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Lipids and Lipoproteins in 2020

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This JAMA Insights explains how recent studies have clarified the role of lipids and lipoproteins in the development of atherosclerotic cardiovascular disease (ASCVD) and led to changes in clinical practice guidelines for the management of dyslipidemia.[1]

Lipids and Lipoproteins in the Development of ASCVD

Cholesterol and triglycerides are the major lipids in humans and are transported in plasma by lipoproteins. A lipoprotein is composed of cholesterol, triglycerides, and a single apolipoprotein B_{100} molecule (apoB) when secreted into plasma by the liver, and is referred to as a *very low-density lipoprotein* (*VLDL*). The triglycerides are rapidly removed by the enzyme lipoprotein lipase and used for energy consumption and storage. As triglycerides are being progressively removed, the lipoprotein is referred to as a *VLDL remnant particle*. After most of the triglycerides have been removed, the lipoprotein becomes denser and is referred to as a *low-density lipoprotein* (*LDL*). However, it is important to recognize that a VLDL particle, a remnant particle, and an LDL particle are merely different names for the same circulating apoB lipoprotein at different stages in its lifecycle, depending on the lipid content that it carries.

At any point in its lifecycle, regardless of its lipid content, an apoB lipoprotein less than 70 nm in diameter can flux across the endothelial barrier, where it may be returned to circulation via the lymphatic system or become trapped in the artery wall. The trapping of an apoB lipoprotein in the artery wall and subsequent release of its cholesterol content to macrophages is the necessary step for the initiation and progression of an atherosclerotic plaque.[2] Over time, the atherosclerotic plaque slowly enlarges as more apoB-containing VLDL, remnant, and LDL particles become trapped in the artery wall (**Figure**).[3]

Measurement of Plasma Lipids and Lipoproteins

Each apoB-containing lipoprotein has a single apoB molecule. Therefore, plasma apoB concentration is a direct measure of the total number of circulating atherogenic apoB particles that can become trapped in the artery wall. However, the standard lipid panel does not typically measure apoB levels. Instead, the number of circulating apoB particles is indirectly estimated by measuring plasma LDL cholesterol (LDL-C) and triglyceride concentration.

LDL-C is an estimate of the total cholesterol content carried by LDL particles, which is an estimate of the concentration of circulating LDL particles.[4] Similarly, plasma triglyceride concentration (mg/dL) divided by 5 is an estimate of the cholesterol content carried by triglyceride-rich lipoproteins, which is an estimate of the concentration of circulating VLDL and remnant particles.[4] These estimates can be combined to derive an estimate of the total cholesterol content carried by all apoB particles, referred to as *non–high-density lipoprotein cholesterol*, which in turn is an estimate of the total circulating concentration of all apoB particles. However, the practice of measuring LDL-C and triglycerides to indirectly estimate the concentration of circulating atherogenic apoB particles has caused confusion about the role of lipids and lipoproteins in the development of ASCVD and uncertainty about the benefit of different types of lipid-lowering therapies. This uncertainty is reflected in current clinical practice guidelines.

Guideline Recommendations

Current guidelines recommend lowering LDL-C with statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors, because these therapies have been shown to reduce the risk of ASCVD events in randomized trials.[1,5] Each of these therapies reduces LDL-C by reducing the number of circulating LDL particles through upregulation of the LDL receptor. In contrast, the guidelines do not recommend therapies that reduce LDL-C by a mechanism other than clearing LDL particles through the LDL receptor or that primarily reduce plasma triglyceride levels, because the clinical benefit of these therapies is uncertain.

