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PCSK9 Inhibition: Does Lipoprotein Size Matter?

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In order to assess the risk of cardiovascular diseases in patients, fasting plasma lipids levels are usually measured as total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) and combined to estimate low-density lipoprotein cholesterol (LDL-C) levels using the Friedewald formula. While this indirect measure is strongly correlated with the risk of cardiovascular diseases in many epidemiological studies, it lacks information related to inter-individual differences and patient's pathophysiological status.[1] Indeed, 2 individuals carrying the same amount of LDL-C could display different numbers of LDL particles (LDL-P) or size. As the correlation between LDL-P and risks of cardiovascular diseases may be stronger than LDL-C, the debate persists on the type of measure that could more accurately predict the best prognosis.[2] Such discrepancies seem to be particularly relevant in patients with metabolic syndrome and diabetes.

The proprotein convertase subtilisin/kexin type 9 (PCSK9) has been identified as a key factor involved in lipoprotein metabolism regulation since its characterization as the third gene of autosomal-dominant hypercholesterolemia in 2003 (ADH).[3] PCSK9 acts as a chaperone protein that binds the LDL receptor (LDLR) at the cell membrane and induces LDLR lysosomal degradation rather than recycling.[4] PCSK9 gain-of-function mutations increase LDLR degradation leading to autosomal-dominant hypercholesterolemia.[5] The identification of the link between PCSK9 loss-of-function mutations, low level of plasmatic LDL-C, and increased protection against cardiovascular diseases has sustained the concept of PCSK9 inhibition as a new therapeutic strategy in hypercholesterolemia.[6] Among PCSK9 inhibitors, the most advanced ones are based on humanized monoclonal antibodies (mAb) targeting extracellular PCSK9[4,7] and 2 of them (alirocumab: Praluent®; evolocumab: Repatha®) have been recently approved by the U.S. Food and Drug Administration and European Medicines Evaluation Agency. The overall outcome of these studies indicated that PCSK9 mAb injections every 2 to 4 weeks led to up to 60% decrease of plasma LDL-C concentrations, either assessed by indirect calculation or by direct measurement.[7] It should be reminded here that LDL-C estimation with Friedewald calculation underestimates true LDL-C values in the lowest ranges (<1.8 mmol/L), a range that it is often achieved with PCSK9 inhibitors.[8] However, little is known about the effect of PCSK9 inhibition on qualitative modifications of LDL-P.

In this issue of *JAHA*, Koren et al[9] investigated the effect of the human PCSK9 mAb alirocumab (150 mg Q2W) on the concentration and size of LDL-P by nuclear magnetic resonance spectroscopy in hypercholesterolemic patients under a stable dose of atorvastatin, who were previously included in a phase II, placebo-controlled, randomized clinical trial.[10] Upon a 12 weeks treatment, the authors showed that concomitantly to LDL-C and HDL-C, LDL-P and HDL-P plasmatic concentrations decreased and increased, respectively, with the same trends in patients treated with alirocumab compared to placebo. The decrease of LDL-P concentration occurred in all subclasses in the alirocumab group, including large (−71.3% versus −21.8% in placebo group) and small LDL-P (−54.0% versus +17.8% in placebo group). Interestingly, alirocumab promoted a substantial increase of large rather than small or medium HDL-P. A decrease of very low-density lipoprotein (VLDL) particles has been also observed in the alirocumab group, which mainly reflected a reduction in medium and small VLDL-P. However, an increased concentration of large VLDL-P was significantly observed in alirocumab-treated patients.

A previous study showed that the level of plasma PCSK9 was negatively correlated with lipoprotein sizes in patients with stable coronary artery disease and without statin treatment.[11] Although indirect, these results indicated a sex effect with a lack of relation between PCSK9 level and lipoprotein size in women. It would be interesting to

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investigate this feature in PCSK9 mAb-treated patients with a larger sample size.

The qualitative lipoprotein modifications described by Koren et al are in accordance with a potential anti-atherogenic effect of alirocumab treatment with a concomitant decrease of small LDL-P and increase of large HDL-P levels. The increase of large VLDL-P levels, which are negatively correlated with a healthy metabolic profile,[12] remains puzzling. Indeed, large VLDL have been shown to be associated with pro-atherogenic effects. However, we have previously demonstrated that PCSK9 knock-out mice displayed a 10% increase of chylomicrons size associated with a better clearance and a significant decrease of postprandial lipemia.[13] Therefore, it may be interesting to investigate the postprandial lipemia in patients treated with PCSK9 mAb and/or patients carrying PCSK9 loss-of-function mutations in order to characterize the relevance of large VLDL-P in patients with low PCSK9.

