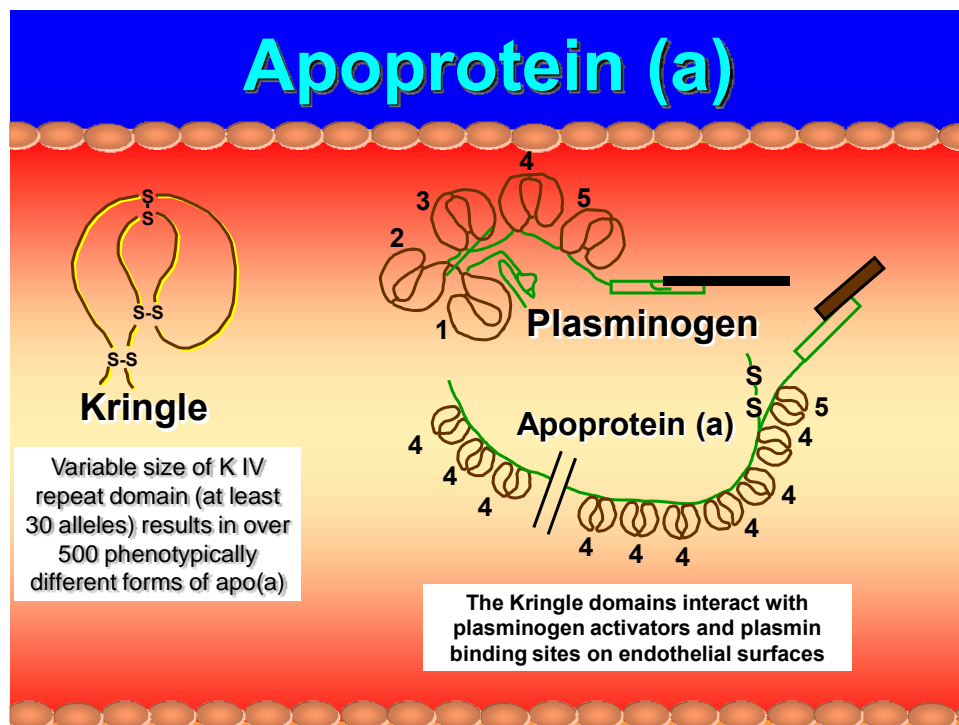
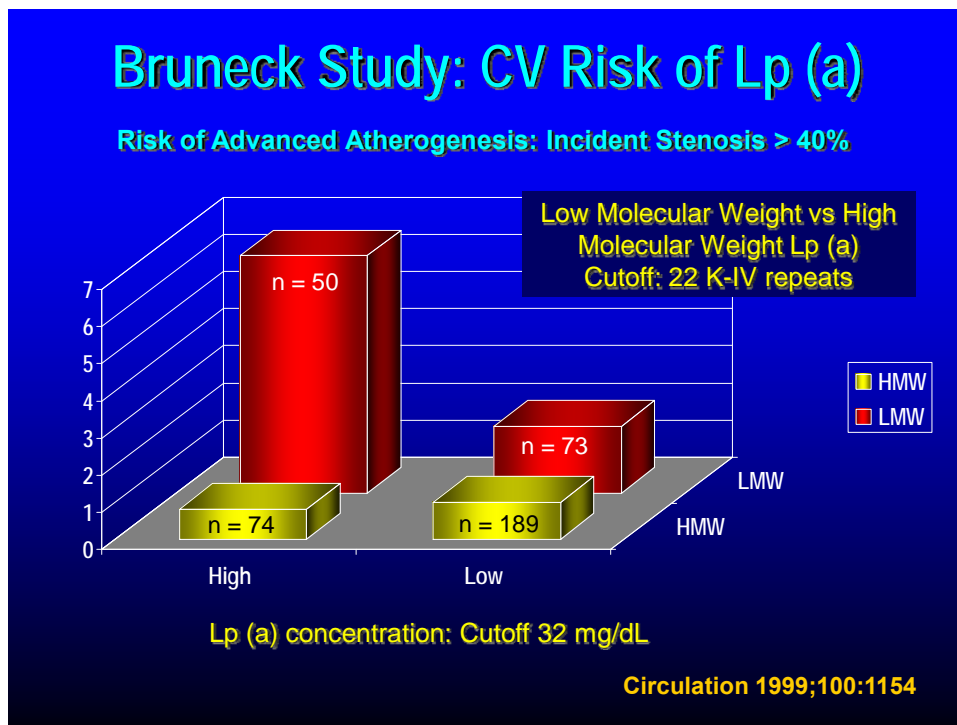
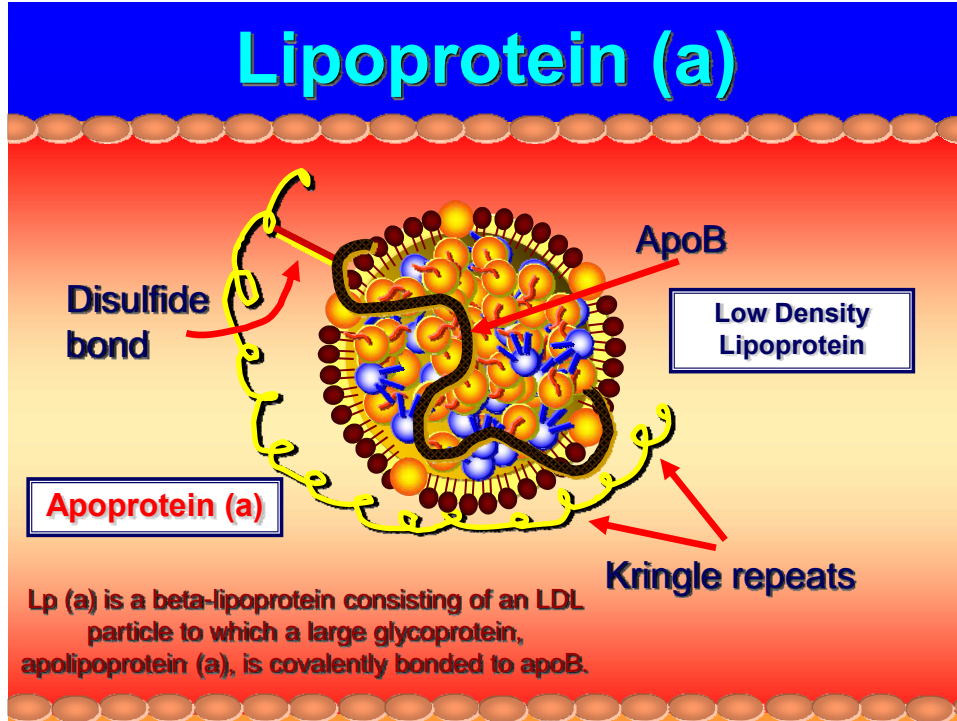


