Apolipoprotein B

The surface apolipoprotein on chylomicrons, chylomicron remnants, VLDL particle and remnants, intermediate and low density lipoproteins
The total serum cholesterol, which is normally around 150-300 mg% is certainly related to atherosclerosis, but has found to be only a crude measure of blood lipid disturbance.

In atherosclerosis there is a relative and absolute increase in the β lipoproteins, even when the blood cholesterol is normal.
Cholesterol is distributed throughout all of the lipoprotein fractions of the plasma.

The preoccupation of cholesterol as a cause of atheromatosis has probably been attributed to then fact that it is relatively easy to measure and does to a certain extent reflect the concentration of lipoproteins.

The view is the lipoproteins may be considered the agent for atherosclerosis.

McGraw Hill, New York, NY  1966
Low density lipoproteins (LDL) transport cholesterol and triglycerides to various cells and tissues throughout the body. The receptor mediated uptake of LDL is triggered by apolipoprotein B-100, which is the only protein component of LDL.

Human apolipoprotein B-100 is a glycoprotein with a molecular mass of about 550 kDa. It associates with hydrophobic molecules in a noncovalent fashion to facilitate their transport and targeting in a hydrophilic environment.
Lipid Transportation

- In vertebrates the predominant means of bulk lipid transport is achieved by apolipoprotein (apo) B containing lipoprotein assembly which is responsible for intestinal chylomicron formation and VLDL assembly in the liver and heart.

- Although apoB-containing lipoproteins are critical for lipid absorption and triglyceride homeostasis, their accumulation plasma induces atherosclerosis.

Shelness GS & Ledford AS Curr Opin Lipidol 2005;16:325-332
### Advanced Lipoprotein Testing

**Smaller Lipoprotein Particles**

**Larger Lipoprotein Particles**

#### Segmented gradient gel electrophoresis

<table>
<thead>
<tr>
<th>LDL Particles</th>
<th>Pattern B</th>
<th>Pattern Intermediate</th>
<th>Pattern A</th>
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<tbody>
<tr>
<td></td>
<td>IVb</td>
<td>IVa</td>
<td>IIIb</td>
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<td>HDL Particles</td>
<td>3c</td>
<td>3b</td>
<td>3a</td>
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<td></td>
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<td>VLDL Particles</td>
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</table>

- Measured ApoB value

#### Berkeley HeartLab Inc.

<table>
<thead>
<tr>
<th>LDL Particles</th>
<th>L1</th>
<th>L2</th>
<th>L3</th>
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<tbody>
<tr>
<td>HDL Particles</td>
<td>H1</td>
<td>H2</td>
<td>H3</td>
</tr>
<tr>
<td>VLDL Particles</td>
<td>V1</td>
<td>V2</td>
<td>V3</td>
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</table>

#### Nuclear Magnetic Resonance

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<th>LDL Particles</th>
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<tbody>
<tr>
<td></td>
<td>L</td>
<td>L</td>
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<tr>
<td>HDL Particles</td>
<td>H1</td>
<td>H2</td>
</tr>
<tr>
<td>VLDL Particles</td>
<td>V1</td>
<td>V2</td>
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#### LipoScience

<table>
<thead>
<tr>
<th>LDL Particles</th>
<th>LDL 4</th>
<th>LDL 3</th>
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<tr>
<td>HDL Particles</td>
<td>HDL3 (d,c,b,a)</td>
<td>HDL2 (a,b,c)</td>
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<tr>
<td>VLDL Particles</td>
<td>VLDL 3b</td>
<td>VLDL 3a</td>
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#### Short, single vertical spin density-gradient ultracentrifugation (Vertical Auto Profile/VAP)

<table>
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<tr>
<th>LDL Particles</th>
<th>Pattern B</th>
<th>Pattern A/B</th>
<th>Pattern A</th>
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<tbody>
<tr>
<td>LDL 4</td>
<td>LDL2</td>
<td>LDL1</td>
<td></td>
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<tr>
<td>HDL Particles</td>
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<tr>
<td>VLDL Particles</td>
<td></td>
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</tbody>
</table>

- In-house calculated apoB value

---

Bays et al. Preventive Cardiology 2003 (fall);VI:187
There is one molecule of apoB on each beta-lipoprotein particle. Because of its 12-3 day half-life, over 90% of apoB particles are LDLs.

