

Apolipoprotein B and Atherosclerosis

Apolipoprotein B-100 (apoB) is the major structural protein found on all atherogenic lipoprotein particles¹ and has been shown to be a causal factor in the development of atherosclerosis (asCVD)². It is believed to be due to its presence on the outer surface of low density lipoprotein particles (LDLp) - which comprise the bulk of the atherogenic lipoproteins found in serum. This causality has been independently confirmed by a statistical/ genomic analysis known as mendelian randomization³.

Biochemical and physiological experiments have shown that apoB is central to developing atherosclerotic lesions in the arterial wall⁴. ApoB-containing lipoproteins enter the arterial subendothelial layer, are subjected to oxidation and other post translation modifications and become bound within the arterial intimal⁵. This entrapment signals cytokines to trigger an inflammatory response, leading to foam cell formation and plaque buildup in the arterial wall⁶.

Other aggregating factors for asCVD - ranked by hazard ratios, include low cardiovascular fitness 1.65⁷, smoking status 1.56⁸, age (>45yr) 1.47⁸, diabetes 1.25⁸, and hypertension 1.16⁸. These risk factors are considered insufficient for the atheroma to progress in the absence of LDL particles⁹.

Structure : ApoB's structural properties may provide a clue to its atherogenicity¹⁰. Amino acid residues external to the particle membrane can be modified by oxidation¹¹, glycation¹² and ceramidylation¹³. These modifications in exposed areas of the amino acid sequence could lead to conformational changes in the particle - possibly resulting in smaller (and therefore more dense) LDL particles¹⁴.

It is generally assumed that all apoB containing lipoprotein particles promote atheroma formation, but its not clear whether they are equally atherogenic¹⁵. VLDL particles and their remnants are an independent marker for risk in individuals with low LDL-C¹⁶. Furthermore residual asCVD risk improved in individuals with fewer remnant VLDL particles¹⁷. Components of these particles subjected to oxidation represent a particularly inflammatory version of apoB. In addition to apoB, phospholipids in the lipid outer layer are also susceptible to oxidation¹¹. Antibodies against oxidized lipoprotein-associated phospholipids (oxPL) and oxidized apoB (LDL^{ox}) have been developed but are not currently commercially available. Future trials investigating these modified forms of lipoprotein particles may solve this question. Consequently current American College of Cardiology guidance is to lower all apoB in serum to below at least 130 mg/dl in order to reduce atherogenic risk¹⁸.

Interventions : Current guidance recommend pharmaceutical interventions and lifestyle changes to lower the risk of atherosclerosis. Table 1 shows the relative benefit of various drugs and lifestyle choices in lowering (HR<1) asCVD risk. Whilst the percentage gains might appear modest, the prevalence of atherosclerosis in humans will result in thousands of lives being saved.

Table 1: Hazard ratios (relative risk) of interventions in reducing asCVD events

Intervention	Hazard Ratio	Confidence Interval 95%	
ACEi / ARB	0.94	0.91-0.97	8
Statins	0.87	0.80-0.93	8
Metformin	0.88	0.84-0.91	8
DPP4 i	0.97	0.91-1.03	8
GLP-1RA	0.76	0.68-0.85	8
SGLT2 i	1.00	0.78-1.28	8
PCSK9i	0.83	0.76-0.91	19
Inclisiran	0.74	0.58-0.94	20
Bempedoic acid	0.80	0.72-0.89	21
Nutrition – Med Diet	0.95	0.91-0.98	22
CV fitness (low)	1.65	1.12-2.44	7

ACEi – angiotensin II converting enzyme inhibitor; ARB – angiotensin receptor blocker; DPP4i – dipeptidyl peptidase IV inhibitor; GLP-1RA – glucagon like peptide 1 receptor agonist; SGLT2i – sodium glucose cotransporter 2 inhibitor; PCSK9i - proprotein convertase subtilisin/kexin type 9 inhibitor; Nutrition Med Diet - Mediterranean diet; CV fitness – cardiovascular fitness.

Lp(a) - It doesn't end there. A fusion variant exists which has the apoB protein covalently bound to another protein called apo(a) in the liver. This larger variant, known as Lp(a), is approximately 6x more atherogenic than apoB on a per particle basis²³. The American College of Cardiology has stated that Lp(a) levels appear to be genetically determined and don't vary through life. Current guidance is to test for it once after the age of five²⁴.

Lp(a) is a complex molecule with a variable molecular weight. The apo(a) moiety can have varying repeat regions within its sequence known as kringles^{25,26}. Kringle IV in particular may bind to oxidised phospholipids (oxPL) on other LDL particles thereby trapping them in the arterial wall²⁷. There is currently no treatment to lower Lp(a). Patients with >30mg/dl are considered high risk for asCVD events whilst a level below 14 mg/dl is considered low risk²⁶.

The case for testing apoB

Discordance : Investigators found that there was discordance between LDL-C / apoB and clinical outcomes in some patients with diabetes²⁸. Gene variants can influence lipoprotein turnover further skewing the discrepancy in some people. Pharmaceuticals such as statins generally lower cholesterol

metrics far more than particle parameters. In the above scenarios clinical outcomes/risk track the underlying apoB metrics more closely than LDL-C^{29,30}.

To assess the optimal marker of cardiovascular risk, a recent cohort study looked at CVD events in a UK Biobank population (n=389529)³¹. They followed apoB, LDL-C and non HDL-C amongst other parameters. The correlation coefficients showed an increased sensitivity for apoB of 5% over non HDL-C and 4% over LDL-C. Given the sample size, this was a statistically significant result (p< 0.001). Nevertheless cholesterol remains the preferred asCVD biomarker despite its slightly inferior association with the disease. LDL-C is cheap, readily available, well understood and supported by a vast body of literature.

Treatment targets – apoB - Clinical opinion is currently divided into two groups. The first group have adopted a “the lower the better” approach, especially in higher risk populations. This presents more patients with potentially favourable clinical outcomes but the approach is not without its economic challenges. Quite simply the cost of new generation lipid-lowering therapy is beyond the reach of many. The second group rely on observational studies to establish treatment targets. This approach has its own limitations which are outlined below.

A recent study reported a J-shaped association between apoB and asCVD events³². They found that in a general population (n=14035 followed for a median 23.2 years) there was a relative increased risk of mortality from coronary heart disease or stroke. An optimal apoB range between 100 mg/dl and 130 mg/dl was observed. These studies have a number of limitations which may affect the results. Observational studies can identify correlations between apoB levels and clinical events. There could be a number of confounding factors affecting the mortality curves produced by these studies. In this case the results were in agreement with the 2019 ACC guidelines¹⁸. Many physicians feel that the 130 mg/dl threshold is too lenient for patients with multiple risk factors and a target of below 70 mg/dl being preferred³³.

Summary

Atherogenic vesicles in human serum are a heterogenous collection of lipoprotein particles which vary widely in size, modification status and cargo content. Unsurprisingly traditional markers of cardiovascular risk are less reliable than the causal particles themselves. A single copy of apoB is present on every atherogenic particle – the apoB assay captures all the asCVD risk, is economical, clinically practicable and a better predictor of clinical outcomes.

ApoB deserves more attention.

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