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 interindividual 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\(^8\); evolocumab: Repatha\(^9\)) 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 \textit{JAMA}, 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...
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, remains puzzling. Indeed, large VLDL-P are known to be associated with pro-atherogenic effects. However, we have previously demonstrated that PCSK9 knock-out mice display a 10% increase of chylomicrons size associated with a better clearance and a significant decrease of postprandial lipemia. 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. 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, 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.

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