Arterioscler Thromb Vasc Biol 1998;18:1046-1053

Handbook of lipoprotein Testing 2nd Ed 2000 AACC Press Washington DC
What determines LDL atherogenicity?

LDL Particle Concentration

- LDL particle concentration is the single best independent predictor that we have of CHD risk.

- Estimated by Apo B-100 concentration. Normal is < 90 mg/dl.

- LDL-P is most accurately measured by NMR spectroscopy. Perfect is < 1000 umol/L.

Because of their longer half-life, 90% of apoB particles are LDL.

LDL particle concentration is the single **best** independent predictor that we have of CHD risk.
What makes an LDL particle atherogenic?

The smaller the size of an apoB particle, the easier it is to enter the arterial intima and the less likely it is to be cleared by hepatic LDL receptors.

However, particle size has no independent ability to predict CV events.

What makes an LDL particle atherogenic?
Lab Analysis of ApoB Lipoproteins

ApoB Concentration

- VLDL-C
- LDL-C
- ApoB Concentration
- Chylomicrons
- VLDLs
- IDL-P
- LDL-P
- VLDL-C
- LDL-C
- VLDL-C
- Non HDL-C
- TC – HDL-C or VLDL-C
- TC – HDL-C or VLDL-C + LDL-C
Non HDL-C and VLDL-C

The variable contributions of VLDL and LDL cholesterol to non-HDL cholesterol.

Because the amount of cholesterol in VLDL particles is variable, the proportion that VLDL cholesterol contributes to non-HDL cholesterol varies.

By contrast, the proportion of VLDL apoB to LDL apoB varies little.

Microsomal Triglyceride Transfer Protein

- Messenger RNA
- Amino Acids
- Endoplasmic Reticulum
- Ribosome
- Lipids
- VLDL Production
- apoB-100 synthesis
Lipidation of Apolipoprotein B

Hepatocyte or Enterocyte

Endoplasmic Reticulum

Membrane

Ribosome

mRNA

MTP = Microsomal TG Transfer Protein

Cytosol

Nascent apoB interacts with lipid free MTP and is ubiquinated

apoB associates with MTP-Lipid complexes and forms a VLDL precursor which after lipidation with TG becomes a mature VLDL in the Golgi

Endosomal free & esterified cholesterol

VLDL Precursor

Golgi

Triglycerides

MatureVL

DL or chylo

NHANES III: Apolipoprotein B Levels in Men by Age 50\textsuperscript{th} and 90\textsuperscript{th} Percentile

Carr M & Brunzell J J Clin Endo & Metab 2004;89:2601-2607
NHANES III: Apolipoprotein B Levels in Women by Age 50th and 90th Percentile

Carr M & Brunzell J J Clin Endo & Metab 2004;89:2601-2607
# Framingham Offspring Study

1988-1991 (exam cycle 4)

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[Image of a table with columns and rows, some cells highlighted in red.]
Population Percentile Cut Points & Goals for LDL-P, LDL-C and Apolipoprotein B

- **Goal for Very High Risk Patients**
- **Goal for High Risk Patients**
- **Goal for Low Risk Patients**

<table>
<thead>
<tr>
<th>LDL-P</th>
<th>LDL-C</th>
<th>ApoB</th>
</tr>
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<tbody>
<tr>
<td>Population Cut Points (NHANES)</td>
<td>Population Cut Points (MESA Study)</td>
<td>Population Cut Points (NCEP ATP-III)</td>
</tr>
<tr>
<td>500 600 700 800 900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900 2000 2100 2200</td>
<td>50 60 70 80 90 100 110 120 130 140 150 160</td>
<td>50 60 70 80 90 100</td>
</tr>
<tr>
<td>Population Cut Points (NCEP ATP-III)</td>
<td>Population Cut Points (MESA Study)</td>
<td>Population Cut Points (NHANES)</td>
</tr>
<tr>
<td>50 60 70 80 90 100 110 120 130 140 150 160 170</td>
<td>50 60 70 80 90 100</td>
<td>50 60 70 80 90 100</td>
</tr>
</tbody>
</table>

- **50**
- **60**
- **70**
- **80**
- **90**
- **100**
- **110**
- **120**
- **130**
- **140**
- **150**
- **160**
- **170**
- **180**
- **190**
- **200**
- **210**
- **220**