Finally, a similar study with PCSK9 mAb should be specifically conducted in diabetic patients as they display greater qualitative modifications of lipoprotein size.[14]

Overall, the study from Koren et al shows the concomitant decrease of LDL-P together with LDL-C, which, as suggested by the authors, could be beneficial for patients with discordant LDL-C and LDL-P. However, as other drugs such as fenofibrate or niacin led to an anti-atherogenic profile without reaching cardioprotective relevance,[15–18] results from the ongoing cardiovascular outcome studies with PCSK9 mAb are needed in order to obtain a clear conclusion on the beneficial aspect of anti-PCSK9 treatments on LDL-P profile and cardiovascular protection.

Disclosures

Cariou has received advisory board fees from Amgen and Sanofi/Regeneron Pharmaceuticals. Si-Tayeb declares nothing to disclose.

References

1. Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol*. 2011;5:105–113.
2. Sniderman A, Kwiterovich PO. Update on the detection and treatment of atherogenic low-density lipoproteins. *Curr Opin Endocrinol Diabetes Obes*. 2013;20:140–147.
3. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003;34:154–156.
4. Cariou B, Le May C, Costet P. Clinical aspects of PCSK9. *Atherosclerosis*. 2011;216:258–265.
5. Cunningham D, Danley DE, Geoghegan KF, Griffor MC, Hawkins JL, Subashi TA, Varghese AH, Ammirati MJ, Culp JS, Hoth LR, Mansour MN, McGrath KM, Seddon AP, Shenolikar S, Stutzman-Engwall KJ, Warren LC, Xia D, Qiu X. Structural and biophysical studies of PCSK9 and its mutants linked to familial hypercholesterolemia. *Nat Struct Mol Biol*. 2007;14:413–419.
6. Cohen JC, Boerwinkle E, Mosley TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354:1264–1272.
7. Shimada YJ, Cannon CP. PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors: past, present, and the future. *Eur Heart J*. 2015;36:2415–2424.
8. Stein EA, Raal FJ. Targeting LDL: is lower better and is it safe? *Best Pract Res Clin Endocrinol Metab*. 2014;28:309–324.
9. Koren MJ, Kereiakes D, Pourfarzib R, Winegar D, Banerjee P, Hamon S, Hanotin C, McKenney JM. Effect of PCSK9 inhibition by alirocumab on lipoprotein particle concentrations determined by nuclear magnetic resonance spectroscopy. *J Am Heart Assoc*. 2015;4:e002224 doi: 10.1161/JAHA.115.002224.
10. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J Am Coll Cardiol*. 2012;59:2344–2353.
11. Xu RX, Li S, Zhang Y, Li XL, Guo YL, Zhu CG, Li JJ. Relation of plasma PCSK9 levels to lipoprotein subfractions in patients with stable coronary artery disease. *Lipids Health Dis*. 2014;13:188.
12. Phillips CM, Perry IJ. Lipoprotein particle subclass profiles among metabolically healthy and unhealthy obese and non-obese adults: does size matter? *Atherosclerosis*. 2015;242:399–406.
13. Le May C, Kourimate S, Langhi C, Chétiveaux M, Jarry A, Comera C, Collet X, Kuipers F, Krempf M, Cariou B, Costet P. Proprotein convertase subtilisin kexin type 9 null mice are protected from postprandial triglyceridemia. *Arterioscler Thromb Vasc Biol*. 2009;29:684–690.
14. Rizzo M, Rini GB, Berneis K. The clinical relevance of LDL size and subclasses modulation in patients with type-2 diabetes. *Exp Clin Endocrinol Diabetes*. 2007;115:477–482.
15. Bays H, Giezek H, McKenney JM, O'Neill EA, Tershakovec AM. Extended-release niacin/laropiprant effects on lipoprotein subfractions in patients with type 2 diabetes mellitus. *Metab Syndr Relat Disord*. 2012;10:260–266.
16. HSP2-THRIVE Collaborative Group, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371:203–212.
17. Chan DC, Hamilton SJ, Rye KA, Chew GT, Jenkins AJ, Lambert G, Watts GF. Fenofibrate concomitantly decreases serum proprotein convertase subtilisin/kexin type 9 and very-low-density lipoprotein particle concentrations in statin-treated type 2 diabetic patients. *Diabetes Obes Metab*. 2010;12:752–756.
18. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR III, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC Jr, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1563–1574. Erratum in: N Engl J Med. 2010;362:1748.

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