Lipoprotein (a)
Thomas Dayspring MD, FACP

Lipoprotein (a), pronounced lipoprotein "little a" is simply an LDL particle (an apolipoprotein B wrapped collection of phospholipids, free and esterified cholesterol and TG), to which a protein called apolipoprotein (a) is attached to the apoB (via a disulfide bond). Apoprotein (a) is a glycosylated, heterogenous protein that has a variable number of genetically determined repeats of a protein domain, kringle 4. There are different apo(a) isoforms that account for a range of Lp(a) molecular weights (from 280 to 800 kDa). Molecular weight isoforms are inversely associated with circulating Lp(a) concentrations.



Apo(a) can also be attached to TG-rich VLDL particles. The Fractional Catabolic Rate of apo(a) is approximately half that of Lp(a) B-100. Apolipoprotein (a), attached to triglyceride-rich lipoprotein apoB-100, is released from the hepatocyte surface. This newly formed Lp(a) particle releases apo(a) as the triglyceride-rich lipoprotein portion is catabolized via receptor-mediated clearance. The free apo(a) then recombines with another apoB-100 particle, most likely of triglyceride-rich lipoprotein origin. Because about 50% of triglyceride-rich lipoprotein is converted to LDL in the fed state, the second Lp(a) particle may survive catabolism (The metabolism of apolipoproteins (a) and B-100 within plasma lipoprotein (a) in human beings. Jennifer L. Jenner et al. *Metabolism Clinical and Experimental* 2005;54:361– 369)



Lipoprotein (a)
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The proper treatment of elevated Lp(a) is to lower apoB or LDL particle concentration (LDL-P) or their lipid surrogates (LDL-C and non HDL-C). Read below: Statins do not seem to lower Lp (a) and in some studies have actually increased Lp (a) levels.