- **20th**
- **50th**
- **80th**
Association of Apo B and Ischemic Heart Disease

- Analysis is based on a cohort of 2,155 men aged 45–76 years who were free of clinical signs of CHD at entry from the Québec Cardiovascular Study

Lamarche B et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Québec Cardiovascular Study. Circulation. 1996;94:273–278, with permission from Lippincott Williams & Wilkins.
Lipids and Major Coronary Events in AFCAPS/TexCAPS

Event Rate per 100 Patient Years of Risk

Risk Reduction

Placebo
Lovastatin

Apo B Tertiles (mg/dl)

Apo B/A-I Tertiles (mg/dl)

<113 124-126 >327 <0.89 1.05-1.02 >1.025

Placebo Overall Event Rate
Lovastatin Overall Event Rate

On Treatment Apo B Predicts Risk >LDL-C

Circulation 2000;101:477-484
Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): Lipids,

- It is well documented by many observational studies, including the Quebec Cardiovascular Study, that apoB is a more powerful independent predictor of CHD than LDL-C.

- Although apoB is associated with known atherogenic lipoprotein species, such as IDL remnants and small, dense LDL (a distinct, highly atherogenic subpopulation), LDL has a variable cholesterol content.

- This variability in the composition of LDL has been hypothesized to explain the clinically observed variation in risk that appears to be independent of LDL-C.

- Our results suggest that it may be more valid to use apoB rather than LDL-C to assess the on-treatment effect of reducing the atherogenic burden, especially when LDL-C is not markedly elevated.

Gotto et al. Circulation 2000;101:477-484
Event Rate by Treatment Group and ApoB/AI Ratio Tertile

Gotto et al. Circulation 2000;101:477-484
Adjusted Logistic Regression Model Relationship of AMCE and On-treatment ApoB

\[
\text{AMCE} = \text{Acute Major Coronary Event}
\]

- **Lovastatin**
- **Placebo**

Gotto et al. Circulation 2000;101:477-484
Adjusted Logistic Regression Model Relationship of AMCE and Baseline & On-treatment ApoB/AI Ratio

Gotto et al. Circulation 2000;101:477-484
NHANES III: Apolipoprotein B Levels by Age 50th and 90th Percentile

Carr M & Brunzell J J Clin Endo & Metab 2004;89:2601-2607
Apo B vs Mortality in 4S Trial

Relationship of Mortality to the decrease in Apo B

Davidson M Amer J Card 2001;87 (suppl):1A-7A
Mortality did not correlate in a linear fashion with treatment LDL-C in 4S.
Apoprotein-related MOrtality RISk AMORIS Study

- 175,553 patients from screening programs
  - 98,722 men and 76,831 women
- Examined relationship of apoproteins and lipids and prediction of fatal MI
- Mean Follow up 66-68 months

Wallidius G et al Lancet 2001;358:2026-2033
Apoprotein-related MOrtality RISk AMORIS Study

- In multivariate analyses adjusted for age, TC and TG
  - The values for Apo B and the ApoB/ApoA-I ratio were strongly and positively related to risk of fatal MI in men and women

- Apo A-I was protective
- Apo B was a stronger predictor of risk than LDL-C in both sexes

Wallidius G et al, Lancet 2001;358:2026-2033
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- **Apolipoprotein B** was a stronger predictor of risk than LDL-C in both sexes

Wallidius G et al. Lancet 2001;358:2026-2033
Apoprotein-related Mortality Risk AMORIS Study

- In multivariate analyses adjusted for age, TC and TG
  - Apolipoprotein B was a stronger predictor of risk than LDL-C in both sexes
  - Apolipoprotein A-I was protective

Wallidius G et al. Lancet 2001;358:2026-2033
Apoprotein-related MOrtality RISk
AMORIS Study

• In multivariate analyses adjusted for age, TC and TG
  ✦ Apolipoprotein B was a stronger predictor of risk than LDL-C in both sexes
  ✦ Apolipoprotein A-I was protective
    • The values for ApoB/ApoA-I ratio were strongly and positively related to risk of fatal MI in men and women

Wallidius G et al. Lancet 2001;358:2026-2033
Apoprotein-related Mortality Risk (AMORIS) Study

Women < 70 y/o

Risk Ratio

ApoAl (g/L)

ApoB (g/L)

1.2 1.43 1.5 1.84

Wallidius G et al Lancet 2001;358:2026-2033
Apoprotein-related Mortality Risk (AMORIS) Study

Women > 70 y/o

Risk Ratio

ApoAI (g/L)

ApoB (g/L)

Wallidius G et al. Lancet 2001;358:2026-2033
Apoprotein-related MOrtality RISk (AMORIS) Study

Men < 70 y/o

Risk Ratio

ApoAI (g/L)

Wallidius G et al. Lancet 2001;358:2026-2033
Apoprotein-related Mortality Risk (AMORIS) Study

Men > 70 y/o

Wallidius G et al. Lancet 2001;358:2026-2033
Four prospective studies showed apoB is a better estimate of risk than LDL-C.

