Alan Remaley, MD, PhD

National Institutes of Health, National Heart, Lung, and Blood Institute, Section Chief, Lipoprotein, Metabolism Laboratory, Cardiovascular and Pulmonary Branch; Captain, United States Public Health Service

Alan Remaley received his B.S. in biochemistry and chemistry from the University of Pittsburgh in 1981, and a M.D. and Ph.D. in biochemistry from the University of Pittsburgh in 1987. In 1990, he completed a residency in clinical pathology at the University of Pennsylvania and became board-certified in clinical pathology in 1992. He joined the NIH in 1990 as a medical staff fellow and did a postdoctoral fellowship on lipoprotein metabolism in the Molecular Disease Branch at the NHLBI. In 1995, Dr. Remaley became a senior staff member of the Department of Laboratory Medicine at the NIH, where he is currently the Director of the Immunoassay and Special Chemistry section. In 2007, he became the Section Chief of the Lipoprotein Metabolism laboratory in the Cardiovascular and Pulmonary Branch of the NHLBI. Dr. Remaley has received numerous honors and awards over his career and is a Captain in the United States Public Health Service. He has published more than 150 peer-reviewed articles and is on the editorial board of several journals, including Journal of Lipid Research, Journal of Pediatric Biochemistry, Atherosclerosis, and Clinical Chemistry. Dr. Remaley is a member of the American Association of Clinical Chemistry (AACC), College of American Pathologists, American Heart Association, and National Lipid Association.
Novel Tools to Enhance Risk Prediction of Cardiovascular Disease to Guide Prevention & Therapies

Back to the Future

Bay Area Silicon Valley
Right Care University of Best Practices

June 2020

Alan Remaley, MD, PhD

Lipoprotein Metabolism Laboratory
Translational Vascular Medicine Branch
National Heart, Lung and Blood Institute
National Institutes of Health
Back to the Future: Rediscovery

1985 ➔ 1955

2020 ➔ 1967

Tony Gotto
Don Fredrickson
Virgil Brown
Demystifying CVD Biomarkers

• Lipoprotein Metabolism

• New equation for LDL-C

• New algorithm for lipoprotein phenotyping

• New ASCVD risk score
Lipoprotein Metabolism Pathways

Triglyceride delivery for energy metabolism
Lipoprotein Metabolism Pathways

Cholesterol Homeostasis
Demystifying Lipid Measurements

• Lipoprotein Metabolism

• New equation for LDL-C

• New algorithm for lipoprotein phenotyping

• New ASCVD risk score
Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge

William T. Friedewald, Robert I. Levy, and Donald S. Fredrickson

A method for estimating the cholesterol content of the serum low-density lipoprotein fraction (S<sub>1</sub>-0-20) is presented. The method involves measurements of fasting plasma total cholesterol, triglyceride, and high-density lipoprotein cholesterol concentrations, none of which requires the use of the preparative ultracentrifuge. Comparison of this suggested procedure with the more direct procedure, in which the ultracentrifuge is used, yielded correlation coefficients of .94 to .99, depending on the patient population studied.

Additional Keyphrases: hyperlipoproteinemia classification - determination of plasma total cholesterol, triglyceride, high-density lipoprotein cholesterol - beta lipoproteins

Methods

Data were obtained from lipid and lipoprotein analyses performed by the Molecular Disease Branch of the National Heart and Lung Institute.
Friedewald Equation

\[ \text{LDL-C} = \text{TC} - \text{HDL-C} - \frac{\text{Tg}}{5} \]

Main sources Chol: LDL, HDL and VLDL (Chylos)

Tg/5: Estimate of VLDL-C

Bill Friedewald
2015
Need to step back and look at big picture
Original Investigation

Comparison of a Novel Method vs the Friedewald Equation for Estimating Low-Density Lipoprotein Cholesterol Levels From the Standard Lipid Profile

Seth S. Martin, MD; Michael J. Blaha, MD, MPH; Mohamed B. Elshazly, MD; Peter P. Toth, MD, PhD; Peter O. Kwiterovich, MD, Roger S. Blumenthal, MD; Steven R. Jones, MD

