

## Apolipoprotein C-III The Small Protein With Sizeable Vascular Risk

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Nearly 60 years have transpired since Albrink and Man<sup>1</sup> first observed an association between high triglyceride levels and coronary artery disease (CAD). Yet, the mechanisms underlying this association gained minimal traction until 2 decades later<sup>2</sup> and even after many years of exhaustive investigative work, remains incompletely understood.<sup>3</sup> What has been clearly demonstrated, however, is that triglyceride serves as a primary mammalian energy source and is not directly atherogenic. Furthermore, triglyceride-rich lipoproteins (eg, chylomicrons, very low-density lipoprotein) develop atherogenic characteristics on their conversion to cholesterol-enriched remnant particles. In this issue of *ATVB*, van Capelleveen et al<sup>4</sup> demonstrate that apoC-III also plays a central role in promoting vascular risk.

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Human apoC-III is an 8.8-kDa polypeptide that contains 79 amino acids and is considerably smaller than other major apolipoproteins regulating lipoprotein metabolism, including apoB<sub>100</sub> (512 kDa, 4563 amino acids), apoE (34 kDa, 299 amino acids), and apoA I (45 kDa, 396 amino acids).<sup>5</sup> ApoC-III resides on the surface of triglyceride-rich lipoproteins and serves several important metabolic functions. They include triglyceride raising by direct inhibition of lipoprotein lipase<sup>6</sup> and via a recently identified lipoprotein lipase-independent mechanism.<sup>7</sup> ApoC-III also inhibits hepatic lipase,<sup>8</sup> delays clearance of apoB containing particles, and accelerates the conversion of light to dense low-density lipoprotein (LDL) particles.<sup>9</sup> These proatherogenic particles gain facilitated entry through the endothelial intima followed by oxidation and uptake by vascular macrophages lining the arterial wall.<sup>10</sup>

Ironically, the clinical relevance of apoC-III in humans was initially uncovered with low triglyceride, rather than hypertriglyceridemia. Specifically, 2 sisters with familial APOA1-C3 deficiency<sup>11</sup> exhibited triglyceride levels of 38 and 61 mg/dL ( $\approx 50\%$ – $75\%$  lower than the median triglyceride during that period), nondetectable apoC-III levels, and increased fractional turnover of very low-density lipoprotein triglyceride consistent with increased lipoprotein lipase activity.<sup>12</sup> More recently, very low triglyceride (mean, 31 mg/dL) combined with a 50% reduction in apoC-III levels was discovered in an Amish cohort

who had inherited a single defective allele (*APOC3*. R19X) that also correlated with reduced coronary calcification.<sup>13</sup> Carriers of several different rare *APOC3* loss-of-function mutations (including R19X) were subsequently found to have low triglyceride and a significantly reduced risk of vascular disease.<sup>14,15</sup>

In contrast, studies examining the effect of apoC-III enrichment in apoB containing lipoproteins (ie, very low-density lipoprotein and LDL) identified increased coronary arteriographic progression and recurrent CAD events.<sup>16,17</sup> Among the 2 large prospective studies that previously examined plasma apoC-III levels and CAD risk, one found a significant association with apoC-III enrichment of LDL but not with plasma apoC-III after adjustment for triglyceride.<sup>18</sup> In the second study, apoC-III levels in the top quartile at baseline were predictive of cardiovascular death over the 15-year follow-up period.<sup>19</sup> However, this effect was attenuated after adjustment for triglyceride and was of borderline statistical significance in the fully adjusted analysis.<sup>19</sup> Finally, a recent meta-analysis that incorporated the aforementioned studies found an  $\approx 33\%$  increased risk of CAD for each 5-mg/dL increment in plasma apoC-III levels<sup>20</sup> although the vast majority of these studies did not adjust for triglyceride.