Risk is highest in persons with apoB > 120 mg/dL and a TG of 120 mg/dL.

- This is typical of insulin resistance dyslipidemia.

In the statin trials apoB levels during treatment relate more strongly to clinical outcomes than do LDL-C levels.

Fasting is not required.

Genest J et al. CMAJ 2003;168:921-924
Canadian Medical Association Recommendations for Management of Dyslipidemia

- Apo B has been standardized and most labs have the equipment to measure it
- Population levels (Canadian)
  - 90 mg/dL 20th percentile
  - 105 mg/dL 50th percentile
  - 120 mg/dL 75th percentile

Genest J et al. CMAJ 2003;168:921-924
Physicians Health Study
HDL-C vs apoB in CV Prediction in Men


HDL-C is inversely related to apoB
However: apoB adds predictive value at any level of HDL-C

Adjusted for age, smoking, BMI, premature family history, diabetes, physical activity, hypertension and alcohol intake

Numbers indicate relative risks; numbers in parentheses indicate number of subjects.
Physicians Health Study
HDL-C vs apoB in CV Prediction in Men

No subject was in the group defined as the lowest tertile of non–HDL-C and highest tertile of apoB.

Only one subject was in the group defined as the highest tertile of non–HDL-C and lowest tertile of apoB.

Within each tertile of non-HDL-C, the risk of CHD increased with increasing apoB.

Numbers indicate relative risks; numbers in parentheses indicate number of subjects.


Adjusted for age, smoking, BMI, premature family history, diabetes, physical activity, hypertension and alcohol intake.
Conclusions—Although non–HDL-C and apoB were both strong predictors of CHD in this male cohort, more so than LDL-C, the findings support the concept that the plasma concentration of atherogenic lipoprotein particles measured by apoB is more predictive in development of CHD than the cholesterol carried by these particles, measured by non–HDL-C.

In conclusion, we found in a generally healthy male population that non–HDL-C is more strongly related to CHD than is LDL-C; however, our study suggests that apoB as a direct measurement of the number of atherogenic lipoprotein particles is more closely related to risk of CHD than the cholesterol concentration provided by these particles.

CV Markers and Prediction of Risk

723 asymptomatic men with no history of CVD

Conclusions: ApoB was the best predictor, non-HDL-C the second best predictor, and LDL-C the poorest predictor of high cardiovascular risk. Subclinical extra-coronary and coronary atherosclerosis, and triglycerides participated to these differences.

Percent increase in risk of having high coronary calcium deposit, extra-coronary plaques at multiple sites, and CHD risk equivalent per increase in one standard deviation of LDLC, non-HDLC, and apoB.

LDL-P was strongly associated with increased CVD risk in both men and women (p<0.0001).

When data for men and women were combined, LDL-P was approximately twice as strongly related to CVD incidence as LDL-C.

Event-free survival among participants with low-density lipoprotein cholesterol (LDL-C) and LDL particle number (LDL-P) above or below the median.

Median values were 131 mg/dL for LDL-C and 1414 nmol/L for LDL-P.

Particle number (LDL-P) is the key risk factor.
### Table 4: Age- and gender-adjusted incidence of cardiovascular disease by quartile of alternative measures of atherogenic lipoprotein concentrations