Median TG:VLDL-C by Non-HDL-C & Triglyceride Strata

Non-HDL-C (mg/dL)

<table>
<thead>
<tr>
<th>Median TG:VLDL-C (mg/dL)</th>
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<tbody>
<tr>
<td>7.48</td>
</tr>
<tr>
<td>5.30</td>
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<tr>
<td>4.08</td>
</tr>
<tr>
<td>2.87</td>
</tr>
<tr>
<td>1.65</td>
</tr>
<tr>
<td>0.43</td>
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<tr>
<td>0.04</td>
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Triglycerides (mg/dL)

<table>
<thead>
<tr>
<th>Median TG:VLDL-C (mg/dL)</th>
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<tbody>
<tr>
<td>8.95</td>
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<tr>
<td>6.95</td>
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<tr>
<td>5.95</td>
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<tr>
<td>4.95</td>
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<td>3.95</td>
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<td>2.95</td>
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<td>1.95</td>
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<td>0.95</td>
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<td>0.05</td>
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doi:10.1001/jama.2013.280532
A meeting with Enrico Fermi

How one intuitive physicist rescued a team from fruitless research.

Enrico Fermi

One of the big turning points in my life was a meeting with Enrico Fermi in the spring of 1948. For a few minutes, Fermi politely listened as I described a programme of research that I had been pressing for several years. He probably saw us from several more moons of fruitless wandering along a road that we had already travelled. I was unusually grateful to him for destroying our illusions and telling us the better truth.

Einstein Drive, Princeton, New Jersey 08540, USA.

Freeman Dyson

I arrived in Fermi’s office. He invited me to sit down, and asked me in a friendly way about the health of my wife and our new-born baby son, now fifty years old. Then he delivered his verdict in a quiet, even voice. “There are two ways of doing calculations in theoretical physics or on solid mathematics. One is to introduce arbitrary cut-off procedures that are not based either on solid physics or solid mathematics. The other is to calculate various quantities by exploiting the fact that certain formalism that are not based on solid physics or solid mathematics. The other is to calculate various quantities by exploiting the fact that certain formalism for the students to have their names on a published paper, we did not abandon our calculations immediately. We finished them and wrote a long paper submitted to the Phys. Rev. with all our names on it. But we discovered to find other ways of work. I escaped to Berkeley, California, to start a new career on the American shores.

Enrico Fermi was right. The crucial discovery that made sense of the strong forces was the quark.

Enrico Fermi

Enrico Fermi

“Hold nuclei together. He made the illusionary way about the health of my wife and our new-born baby son, now fifty years old. Then he delivered his verdict in a quiet, even voice. “There are two ways of doing calculations in theoretical physics or on solid mathematics. One is to introduce arbitrary cut-off procedures that are not based either on solid physics or solid mathematics. The other is to calculate various quantities by exploiting the fact that certain formalism for the students to have their names on a published paper, we did not abandon our calculations immediately. We finished them and wrote a long paper submitted to the Phys. Rev. with all our names on it. But we discovered to find other ways of work. I escaped to Berkeley, California, to start a new career on the American shores.

Enrico Fermi was right. The crucial discovery that made sense of the strong forces was the quark.

Enrico Fermi

Enrico Fermi

“I remember my friend Jonny von Neumann used to say, with four parameters I can fit an elephant, and with five I can make him wiggle his trunk.”
VAP Method for Lipoproteins


Preparative and quantitative isolation of plasma lipoproteins: rapid, single discontinuous density gradient ultracentrifugation in a vertical rotor

Byung H. Chung, Thomas Wilkinson, Jack C. Geer, and Jere F. Segrest

Departments of Pathology, Biochemistry, and Microbiology, Institute of Dental Research and Comprehensive Cancer Center, University of Alabama in Birmingham Medical Center, Birmingham, AL 35294

...to be well suited for the separation of lipoprotein fractions. However hyperlipidemic disorders involving elevated chylomicrons will need a preliminary centrifugation step to remove the chylomicrons, since this lipoprotein fraction tends to stick onto the inboard wall of the tube during centrifugation.