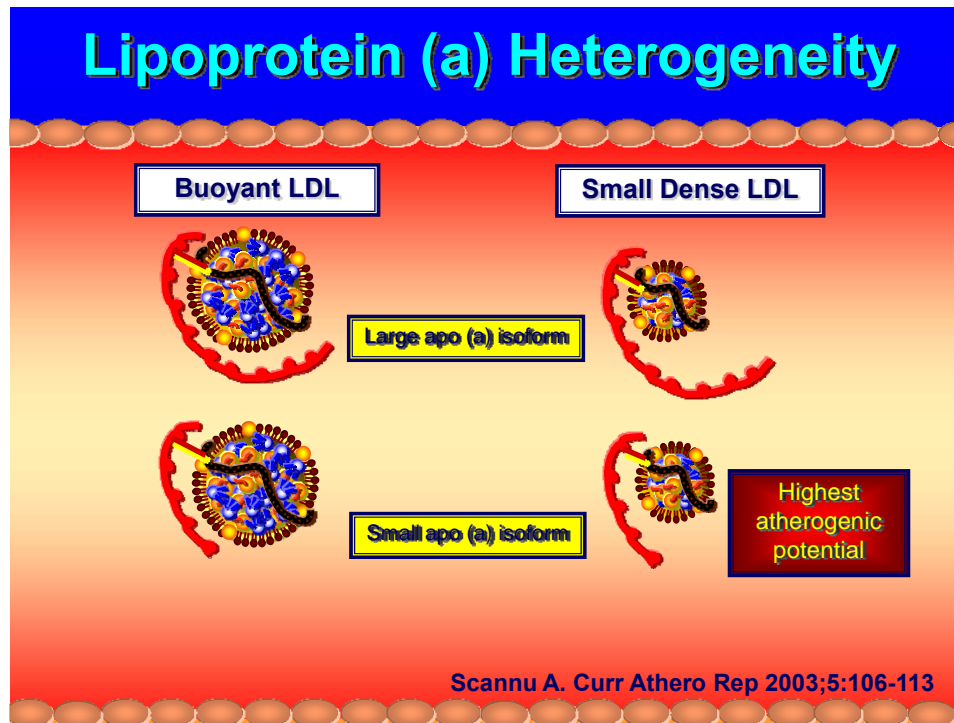
Lipoprotein (a) is an LDL particle with an apoprotein (a) attached via a disulfide bond to the apoprotein B (apoB) on the surface of the LDL particle. In effect the apo(a) camouflages the apoB from hepatic LDL receptors. However, patients with elevated Lp(a) have the apo(a) attached to some but not all of their LDL particles. Apo(a) also exists in several isoforms: low and high molecular weight and the LMW isoform seems to be most associated with atherothrombotic events. Unfortunately isoform testing is not available for the practicing clinician.

In most of the epidemiological studies the risk of elevated apo(a) depends in a linear fashion on the LDL-C concentration. Indeed, data from the large Physicians Health Study, revealed that Lp(a) conveyed no risk if the LDL-C was less than 160 mg/dL. In the Women's Health Study Lp (a) conveyed no risk unless it was extremely elevated (>90th percentile) and the LDL-C (apoB) was also elevated. Thus elevated Lp(a) in the face of normal LDL-C is not a risk factor.

