Lipoprotein(a) Removal Still a Mystery

Paul Nestel, MD

The article by Shapiro et al in this issue of the Journal of the American Heart Association (JAMA) deals with 2 lipids that have, in recent years, expanded the profile of cardiovascular risk, providing further insight into the complexity of lipid metabolism.1 Lipoprotein(a), although well characterized over many years, has relatively recently been confirmed as a major risk factor in a substantial proportion of Western populations.2–5 By contrast, genetically low lipoprotein(a) levels are associated with reduced cardiovascular disorders beyond coronary heart disease, including stroke, peripheral arterial disease, aortic stenosis, and heart failure.6 Yet, the metabolism of this lipoprotein is not fully known.7 Apolipoprotein(a) is synthesized in the liver and becomes bound covalently to apolipoprotein B within a low-density lipoprotein (LDL)–like particle. However, its clearance from the circulation after undergoing cleavage is poorly understood other than that degraded products are excreted through the kidneys.7

The article from the Oregon Health Center focuses on this issue and in particular on the role of the LDL receptor (LDLR). They have analyzed the relative reductions of plasma LDL cholesterol (LDLC) in patients treated with the monoclonal inhibitor of the serine protease PCSK9 (proprotein convertase stabilisin/kexin type 9) that result in increased survival of the LDLR and hence substantial decrease in LDLC. Because the inhibitor reduces lipoprotein(a) also, but much more modestly, by approximately half that of LDLC, the authors hypothesized that the relative reductions in LDLC and lipoprotein(a) may indicate the relative removal of lipoprotein(a) by the LDLR. They did, in fact, observe an anticipated divergence or discordance in the percentage of the lipoproteins removed, which was calculated at ∼28% when the lipoprotein(a) baseline concentration was 50 mg/dL (while not claiming that 72% was, therefore, removed via LDLR).

This indirect approach confirms earlier observations of the limited role of the LDLR in lipoprotein(a) removal, although in studies of patients treated with PCSK9, the reductions in LDLC and lipoprotein(a) have been correlated.8,9 In human HepG2 cells, the lipoprotein(a)-cell association was reduced by coincubation with LDL and with PCSK9 but reversed by addition of a PCSK9 inhibitor, suggesting that LDLR availability was a limiting factor for lipoprotein(a) removal.9 As yet, no specific receptor for lipoprotein(a) has been demonstrated. Statin therapy, which lowers LDLC by activating LDLR, has been conclusively shown not to lower lipoprotein(a); indeed, some statins may increase lipoprotein(a) level.7 A meta-analysis of 7 major randomized controlled trials in 29,069 patients with previous cardiovascular events who experienced 57,511 further cardiovascular events over 95,576 patient-years at risk revealed continuous predictable risk from elevated lipoprotein(a) that was independent of the statin effect on LDLC.5 Similar findings have been reported on the basis of LPA variants in which genetic variations in the LPA locus remained predictive for coronary heart disease events independently of statin-lowered LDLC.10

On the other hand, familial hypercholesterolemia patients with partial or total loss of LDLR activity frequently also have elevated lipoprotein(a) concentrations11,12 that may reflect partial dependence of lipoprotein(a) clearance through the LDLR and incidentally increase their risk of coronary heart disease. Interestingly, however, homozygous hypercholesterolemic patients without active LDLR did lower lipoprotein(a) concentration with PCSK9 treatment.9 Lipoprotein kinetic studies in patients being treated with the PCSK9 inhibitor alirocumab have been reported to show an increased fractional removal rate of lipoprotein(a) of ∼25% without appreciable change in production rate.13 That may represent clearance by upregulated LDLR but may also reflect other processes, including direct clearance by the kidney of degraded apolipoprotein(a) particles. PCSK9 may also inhibit lipoprotein(a) production or assembly that probably requires availability of apolipoprotein B because patients with low levels of apolipoprotein B also have low levels of lipoprotein(a).8 Although atorvastatin paradoxically increases lipoprotein

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Baker Heart & Diabetes Institute, Melbourne, Australia.

Correspondence to: Paul Nestel, MD, Baker Heart & Diabetes Institute, PO Box 6492, St Kilda Road Central, Melbourne 8008, Australia. E-mail: paul.nestel@baker.edu.au

J Am Heart Assoc. 2019;8:e011903. DOI: 10.1161/JAHA.118.011903.

© 2019 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
(a) levels, niacin or nicotinic acid and cholesteryl ester transfer protein inhibitors both lower lipoprotein(a) by amounts similar to that of the PCSK9 inhibitors. Yet, neither niacin nor torcetrapib is likely to have achieved this effect through increased LDLR activity. Thus, the question of mechanisms responsible for lipoprotein(a) removal remains largely unanswered. This uncertainty has led to approaches to inhibit production at the genomic level.