Reasons for New LDL-C Equation

• Equations are easier to implement
• Limitation VAP method
• Quantile nature of Martin table
• New AAC/AHA fasting recommendations
Structure of human serum lipoproteins inferred from compositional analysis

(lipoprotein composition/lipoprotein lipid space-filling model/lipid-protein interactions/surface and core components in lipoproteins/polar lipid monolayers)

From the Small to the Huge

Three scientists have proposed a novel theory to explain how characteristics like body size and energy consumption differ from species to species along fixed scales. Their theory derives from analysis of the circulatory system.

An Example of Scaling: Metabolic Rate

<table>
<thead>
<tr>
<th>METABOLIC RATE (KCAL/DAY)</th>
<th>0.1</th>
<th>10 oz.</th>
<th>1 lb.</th>
<th>10 lb.</th>
<th>100 lb.</th>
<th>1,000 lb.</th>
<th>10,000 lb.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10,000</td>
<td>200</td>
<td>2,000</td>
<td>200</td>
<td>20</td>
<td>2</td>
<td>0.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Size and Efficiency

The average elephant weighs 220,000 times as much as the average mouse, but requires only about 10,000 times as much energy in the form of food calories to sustain itself. The reason lies in the mathematical and geometric nature of networks that distribute nutrients and carry away wastes and heat. The bigger the animal, the more efficiently it uses energy.
Effect of TG and NonHDL-C on VLDL-C
"Sculpting" the Terms

\[ \text{VLDL} - C = \frac{T}{8.59} + \frac{TN}{2.250} - \frac{T^2}{16.500} \]

\( T = \text{TG} \)
\( N = \text{NonHDL-C} \)

Linear contribution of TG.
Relates to mean VLDL lipid composition.
“Sculpting” the Terms

\[ \text{VLDL} - C = \frac{T}{8.59} + \frac{T}{2.250} - \frac{T^2}{16.500} \]

\[ T = \text{TG} \]

\[ N = \text{NonHDL-C} \]

Interaction term for cholesterol enrichment of VLDL by CETP

Term Values
“Sculpting” the Terms

\[ VLDL - C = \frac{T}{8.59} + \frac{TN}{2.250} - \frac{T^2}{16.500} \]

\( T = TG \)
\( N = \text{NonHDL-C} \)

Correction factor. Accounts for low cholesterol content of Chylos and nascent VLDL

Term Values

[Graph showing the relationship between TG (mg/dL) and Subequation-1 coefficients for different values of TN at N = 50, 100, 150, 200]
VLDL-C Contour Plots

Beta-Quant

Freidewald

Martin

NIH
Factor Contour Plots

Beta-Quant

T, TN

NIH

Martin
VLDL-C Estimate

Freidewald

\[ y = 1.102x + 2.39 \]
\[ \text{RMSE} = 33.7 \]
\[ R^2 = 0.8341 \]

Martin

\[ y = 0.785x + 7.23 \]
\[ \text{RMSE} = 22.1 \]
\[ R^2 = 0.9425 \]

NIH

\[ y = 0.9412x + 4.46 \]
\[ \text{RMSE} = 13.6 (13.85) \]
\[ R^2 = 0.9585 (0.9555) \]
Equation for LDL-C

\[ \text{LDL-C} = \frac{C}{0.948} - \frac{H}{0.971} - \frac{T}{8.56} - \frac{TN}{2140} + \frac{T^2}{16100} - 9.44 \]

C = Total Cholesterol
H = HDL-C
T = TG
N = NonHDL-C
Mean Absolute Difference Plots
VLDDL-C Contour Plots
VLDL-C Contour Plots
Equation 1: VLDLC = \frac{T}{8.59} + \frac{TN}{2250} - \frac{T^2}{16500}

Martin Factor Table Follows Equation-1

**Martin**

\[ y = 0.9958x + 0.0985 \]