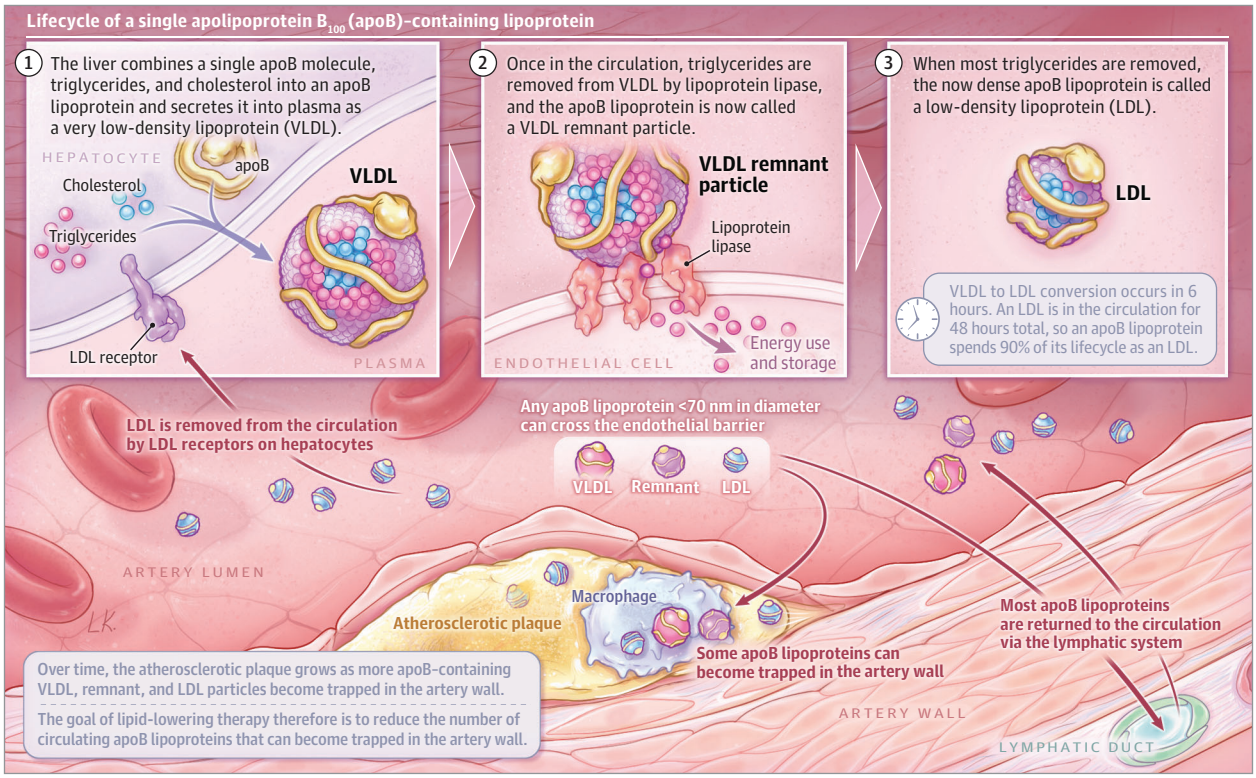
Role of apoB in Estimating the Clinical Benefit of Novel Lipid-Lowering Therapies

Recent studies have helped clarify the role of lipids and lipoproteins in the development of atherosclerosis. For example, a cholesteryl ester transfer protein inhibitor blocks the transfer of cholesterol esters to LDL particles, thus reducing plasma LDL-C by reducing the amount of cholesterol carried by LDL particles. However, mendelian randomization studies and randomized trials have demonstrated that the clinical benefit of a cholesteryl ester transfer protein inhibitor is proportional to the absolute reduction in circulating LDL particles as measured by apoB, rather than the reduction in the cholesterol carried by those particles as measured by LDL-C.[6,7] Another mendelian randomization study demonstrated that genetic variants that mimic LDL-C–lowering therapies and triglyceride-lowering therapies were associated with the same reduction in ASCVD risk for the same change in apoB concentration, despite being associated with markedly different changes in plasma LDL-C and triglyceride concentrations.[8] These data strongly suggest that the risk of ASCVD is determined by the total concentration of circulating apoB particles regardless of the lipid content they carry, and therefore the clinical benefit of any lipid-lowering therapy should be proportional to the absolute achieved reduction in apoB concentration regardless of the corresponding changes in LDL-C or triglycerides.

Implications for Clinical Practice

The emerging evidence suggests that the optimal lipid-lowering therapy for any person will be the one that produces the greatest absolute reduction in apoB. Under most circumstances, 90% of circulating apoB particles are LDL particles.[3] Therefore, a therapy that reduces LDL-C by reducing LDL particles through upregulation of the LDL receptor, such as a statin, will likely be the optimal first lipid-lowering therapy for most people. If additional lipid lowering is required, another therapy that reduces LDL-C by reducing LDL particles will likely produce the greatest absolute reduction in apoB for most people without markedly elevated triglycerides levels, and thus will be the preferred next therapy. In contrast, for some people with markedly elevated triglycerides and low LDL-C levels, triglyceride-rich VLDL remnant particles may compose a greater proportion of circulating apoB particles than LDL. For these individuals, a novel agent that substantially lowers plasma triglycerides could produce

Figure. Role of Apolipoprotein B_{100} Molecule (apoB)–Containing Lipoproteins in the Development of Atherosclerosis



a greater absolute reduction in apoB and therefore would be the preferred next therapy to add.

Based on the evidence described above, the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidaemia[1] became the first major international guideline to state that measurement of apoB levels "is recommended" to help assess ASCVD risk and to estimate the expected clinical benefit from lipid-lowering therapy. This is a forward-looking statement that anticipates the availability of novel lipid-lowering therapies in the future and the need to measure apoB to help guide selection of the optimal therapy for each person, as outlined above. Therefore, because future clinical practice guidelines may recommend using apoB measurements to help select the appropriate therapy for each patient, clinicians should be aware of the central role of apoB-containing lipoproteins in the development and management of ASCVD.

ARTICLE INFORMATION

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