JACC: HEART FAILURE
VOL. 4, NO. 1, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2015.11.001

EDITORIAL COMMENT

Lipoprotein(a) and Heart Failure

Another Reason to Study Interventions in Patients With Very High Levels of Lipoprotein(a)?*

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Kamstrup and Nordestgaard (1) in this issue of *JACC: Heart Failure*, have continued their studies examining the associations of high levels of lipoprotein(a) [Lp(a)], *LPA* genotypes, and risk for cardiovascular disease (CVD) and have provided novel information about risk for heart failure. This study shows the power of adding genetic data to large well-characterized population studies to go beyond observations of statistically significant associations and ask questions of whether high levels of Lp(a) are causally related to increased heart failure with Mendelian randomization.

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Several noteworthy features of this study are relevant to the use of Mendelian randomization. Kamstrup and Nordestgaard (1) combined data from both the Copenhagen City Heart Study (n = 10,855) and the Copenhagen General Population Study (n = 87,242) with careful phenotyping (standardized measurements of Lp(a) and other biochemical variables), genotyping of *LPA*, and 100% long-term follow-up with 4,122 heart failure and 4,221 myocardial infarction endpoints. In summary, a large number of participants, comprehensive phenotyping and genotyping, and careful follow-up with a large number of endpoints are required to have sufficient power to perform these types of analyses, that is, not just "big data" but "big high-quality comprehensive data," which could not be obtained from routine medical records.

Kamstrup and Nordestgaard (1) conducted instrumental variable analyses and showed that genetically determined increased levels of Lp(a) were associated with increased risk for heart failure. These analyses are convincing but raise several questions. Although the number of kringle repeats is clearly a determinant of Lp(a) levels, rs3798220 has very little correlation with the number of kringle repeats but is associated with the more extreme elevations of Lp(a). Although rs3798220 is present in only 3% of the population, it is present in 40% of individuals with Lp(a) level above the 99th percentile. *LPA* rs10455872 was present in 14% of the population, and in 49% of those with Lp(a) level above the 99th percentile. It would be of interest to examine data on the phenotypes of individuals who are homozygous for either single nucleotide polymorphism (SNP) or compound heterozygotes for both, as they would be predicted to have even more extreme elevations of Lp(a) and even greater risk.

Mediational analyses showed that 47% of the increased risk for heart failure that was due to Lp(a) levels was mediated through myocardial infarction and 21% through aortic stenosis, with 37% not explained by either myocardial infarction or aortic valve disease. In regard to the genetic variants, Kamstrup and Nordestgaard (1) noted that although the confidence intervals were wide, rs3798220, which was present in only 3% of the population, was strongly associated with heart failure that was not explained by myocardial infarction or aortic valve stenosis, whereas all the effect of rs10455872 on heart failure was explained by myocardial infarction or aortic valve stenosis. Kamstrup and Nordestgaard (1) postulate that high levels of Lp(a) may increase arterial stiffness,

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

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including noncompliance of the aorta. This hypothesis could be examined by measurement of pulse wave velocity and central aortic pressure. If confirmed, this could be another parameter to be examined in trials of treatments for Lp(a).

PRACTICAL IMPLICATIONS

High levels of Lp(a) are associated with increased risk for myocardial infarction, stroke, aortic stenosis, and, as now shown, heart failure. Two SNPs, *LPA* rs3798220 and *LPA* rs10455872, were present in 3% and 14%, respectively, of the population in Copenhagen. These 2 SNPs and the number of kringle repeats as determined by reverse transcriptase polymerase chain reaction explain almost one-half of the variation in Lp(a) levels. Genetic variants in *LPA,* the gene encoding apolipoprotein(a), are one of the most important causes of CVD, yet we have a paucity of data regarding the optimal approach to reduce CVD events in individuals with markedly increased levels of Lp(a).

CLINICAL TRIAL DATA

In the AIM-HIGH study (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes), Lp(a) levels at baseline and on treatment were predictive of CVD events in both the simvastatin monotherapy group (hazard ratio [HR]: 1.24 [p = 0.002] and 1.21 [p = 0.017], respectively) and the simvastatin-niacin group (HR: 1.25 [p = 0.001] and 1.18 [p = 0.028], respectively); simvastatin-niacin decreased Lp(a) by 21% but did not reduce CVD events (2). In an analysis of white patients in the JUPITER study (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), each 1-SD increment in Ln[Lp(a)] was associated with an adjusted HR for incident CVD of 1.18 (95% confidence interval [CI]: 1.03-1.34; p = 0.02) for baseline Lp(a) concentrations and 1.27 (95% CI: 1.01-1.59; p = 0.04) for Lp(a) concentrations on rosuvastatin (3). Median Lp(a) level was not changed in either the rosuvastatin or placebo group, but rosuvastatin treatment significantly reduced incident CVD in patients with baseline Lp(a) either greater than or equal to the median (HR 0.62; 95% CI: 0.43-0.90) or less than the median (HR 0.46; 95% CI: 0.30-0.72). Results were similar in analyses that included nonwhites (3). Thus, statins reduced risk for CVD events in individuals with high levels of Lp(a), but individuals continued to have increased risk after statin therapy and Lp(a) level on treatment was significantly associated with residual CVD risk. Trials of proprotein convertase subtilisin/kexin type 9 inhibitors have reported reductions in median Lp(a) from baseline of 3% to 35% (4), with most studies showing reductions in Lp(a) levels of approximately 25% to 30%, which is one-half the observed low-density lipoprotein cholesterol reductions of 50% to 60%.

Although cholesteryl ester transfer protein inhibitors reduce levels of low-density lipoprotein cholesterol and Lp(a), the recent failure of evacetrapib raises considerable doubt as to whether this approach will ever be useful in the treatment of patients with high levels of Lp(a). Finally, a modified antisense oligonucleotide drug has recently been shown to lead to dose-dependent reduction of Lp(a) up to 78% (5).

Although several large trials of proprotein convertase subtilisin/kexin type 9 inhibitors are ongoing, clinical trials of all comers are unlikely to provide the necessary data to answer clinical questions about Lp(a). CVD risk is markedly increased in individuals with Lp(a) levels above the 90th percentile and even greater in those with Lp(a) levels above the 95th percentile. Future studies will need to focus on individuals with very high Lp(a) levels and be designed to enrich enrollment of these individuals. Furthermore, endpoints in such trials should include not only the typical atherosclerosis endpoints of myocardial infarction, stroke, and revascularization, but also aortic stenosis and heart failure.

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KEY WORDS genetics, heart failure, lipoprotein(a), lipoproteins