<table>
<thead>
<tr>
<th></th>
<th>Lowest LDL-C Quartile</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
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</thead>
<tbody>
<tr>
<td><strong>LDL-C</strong></td>
<td>&lt; 111 men &lt; 102 women</td>
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<tr>
<td>Median (mg/dL)</td>
<td></td>
<td>92</td>
<td>118</td>
<td>142</td>
<td>170</td>
</tr>
<tr>
<td>No. of events</td>
<td></td>
<td>75</td>
<td>100</td>
<td>114</td>
<td>142</td>
</tr>
<tr>
<td>CVD event rate per 1000 person-years (95% CI)</td>
<td>81 (57–103)</td>
<td>86 (63–108)</td>
<td>88 (66–110)</td>
<td>119 (92–144)</td>
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</tbody>
</table>

|                | Lowest LDL-P Quartile  |            |            |            |            |
| **LDL-P**      | 1252 men < 1061 women  |            |            |            |            |
| Median (nmol/L)|                        | 967        | 1279       | 1548       | 1931       |
| No. of events  |                        | 55         | 109        | 101        | 166        |
| CVD event rate per 1000 person-years (95% CI) | 59 (38–79) | 89 (66–112) | 81 (60–102) | 139 (110–166) |

*Quartiles were gender-specific. LDL-C cutpoints were 111, 134, and 156 mg/dL for men; 102, 124, and 150 mg/dL for women. Non–HDL-C cutpoints were 134, 159, and 183 mg/dL for men; 118, 144, and 174 mg/dL for women. LDL-P cutpoints were 1252, 1511, and 1785 nmol/L for men; 1061, 1313, and 1617 nmol/L for women.
The graph makes a very simple point.

When LDL-C and LDL-P are both high there is risk and when the two indices are both low, risk is low.

The issue is what happens when the two indices are discordant:

- When LDL-P is low, even though LDL-C is high, risk is low. Similarly when LDL-P is high and LDL-C is low, risk is high.

Risk follows LDL-P, not LDL-C.

### Evidence Supporting Apo B over LDL-C: Prospective Epidemiologic Studies & Placebo Wing of Major Statin Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
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<tr>
<td>QCVS-13:</td>
<td>Quebec Cardiovascular Study 13 year follow up</td>
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<tr>
<td>THROMBO MS</td>
<td>Thrombogenic Factors &amp; Recurrent Coronary Events Metabolic Synd</td>
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<tr>
<td>LIPID</td>
<td>Long-term Intervention with Pravastatin in Ischemic Disease</td>
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<tr>
<td>AFCAPS/TexCAPS</td>
<td>Air Force Texas Coronary Atherosclerosis Prevention Study</td>
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<td>Scandinavian Simvastatin Survival Study</td>
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<td>Women’s Heart Study</td>
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<td>Thrombogenic Factors &amp; Recurrent Coronary Events</td>
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<td>NPHS</td>
<td>Northwick Park Heart Study</td>
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<td>AMORIS</td>
<td>Apolipoprotein-related Mortality Risk</td>
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<td>QCVS-5</td>
<td>Quebec Cardiovascular Study 5 year follow up</td>
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Evidence Supporting Apo B over Non HDL-C: Prospective Epidemiologic Studies & Placebo Wing of Major Statin Trials

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<th>Description</th>
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<td>Casale Monferrator Study</td>
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<td>HHMS</td>
<td>Harvard healthy Men Study</td>
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<tr>
<td>Womens HS</td>
<td>Women’s Heart Study</td>
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<tr>
<td>J-DM</td>
<td>Jiang Diabetes Mellitus</td>
</tr>
</tbody>
</table>

ApoB Superior as a Predictor

Equal Predictors of Risk

All of the national and transnational screening and therapeutic guidelines are based on total or LDL cholesterol.

This presumes that cholesterol is the most important lipoprotein-related proatherogenic risk variable.

On the contrary, risk appears to be more directly related to the number of circulating atherogenic particles that contact and enter the arterial wall than to the measured concentration of cholesterol in these lipoprotein fractions.

Each of the atherogenic lipoprotein particles contains a single molecule of apolipoprotein (apo) B and therefore the concentration of apo B provides a direct measure of the number of circulating atherogenic lipoproteins.

Evidence from fundamental, epidemiological and clinical trial studies indicates that apo B is superior to any of the cholesterol indices to recognize those at increased risk of vascular disease and to judge the adequacy of lipid-lowering therapy.

The evidence also indicates that the apo B/apo A-I ratio is superior to any of the conventional cholesterol ratios in patients without symptomatic vascular disease or diabetes to evaluate the lipoprotein-related risk of vascular disease.

apo B measures total atherogenic particle number in plasma and is superior to LDL cholesterol as an index of the lipid-related risk of vascular disease and as a guide to the adequacy of LDL-lowering therapy.