1) Men: High Lp(a) predicts risk of angina, and the risk is substantially increased with high concomitant LDL-cholesterol (reported as > 160 mg/dL). The study found that Lp(a) concentration strongly contributed to CHD risk when LDL-C was concomitantly increased, consistent with several other studies. In other words the risk of Lp(a) is not there if LDL-C is OK (< 160 mg/dL). The men with the highest risk had Lp(a) concentrations > than the 80th percentile and LDL-C > 160 mg/dL. The reference is: Apolipoprotein(a) Size and Lipoprotein(a) Concentration and Future Risk of Angina Pectoris with Evidence of Severe Coronary Atherosclerosis in Men: The Physicians' Health Study Nader Rifai et al. *Clinical Chemistry* 2004;50:1364–1371.

2) Women: In this cohort of initially healthy women, extremely high levels of lipoprotein(a) (90th percentile), measured with an assay independent of apolipoprotein(a) isoform size, were associated with increased cardiovascular risk, particularly in women with high levels of LDL-C. However, the threshold and interaction effects observed do not support routine measurement of lipoprotein(a) for cardiovascular stratification in women. Lipoprotein(a), Measured With an Assay Independent of Apolipoprotein(a) Isoform Size, and Risk of Future Cardiovascular Events Among Initially Healthy Women Jacqueline Suk Danik, et al. *JAMA*. 2006;296:1363-1370

Also keep in mind that all LDL particles, including those with apoprotein (a) attached, are heterogeneous in size (due to TG content, etc.). Small LDL particles with apo (a), if present in increased concentrations increase risk significantly. The worse scenario would be too many small LDL particles with apoprotein (a) attached. There is a study, demonstrating that small LDL particles with apo (a) attached are associated with higher CHD risk than larger particles with apo (a) attached.



Many labs perform apolipoprotein (a) concentrations: however this assay is very tricky and by no means standardized. It is very important to know how the Lp(a) is measured. Labs report Lp(a) as mg/dL or nmol/L (number of Lp(a) particles). The NHLBI issued a position paper which advised: The expression of Lp(a) values in terms of total Lp(a) mass **should be abandoned** because what is measured is the protein component of Lp(a) and not its lipid and carbohydrate content. In addition, to correctly reflect the number of Lp(a) particles and to compare data from different studies, the values should be expressed in terms of nmol/L of Lp(a) protein (see Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein(a) and Cardiovascular Disease: Recent Advances and Future Directions Santica M. Marcovina, et al. Clinical Chemistry 2003;49:11:1785–1796). LipoScience reports Lp(a) in molar concentrations but Berkeley does not. VAP reports how much cholesterol is within the Lp(a) particles and thus provides Lp(a)-C concentrations. Since the risk of apo(a) seems to be related to LDL-C (see below) some find the Lp(a)-C measurement helpful. Be sure you know how your lab reports the data and insist on molar concentrations. I believe looking at apo(a) molar concentrations with respect to LDL-P or apoB is a far better way to understand the risk.

Statins deplete the LDL cholesterol, apoB and LDL-P levels by inhibiting hepatic HMG CoA reductase mediated production of cholesterol. The liver in an attempt to restore hepatic cholesterol levels (necessary for bile acid synthesis) upregulates LDL receptors. The apoB on the LDL (or other betalipoprotein surface) is a major ligand for LDL receptors.

Lipoprotein (a)
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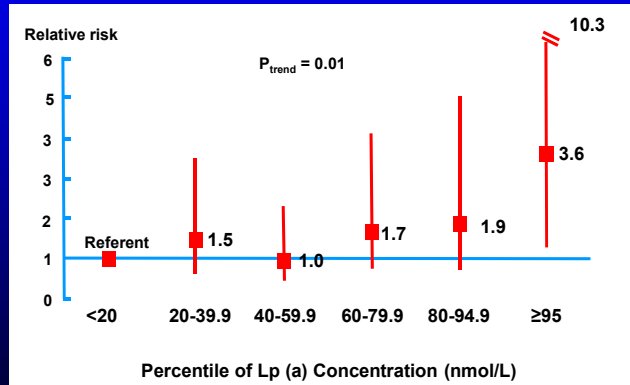
Of course the best proven way to reduce atherosclerosis is to reduce apoB or LDL-P (or their lipid surrogates like LDL-C and Non HDL-C). Any LDL particle with an apoprotein (a) attached in effect has a camouflaged apoB on its surface. Such particles are far less susceptible to removal via the LDL receptor (LDLr) mechanism (upregulated by statins and ezetimibe), as the apoB is not visible to the LDL receptor. Of course LDL particles that do not have the apoprotein (a) attached to their apoB are cleared normally by statin or statin/ezetimibe upregulated LDLr. This scenario of removal of normal LDL particles, but no removal of Lp(a) particles would result in little change of Lp(a) levels with statin therapy even though LDL-C, apoB and LDL-P and clinical risk would be reduced. Thus the most potent therapy to most significantly upregulate LDL receptors and lower LDL-P is combination therapy with a statin and ezetimibe or bile acid sequestrant. Thus one can normalize LDL-C, LDL-P, apoB and lower CV risk without doing anything to apo(a) levels.