The article raises other issues of a more general nature, including the concentration of lipoprotein(a) at which increased risk becomes clinically significant. Both the level of the lipoprotein and the LPA gene show the risk to be linear, although possibly log-linear for LPA. A mendelian randomization study showed a doubling in risk for lipoprotein (a). The levels suggested for lipoprotein(a) at which future treatment could be considered are 30 and 50 mg/dL both well above the median value among Western populations (<15 mg/dL). The 90th percentile in the LIPID (Long-Term Intervention With Pravastatin in Ischemic Disease) secondary prevention trial and in the primary prevention Copenhagen Heart Study was ~70 mg/dL, at which the inflection for risk becomes clear. In the recent meta-analysis of 7 secondary prevention statin trials, the hazard ratio increased linearly at >30 mg/dL and reached a hazard ratio of 1.31 at 50 mg/dL (~80th percentile in Western populations).

The benefit of lowering lipoprotein(a) levels has become pertinent given the impending trials of antisense therapy and the expected high cost of the medications. A mendelian randomization analysis of the extensive UK Biobank database suggested requirement for large reductions in lipoprotein(a) compared with that for LDLC lowering. In the comparison of >62,000 patients with coronary heart disease and >127,000 controls, it was calculated that for each 10-mg/dL reduction in lipoprotein(a), risk decreased by 5.8%. By contrast, a 10-mg/dL reduction in LDL would provide greater benefit, 14.5%. The equivalent of reducing LDL by 38.67 mg/dL (1 mmol/L readily achievable with statin therapy) may be 101.5 mg/dL for lipoprotein(a), a substantial task. Whether this represents a likely number will await clinical trials.

Although the PCSK9 inhibitors lower lipoprotein(a) by <30%, the 2 current approaches, through antisense technology, promise much larger reductions. Large reductions in lipoprotein(a) have been realized with the antisense oligonucleotide that inhibits the gene LPA in the liver. Oligonucleotide directed to inhibit messenger RNA for LPA has led to reductions in circulating lipoprotein(a) by as much as 90%, with minimal adverse effects. The second approach, called ORION, has been through RNA silencing of the PCSK9 gene that lowered LDLC and apolipoprotein B and incidentally also lowered lipoprotein(a). The appeal of the second approach, although directed at LDL lowering, is that it appears to require only 2 injections annually. The obvious disadvantage of the anti-PCSK9 technology is that its primary focus is on lowering LDLC and, therefore, the reduction in lipoprotein(a) is considerably less compared with the technology that is directed against lipoprotein(a) production.

Cost-effectiveness at likely market pricing will require careful analysis. By analogy with discussed recommendations for the use of PCSK9 inhibitors, the drugs may become appropriate for high-risk patients with elevated lipoprotein(a) and severe atherosclerotic cardiovascular disease. The initial priority is likely to include those with recurrent acute coronary syndrome and other comorbidities, such as familial hypercholesterolemia and diabetes mellitus. Intolerance for statins and a high concentration of lipoprotein(a) as the sole major risk factors (increasingly identified in younger patients with acute coronary syndrome) are likely early candidates.

The article by Shapiro et al adds to the considerable evidence that the LDLR system plays, at best, a partial role in the removal of lipoprotein(a). Until the full process of removal is elucidated, efforts to reduce lipoprotein(a) rest with inhibitors of its production in the liver.

Disclosures
None.

References
1. Shapiro MD, Minnier J, Tavori H, Kassahun H, Flower A, Somaratne R, Fazio S. Relationship between low-density lipoprotein-cholesterol and lipoprotein(a) lowering in response to PCSK9 inhibition with evolocumab. J Am Heart Assoc. 2019;8:e010932. DOI: 10.1161/JAHA.118.010932.
2. Kamstrup PR, Benn M, Tjøbaø-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population. Circulation. 2008;117:176–184.
3. Nestel PJ, Barnes EH, Tonkin AM, Simes J, Fournier M, White HD, Colquhoun DM, Blankenberg S, Sullivan DR. Plasma lipoprotein(a) concentration predicts future coronary and cardiovascular events in patients with stable coronary heart disease. Arterioscler Thromb Vasc Biol. 2013;33:2902–2908.
4. Waldeyer C, Makarova N, Zeller T, Schnabel RB, Brummer F, Jorgensen T, Linneberg A, Niiranen T, Saloma F, Joussilahti P. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. Eur Heart J. 2017;38:2490–2498.
5. Willeit P, Rieder PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, Schwartz GG, Olsson AG, Colhoun HM, Kronenberg F, Drechsler C, Wanner C, Lesogor S, Tsimikas S, Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. Lancet. 2018;392:1311–1320.
6. Emdin CA, Khera AV, Natarajan P, Won H-H, Pelosi GM, Stitziel NO, Nomura A, Zekavat SM, Bick AG, Gupta N, Assetta R, Duga S, Merlina PA, Correa A, Kessler T, Wilson JG, Brown MJ, Hall AS, Brandu PS, Samani NJ, Schunkert H, Marrugat JM, Elosua R, McPherson R, Farrall M, Watkins H, Willer C, Abecasis GR, Felix JF, Vasan RS, Lander E, Rader DJ, Danesh J, Ardissino D, Saleheen D, Kathiresan S. Phenotypic characterization of genetically lowered human lipoprotein(a) levels. J Am Coll Cardiol. 2016;68:2761–2772.
7. Tsimikas S. A test in context: lipoprotein (a). J Am Coll Cardiol. 2017;69:692–711.
8. Rael FJ, Giugliano RP, Sabatine MS, Koren MJ, Langslet G, Bays H, Blom D, Eriksson M, Dent R, Wasserman SM, Huang F, Xue A, Albizum M, Scott R, Stein EA. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145). J Am Coll Cardiol. 2014;63:1278–1288.
Lipoprotein(a) Clearance Uncertain  Nestel

9. Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Blom D, Nabil G, Honarpour M, Lira A, Xue A, Chiruvolu P, Jackson S, Wasserman SM, Scott R, Stein ES. PCSK9 inhibition-mediated reduction in Lp(a) with evolocumab: an analysis of 10 clinical trials and the LDL receptor’s role. J Lipid Res. 2016;57:1086–1096.

10. Wei WQ, Li X, Feng Q, Kubo M, Peissig PL, Karlson EW, Jarvik GP, Lee MTM, Shang N, Larson EA, Shaffer CM, Mosley JD, Maeda S, Horikoshi M, Ritchie M, Williams MS, Larsen EB, Crosslin DR, Bland ST, Pacheco JA, Rasmussen-Torvik LJ, Cronkite D, Hipcsak G, Cox NJ, Wilke RA, Stein CM, Rotter JI, Momozawa Y, Krauss RM, Denny JC. LPA variants are associated with residual cardiovascular risk in patients receiving statins. Circulation. 2017;138:1839–1849.

11. Langsted A, Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective study. Lancet Diabetes Endocrinol. 2016;4:577–587. DOI: 10.1016/S2213-8587.

12. Li S, Wu N-Q, Zhu C-G, Zhang Y, Guo Y-L, Li X-L, Qing P, Cui C-J, Xu R-X, Sun J, Liu G, Dong Q, Li J-J. Significance of lipoprotein(a) levels in familial hypercholesterolemia and coronary artery disease. Atherosclerosis. 2017;260:67–74.

13. Reyes-Sofer G, Pavlyha M, Ngai C, Thomas T, Holleran S, Ramakrishnan R, Karmally W, Nandakumar R, Fontanez N, Obunike JC, Marcovina SM, Lichtenstein AH, Matthau NR, Matta J, Maroccia M, Becue F, Potiers F, Swanson B, Sasiela WJ, Surks HK, Ginsberg HB. Effects of PCSK9 inhibition with alirocumab on lipoprotein metabolism in healthy humans. Circulation. 2017;134:352–362.

14. Arsenault BJ, Petrides F, Tabet F, Bao W, Hovingh GK, Boekholdt SM, Ramin-Mangata S, Mehlhac O, DeMicco D, Rye KA, Waters DD, Kastelein JJP, Barter P, Lambert G. Effects of atorvastatin, cholesterol ester transfer protein inhibition, and diabetes mellitus on circulating proprotein subtilisin kexin type 9 and lipoprotein(a) levels in patients at high cardiovascular risk. J Clin Lipidol. 2018;12:130–136.

15. Clarke R, Peden JF, Hopewell JC. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009;361:2518–2528.

16. Kamstrup PR, Tybjærg-Hansen A, Steffensen R, Nordestgaard BG. Gently elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009;301:2331–2339.

17. Burgess S, Ference BA, Staley JR, Freitag DF, Mason AM, Nielsen SF, Willett P, Young R, Suendran P, Karthikeyan S, Bolton TR, Peters JE, Kamstrup PR, Tybjærg-Hansen A, Benn M, Langsted A, Schnohr P, Vedel-Krogstrup S, Kobylyckaja C, Ford I, Packard C, Trompet S, Jukema JW, Sattar N, Di Angelantonio E, Saleheen D, Howson JMM, Nordestgaard BG, Butterworth AS, Danesh J. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a) lowering therapies: a Mendelian randomization analysis. JAMA Cardiol. 2018;3:619–627.

18. Viney NJ, Capelleveen JC, Geary RS, Xia S, Marcovina SM, Hughes SG, Graham MJ, Crooke RM, Witztum JL, Stroes ES, Tsimikas S. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised apolipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet. 2016;388:2239–2253.

19. Ray KK, Stoekenbroek RM, Kallend D, Leiter LA, Landmesser U, Wright RS, Wijngaard P, Kastelein JJP. Effect of siRNA therapeutic targeting PCSK9 on atherogenic lipoproteins. Circulation. 2018;138:1304–1316.

Key Words: Editorials • antisense silencing of LPA gene • cardiovascular risk • LDL receptor • lipoprotein(a) • proprotein convertase stabilisin/kexin type 9 inhibitor