Measurement of apo B is simple, standardized and does not require fasting plasma.

apo B is a better guide than any of the cholesterol indices for judging the adequacy of LDL-lowering therapy.

The apo B/apo A-I ratio appears to be superior to any of the cholesterol ratios for quantifying the lipoprotein-related risk of vascular disease.

We recommend that apoB and the apoB/A-I ratio be determined after the measurement of LDL-C, non-HDL-C and the ratio of total cholesterol/HDL-cholesterol to better predict CAD and assess its efficacy to treatment.
Lipoprotein Management in Patients With Cardiometabolic Risk

Consensus statement from the American Diabetes Association and the American College of Cardiology Foundation

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Particle Quantification

- In particular, apoB should be used to guide adjustments to therapy.
- LDL-P as measured by NMR appears equally informative as apoB.
- The panel recommends that the apoB goal be reached.

Brunzell JD, Davidson M, Furberg CD et al. Diabetes Care 2008;31:811-822
ADA and ACC Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk

TREATMENT GOALS

**Highest-risk patients**, including those with 1) known CVD or 2) Diabetes plus one or more additional CVD risk factor

**High-risk patients**, including those with 1) no diabetes or known clinical CVD but 2 or more additional major CVD risk factors or 2) Diabetes but no other CVD risk factors

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
<th>ApoB (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 70</td>
<td>&lt; 100</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>&lt; 130</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

Brunzell JD, Davidson M, Furberg CD et al. Diabetes Care 2008;31:811-822
Anything that raises hepatic triglycerides will increase VLDL production or size.
Hepatic VLDL Lipolysis
Normal Lipoprotein Metabolism

Lipolysis or hydrolysis of triglycerides

Beta-lipoprotein Concentration = Apo B or NMR LipoProfile

Beta-lipoprotein Estimate = VLDL-C + IDL-C + LDL-C

Beta-lipoprotein Estimate = Non HDL-C
Lipoproteins are heterogeneous and come in various sizes and densities: each patient has all sizes of lipoproteins, but each has a predominant particle size or phenotype.
Strong Heart Study
Mean Apo B in Diabetics

Diabetic Women (n=2703)

Difference between participants with and without diabetes mg/dl

P = 0.0005

Diabetes and apoB

Phenotype Frequencies based on TG and apoB or TG and LDL-C

CONCLUSIONS: The dyslipidemic profile of patients with type 2 diabetes is not uniform.

A substantial group have normal lipids and normal LDL particle number and size whereas others have markedly abnormal profiles.

Diagnosis based on triglycerides and apoB rather than triglycerides and LDL cholesterol revealed that more than one in five had hypertriglyceridemic hyper-apoB, which is characterized by hypertriglyceridemia, marked elevation of LDL particle number, small dense LDL, and low HDL.

This constellation of abnormalities that is associated with markedly accelerated atherogenesis and therefore justifies intensive medical therapy.
LDL Particle Number Distribution in T2DM Subjects with Normal, at Goal LDL-C

Percent of Subjects

1% (n=19) 24% (n=364) 43% (n=631) 
5th percentile

20th percentile

30th percentile

50th percentile

80th percentile

Percent of Subjects

16% (n=147) 43% (n=377) 30% (n=260) 9% (n=76) 2% (n=15)

LDL-C 71-99 mg/dL (n=1,484)

LDL-C ≤ 70 mg/dL (n=871)

Cromwell W & Otvos J (Am J Cardiol 2006;98:1599–1602)
NEPTUNE II Survey Non HDL-C Goal

NCEP Evaluation Project Utilizing Novel Technology

Optional Goals (n=170)
LDL-C < 100 mg/dL
Non HDL-C < 130 mg/dL

Optional Goals (n=311)
LDL-C < 70 mg/dL
Non HDL-C < 100 mg/dL

Am J Cardiol 2005;96:556-563
Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS)

- Baseline and on-treatment Non HDL-C levels correlated better with apoB than did LDL-C
- Baseline TG levels did not greatly influence the strength of this correlation
- Unlike LDL-C, non HDL-C is not affected by rising TG concentrations
- Using non HDL-C may provide superior guidance as to how aggressively dyslipidemic patients should be treated
- This would require treating patients more aggressively than is current practice, particularly in those with highest risk

Ballantyne C, Amer J Cardiol. 2001;88:265-269
• ApoB and Non HDL-C are highly correlated but only moderately concordant—that is, for any given value of one, there is a substantial range of values for the other.