The drugs that inhibit hepatic apo (a) synthesis (niacin, fenofibrate, estrogen, raloxifene) will cause less apoprotein (a) to be attached to LDL particles. These drugs reduce Lp(a) levels but none as monotherapy are particularly efficacious as statins in reducing LDL-P or LDL-C. There are no outcome studies relating clinical event reduction to what a drug does to Lp(a) levels. There are all sorts of studies showing lowering LDL-C or LDL-P saves lives and that is why those surrogates are what NCEP strongly suggests clinician's direct therapy at. Some advocate the use of niacin to lower apo (a) levels, yet there is no clinical trial evidence whatsoever that clinical events would be affected. Many people have extremely high Lp(a) levels. Niacin can only lower it 25-30% which would never get the Lp(a) concentration close to a normal level. Since atherosclerosis risk depends on apoB or LDL-P, if we simply normalize those measures or their lipid surrogates (LDL-C and Non HDL-C) there will likely be few events.

Dr Greg Brown has reported: "In an analysis by Maher et al. of the Lp(a) data in the FATS trial, lowering LDL levels in those with high LDL and high Lp(a) levels dramatically reduced risk. Without treatment, these patients had a 42% risk of a major clinical event, including MI, the need for revascularization, or CV death over the 2.5 year study. When LDL levels were lowered aggressively, even though the Lp(a) levels remained high, the risk of this group was reduced to less than 10%, for a roughly 75% reduction in the risk of a major cardiovascular event. While Lp(a) (and probably risk) may be modestly lowered with niacin therapy, and with estrogens in women, aggressive lowering of LDL levels appears to be the most reliable way to treat patients at high risk due to elevated Lp(a)."

The Physician's Health Study Apolipoprotein (a) Size and Lipoprotein (a) Concentration and Risk of CHD

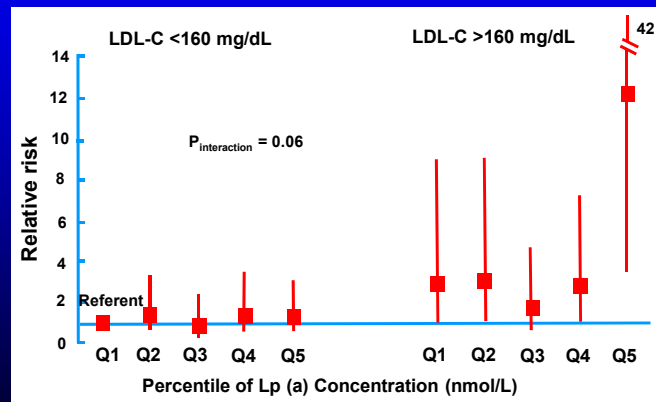
Association Between Future Risk of Angina and Lp (a)



Rifai N. et al, *Clinical Chemistry* 50:81364–1371 (2004)

The Physician's Health Study Apolipoprotein (a) Size and Lipoprotein (a) Concentration and Risk of CHD

