Triglyceride-Rich Lipoprotein Remnant Particles and Risk of Atherosclerosis

Howard N. Hodis, MD

More than 3 decades of clinical research have suggested a relationship between triglycerides and coronary heart disease. However, because of the complexity of what is actually measured by a plasma triglyceride determination, establishing a firm relationship between triglycerides and coronary heart disease has been difficult. Triglycerides are carried in virtually all plasma lipoproteins and present a different risk profile in both the fasting and postprandial states, making triglyceride-rich lipoproteins highly heterogeneous. This heterogeneity is a major contributing factor to the complexity of the relationship between triglycerides and coronary heart disease.

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Accumulating evidence indicates that specific triglyceride-rich lipoprotein remnants of differing size and composition, such as VLDL, IDL, lipoprotein B–containing particles (LP-B:C, LP-B:C:E, and LP-A-II:B:C:D:E), and markers of triglyceride-rich lipoprotein metabolism such as apolipoprotein C-III (apoC-III), are more related to progression of atherosclerosis than triglycerides per se. The assertion by Kugiyama et al that fasting remnant lipoproteins are more atherogenic than triglycerides is consistent with evidence that these remnants are partially delipidized lipoproteins and their contribution to atherosclerosis. Remnant lipoproteins are partially catabolized chylomicrons and VLDLs that are reduced in size, partially depleted of triglycerides, and enriched with cholesterol esters. Remnants formed from catabolism of VLDL consist of smaller VLDLs and IDL.

Triglyceride-rich lipoproteins comprise a great variety of nascent and metabolically modified lipoprotein particles differing in size, density, and lipid and apolipoprotein composition. Although the exact physical-chemical composition of an atherogenic lipoprotein is not known, evidence indicates that size and specific structural arrangement of lipids and apolipoproteins are the main factors determining atherogenicity. Studies have consistently shown an inverse relationship between lipoprotein particle size and capacity for lipoproteins to enter the arterial wall. Accordingly, chylomicrons and large VLDLs (Svedberg flotation unit [Sf] 60 to 400) do not seem capable of entering the arterial intima. On the other hand, small VLDLs (Sf 20 to 60) and IDLs (Sf 12 to 20) seem to share a similar mechanism and potential for penetrating the arterial intima. As such, certain triglyceride-rich lipoproteins are atherogenic, whereas others are not. In particular, small VLDLs and IDLs have been shown to be independently associated with the presence, severity, and progression of atherosclerosis.

Serial arterial imaging studies have provided an excellent opportunity to extend cross-sectional associations between triglycerides and coronary heart disease to studies that permit the examination of the relationships between triglyceride-rich lipoproteins and the progression of atherosclerosis. In a subgroup analysis of lipoprotein mass concentrations measured by analytical ultracentrifugation at baseline and after 2 years in the Type II Coronary Intervention Study, change in IDL mass (S 12 to 20) was significantly predictive of coronary artery lesion progression at 5 years. With the same analytical ultracentrifugation methodology, lipoprotein mass concentrations were measured at baseline and every 6 months for 2 years in 220 subjects participating in the Monitored Atherosclerosis Regression Study (MARS). Lipoproteins in the S 12 to 60 range (IDLs and small VLDLs) emerged as the independent correlates of coronary artery atherosclerosis progression.

In the same MARS cohort, apoC-III in the LDL-VLDL subfraction was also found to be significantly correlated with coronary artery lesion progression. ApoC-III is a marker of triglyceride-rich lipoprotein metabolism and clearance of VLDLs and chylomicrons. Inhibition of lipoprotein lipase–activated lipolysis by VLDL-associated apoC-III prolongs the circulatory residence time of VLDL and therefore increases the exposure time of the arterial wall to this atherogenic particle. ApoC-III in VLDL is associated with denser, smaller VLDL subclasses believed to be particularly atherogenic.

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

From the Atherosclerosis Research Unit, Division of Cardiology, University of Southern California School of Medicine, Los Angeles, Calif.

Correspondence to Howard N. Hodis, MD, Associate Professor of Medicine and Preventive Medicine, Director, Atherosclerosis Research Unit, Division of Cardiology, University of Southern California School of Medicine, 2250 Alcezar St, CSC 132, Los Angeles, CA 90033.

