;126:2408–17.
16. Leebmann J, Roeseler E, Julius U, et al. Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)-hyperlipoproteinemia, and progressive cardiovascular disease: prospective observational multicenter study. Circulation 2013;128:2567–76.
17. Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet 2010;375:998–1006.

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