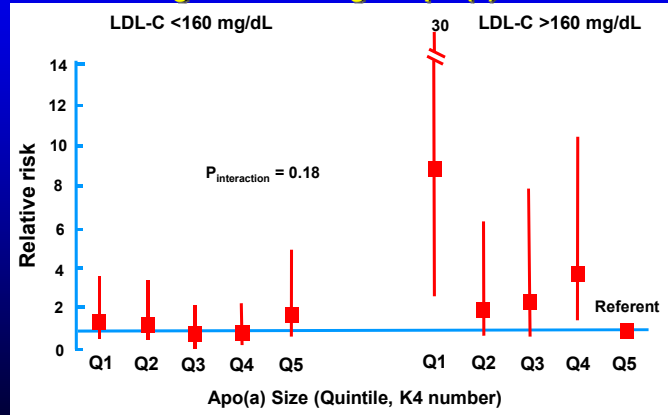
Risk of Angina According to Lp(a) Concentration & LDL-C



Rifai N. et al, *Clinical Chemistry* 50:81364–1371 (2004)

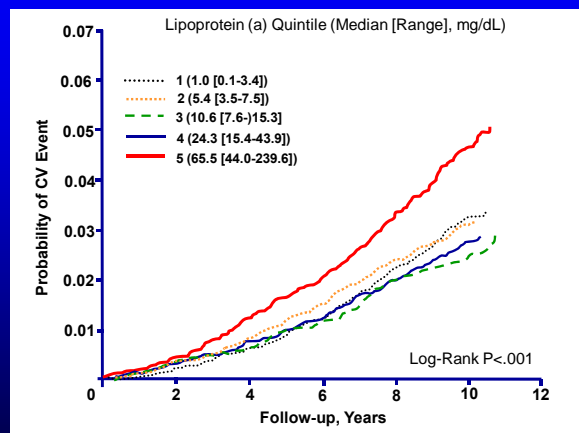
The Physician's Health Study Apolipoprotein (a) Size and Lipoprotein (a) Concentration and Risk of CHD

Risk of Angina According to Apo (a) Size & LDL-C



Rifai N. et al, *Clinical Chemistry* 50:81364–1371 (2004)

Women's Health Study: Probability of an Event According to Lp(a) Quintile



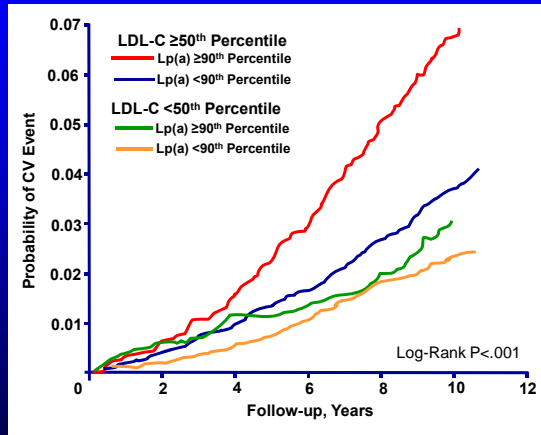
After adjusting for age, smoking, blood pressure, body mass index, TC, HDL-C, diabetes, hormone use, C-reactive protein, and randomization treatment groups, women in the highest quintile of Lp(a) (44.0 mg/dL) were 1.47 times more likely (95% CI, 1.21-1.79; P for trend .001) to develop cardiovascular events than women in the lowest quintile (3.4 mg/dL).

This association, however, was due almost entirely to a threshold effect among those with the highest lipoprotein (a) levels.

Used a new assay that uses a latex-enhanced immunoturbidimetric method, independently of apolipoprotein (a) isoform size and kringle IV type-2 repeats

Jacqueline Suk Danik et al. *JAMA*. 2006;296:1363-1370

Women's Health Study: Probability of an Event According to Lp(a) & LDL-C



In this cohort of initially healthy women, extremely high levels of lipoprotein (a) (90th percentile), measured with an assay independent of apolipoprotein (a) isoform size, were associated with increased cardiovascular risk, particularly in women with high levels of LDL-C.

The threshold and interaction effects observed do not support routine measurement of lipoprotein (a) for cardiovascular stratification in women.

Jacqueline Suk Danik et al. JAMA. 2006;296:1363-1370