The study by van Capelleveen et al<sup>4</sup> confirms the association between plasma apoC-III levels and incident CAD. Although these effects were attenuated after adjustment for triglyceride, subgroup analysis found apoC-III to remain independently associated with CAD in subjects with high triglyceride (median,  $>1.7$  mmol/L or 150 mg/dL). Interestingly, the combination of high triglyceride and low apoC-III was not associated with increased CAD risk. This supports the concept that high apoC-III may potentiate vascular risk, especially in the setting of hypertriglyceridemia. As illustrated in the Figure, there are at least 3 potential pathways promoting these effects. Inhibition of lipoprotein lipase and hepatic lipase results in delayed clearance of triglyceride-rich lipoproteins and atherogenic remnants, the latter of which are incorporated by vascular macrophages lining the vascular wall. ApoC-III also inhibits removal of large LDL and remnants by inhibiting hepatic lipoprotein receptors that interact with apoB and apoE, culminating in facilitated conversion to smaller proatherogenic particles (eg, small dense LDL). Finally, apoC-III induces proinflammatory cellular signaling by activating vascular cell adhesion molecule-1 and nuclear factor  $\kappa$ B.<sup>21</sup> In effect, the association between apoC-III and incident CAD reported by van Capelleveen et al<sup>4</sup> was largely attributable to increased triglyceride-rich lipoprotein, remnants, sdLDL (small, dense LDL), and high sensitivity C-reactive protein, a biomarker of systemic inflammation.

Overall, the current study suggests that high apoC-III levels provide incremental discriminatory power in the assessment of CAD risk, particularly in hypertriglyceridemia states. However, before routine screening for high apoC-III

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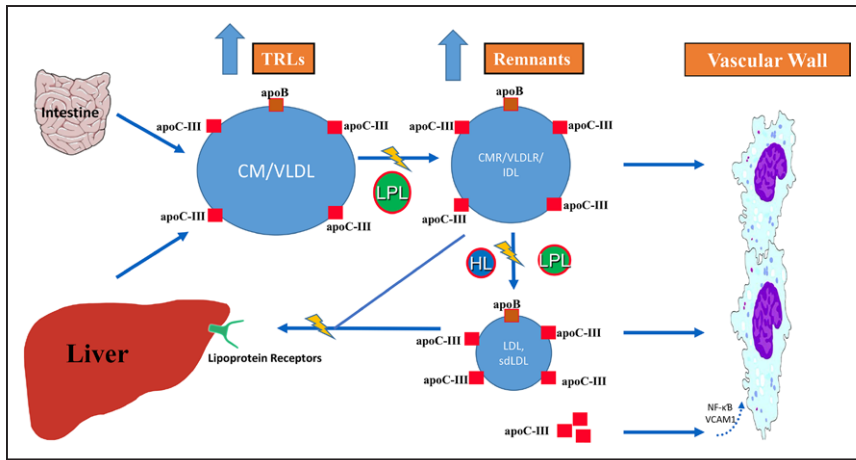
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**Figure.** Potentiation of vascular risk induced by ApoC-III. The 4 molecules of apoC-III on each of the depicted lipoproteins is for illustration purposes only. It is estimated that there are 10 to 20 apoC-III molecules for each low-density lipoprotein (LDL) particle.<sup>18</sup> There is only 1 apoB molecule (as depicted) for each lipoprotein particle. CM indicates chylomicron; CMR, chylomicron remnant; HL, hepatic lipase; IDL, intermediate density lipoprotein; LPL, lipoprotein lipase; NF- $\kappa$ B, nuclear factor- $\kappa$ B; sLDL, small, dense LDL; TRL, triglyceride-rich lipoprotein; VLDL, very low-density lipoprotein; and VLDLR, very low-density lipoprotein receptor.

is recommended, it would seemingly be most reasonable to first establish whether lowering triglyceride (+/- apoC-III) reduces CAD risk. Fortunately, ongoing randomized clinical trials are well underway<sup>22,23</sup> and together with novel therapies targeting apoC-III<sup>7</sup> should move us a step closer to satisfactorily addressing this clinical conundrum in the near future.

## Disclosures

Dr Miller serves on the Steering Committee for the REDUCE IT Study (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial).

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