• Agreement, not surprisingly, is greater in normotriglyceridemic compared to hypertriglyceridemic subjects. However, even within the normotriglyceridemic group, there is only moderate concordance between the two methods.

• The net result is that for individuals, the value of ApoB is not accurately predictable from the value for non HDL-C.

On Therapy LDL-C vs Non HDL-C vs ApoB

N = 17,035

The decrease in non–HDL-C was significantly less (P < 0.001) than the decrease in LDL-C, whereas the decrease in ApoB was significantly less than the decrease in either LDL-C or non–HDL-C (P < 0.001).

Findings in the eight studies with 889 subjects in which LDL-P was measured by nuclear magnetic resonance are very similar to those obtained with ApoB, and are equally consistent.

Average percent decreases in LDL-C and LDL-P were 35.9 ± 3.5% and 30.6 ± 2.8%, respectively.

LDL-C, on average, was reduced to a level equal to the 22nd percentile of the reference population. The corresponding average concentration achieved for non–HDL-C was the 29th percentile value, which was a significantly lesser change than achieved with LDL-C (P 0.001). Both differ substantially with the findings obtained for ApoB. ApoB was only decreased to the 55th percentile of the population, a drop that is significantly less than achieved with LDL-C or non HDL-C (P 0.001 in both comparisons).

On Therapy LDL-C vs LDL-P

Very similar results were obtained in eight studies of LDL lowering in 889 subjects in which the responses of LDL-C and LDL particle number (LDL-P) assessed by nuclear magnetic resonance spectroscopy were compared.

LDL-C was reduced to the 27th percentile of the population, whereas LDL-P was only reduced to the 51st percentile of the population (P<0.007).

Thus, the reduction in LDL-P was significantly less than LDL-C.

The decrease in LDL-C to LDL-lowering therapy was significantly greater than the decrease in non HDL-C. However, the decrease in ApoB and LDL-P was significantly less than either, whether expressed as percent decrease or percentile of the population achieved.

Given that LDL particles make up the vast majority of total plasma ApoB, agreement between ApoB and LDL-P is anticipated.

Nevertheless, the concordance of the responses of ApoB and LDL-P to LDL-lowering therapy provides powerful confirmation of the principal findings— the discordance between the extent of the response of the cholesterol measures on the one hand, and the atherogenic particle number measures on the other.

There are two explanations for the discordance between the response of cholesterol and particle number to statins.

1. The first relates to changes in LDL composition, but not size, with statin therapy.
2. LDL particle size is generally unchanged by statin therapy, but that does not mean LDL composition remains fixed.

A recent Framingham report showed that there were 10% to 25% fewer cholesterol molecules per LDL particle in individuals with LDL-C 100 mg/dL compared to those with LDL-C 160 mg/dL.

This was independent of plasma triglyceride and was not associated with any difference in LDL particle size. It was postulated that LDL particles of individuals with low LDL-C become relatively cholesterol-depleted and triglyceride-enriched as a result of core lipid exchange mediated by cholesterol ester transfer protein.

Therefore, statin therapy results in triglyceride enrichment and cholesterol depletion of LDL particles. Because triglycerides persist within the particle core, LDL composition, but not LDL size, changes.

Changes in core lipid composition of LDL can, therefore, be driven not only by very LDL triglyceride elevation, ie, the usual model, but also by LDL-C reduction, ie, the statin model.

These data establish that basing LDL-lowering therapy only on the cholesterol indexes results in a treatment gap in a large group of patients: a treatment gap that can be recognized and closed with more intensive therapy only if the atherogenic particle number is measured.

Many patients who achieve LDL-C and non–HDL-C target levels will not have achieved correspondingly low population-equivalent ApoB or LDL-P targets. Reliance on LDL-C and non–HDL-C can create a treatment gap in which the opportunity to give maximal LDL-lowering therapy is lost.
We KNOW what causes disease within our arteries but can only guess at what precipitates clinical events. It follows that prevention of coronary disease would be much more effective if we focused on PREVENTING disease developing within our arteries rather than trying to predict who is just about to become a victim and then trying frantically, at what may be just one minute before their final midnight, to rescue them.

If we prevent the disease, we will prevent the events.

Take away the apoB particles and