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particles were isolated by column immunoaffinity tech-
niques. Subjects with coronary artery lesion progression had 
significantly higher levels of LP-B, a (summed measure of 
triglyceride-rich lipoproteins) and LP-A-II:B:C:D:E particles 
of small VLDL and/or IDL-like sizes. A specific triglyceride-rich lipoprotein particle with a low 
affinity for lipoprotein lipase and a long circulatory residence 
time that most likely contributes to its atherogenicity. The 3 independent techniques for identifying triglyceride-
rich lipoproteins outlined above are based on different 
physical-chemical properties: protein composition (electro-
immunoassay for apoC-III), lipoprotein mass (analytical ul-
tracentrifugation), and lipoprotein particles (column immu-
noaffinity). These results provide compelling evidence for 
the relationship between the progression of coronary artery ath-
erosclerosis and triglyceride-rich lipoprotein remnants. Other 
sto, such as the Cholesterol Lowering Atherosclerosis 
Study and the Program on the Surgical Control of the 
Hyperlipidemias, have also demonstrated a relationship 
between coronary artery lesion progression and apoC-III and 
VLDL, respectively.

The aforementioned findings have a particular importance 
in that triglyceride-rich lipoproteins such as small VLDLs 
and apoC-III are related to the progression of mild/moderate 
(<50% diameter stenosis) rather than severe (≥50% diame-
ter stenosis) coronary artery lesions. This is relevant to the 
findings of Kugiyama et al because coronary artery lesions of 
<50% diameter stenosis appear to be the lesions that 
predict clinical coronary events. Triglyceride-rich lipopro-
teins may contribute to lesion progression, plaque rupture, 
and clinical coronary events through a variety of mechanisms. 
Triglyceride-rich lipoproteins are susceptible to peroxidative 
damage, can be taken up by macrophages directly without 
oxidative modification to produce foam cells, and are inti-
mately associated with the clotting and fibrinolytic pathways, 
thus linking atherosclerosis and thrombosis.

Results from the Bezafibrate Coronary Atherosclerosis 
Intervention Trial and the Lapid Coronary Angiographic 
Trial, randomized serial coronary angiographic clinical 
trials that tested bezafibrate and gemfibrozil, respectively, 
support the growing evidence for the relationship between 
triglyceride-rich lipoproteins and atherosclerosis. In these 
trials, a reduction in triglycerides with essentially no change 
in LDL-cholesterol levels resulted in a reduction in the 
progression of coronary artery atherosclerosis in both native 
arteries and aortocoronary bypass grafts to a similar degree as 
LDL-cholesterol lowering with the HMG-CoA reductase 
inhibitors. These studies suggest that triglyceride-rich lipopro-
tein reduction by fibric acid derivatives, perhaps through the downregulation of apoC-III gene expression and 
reduction in VLDL-associated apoC-III levels, results in the 
reduction of atherosclerosis progression.

The accumulated literature has consistently indicated tri-
glyceride-rich lipoprotein remnants to be a risk factor for the 
progression of atherosclerosis and presents plausible mecha-
nisms by which these lipoproteins may be atherogenic and 
result in clinical coronary events. Small VLDL, IDL, apoC-
III, and lipoprotein B-containing particles measured in the 
fasting state most likely represent specific remnant lipopro-
teins contained in the fasting remnant lipoprotein immunoaf-
finity mixed-gel measurement by Kugiyama et al. On the 
basis of current knowledge concerning the heterogeneity of 
triglyceride-rich lipoproteins, it is no surprise that several 
independent measures of specific triglyceride-rich lipopro-
teins correlate with the progression of atherosclerosis. Each of 
these specific triglyceride-rich lipoproteins represents one 
component of the overall remnant particle risk. Although 
unravelling the complexity of triglyceride-rich lipoproteins 
will be an ominous task, it has important implications. For 
example, studies that have reported separation of IDL from 
LDL have failed to show a relation between LDL and 
progression of atherosclerosis. Whether there is a single 
measure or combination of measurements that best represents 
the triglyceride-rich lipoprotein remnant particle risk of 
atherosclerosis still needs to be determined, but it is clear that 
such a pursuit is warranted and well justified.

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