**NIH**

\[ y = 0.446x + 4.14 \]
### Misclassification Analysis of LDL-C Equations

#### Table 1: Misclassification Analysis

<table>
<thead>
<tr>
<th>TG 400-800</th>
<th>LDL-C</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Total error 22.3%</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>3.65</td>
</tr>
<tr>
<td>Martin Total error 31.9%</td>
<td>LDL-C 70-99 mg/dL</td>
<td>2.29</td>
</tr>
<tr>
<td>Friedewald Total error 34.2%</td>
<td>LDL-C 100-189 mg/dL</td>
<td>0.17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TG&lt;400</th>
<th>LDL-C</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Total error 10.4%</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>2.58</td>
</tr>
<tr>
<td>Martin Total error 11.0%</td>
<td>LDL-C 70-99 mg/dL</td>
<td>1.36</td>
</tr>
<tr>
<td>Friedewald Total error 12.6%</td>
<td>LDL-C 100-189 mg/dL</td>
<td>0.43</td>
</tr>
</tbody>
</table>

*Graphical representation of misclassification analysis with color-coded categories.*
**Drawing an elephant with four complex parameters**

Jürgen Mayer  
Max Planck Institute of Molecular Cell Biology and Genetics, Pfarrhoferstr. 108, 01307 Dresden, Germany

Khaled Khairy  
European Molecular Biology Laboratory, Meyerhofstrasse 1, 69117 Heidelberg, Germany

Jonathon Howard  
Max Planck Institute of Molecular Cell Biology and Genetics, Pfarrhoferstr. 108, 01307 Dresden, Germany

(Received 20 August 2008; accepted 5 October 2009)

We define four complex numbers representing the parameters needed to specify an elephantine shape. The real and imaginary parts of these complex numbers are the coefficients of a Fourier coordinate expansion, a powerful tool for reducing the data required to define shapes. © 2010 American Association of Physics Teachers.  
[DOI: 10.1119/1.3254017]

---

\[
x(t) = \sum_{k=0}^{\infty} (A_k^r \cos(kt) + iB_k^r \sin(kt)),
\]

\[
y(t) = \sum_{k=0}^{\infty} (A_k^i \cos(kt) + iB_k^i \sin(kt)),
\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Real part</th>
<th>Imaginary part</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_1=50-30i$</td>
<td>$B_1=50$</td>
<td>$B_1=-30$</td>
</tr>
<tr>
<td>$p_2=18+8i$</td>
<td>$B_2=18$</td>
<td>$B_2=8$</td>
</tr>
<tr>
<td>$p_3=12+16i$</td>
<td>$A_3=12$</td>
<td>$B_3=-16$</td>
</tr>
<tr>
<td>$p_4=14+60i$</td>
<td>$A_4=-60$</td>
<td>$B_4=14$</td>
</tr>
<tr>
<td>$p_5=40+20i$</td>
<td>$A_5=-40$</td>
<td>$B_5=-20$</td>
</tr>
</tbody>
</table>

Wiggle coeff. = 40
Demystifying CVD Biomarkers

• Lipoprotein Metabolism
• New equation for LDL-C
• New algorithm for lipoprotein phenotyping
• New ASCVD risk score
Fredrickson’s Classification of Hyperlipidemias

“It is hoped that the systematic way of using some of the simpler tools for lipoprotein analyses described will encourage wider application of lipoprotein patterns in clinical practice so that more specific diagnoses will replace certain of the time-worn clichés......."
MEDICAL PROGRESS

FAT TRANSPORT IN LIPOPROTEINS — AN INTEGRATED APPROACH TO MECHANISMS AND DISORDERS

DONALD S. FREDRICKSON, M.D.,† ROBERT I. LEVY, M.D.,‡ AND ROBERT S. LEES, M.D.¶

BETHESDA, MARYLAND

The subjects of this review are the plasma lipoproteins, their structure and functions and the ways in which they are disordered in certain diseases. The intent is not to discuss lipoproteins for their own sake, however, but to exploit their potential for illuminating the common and often frustrating clinical problem of hyperlipidemia. The finding of an abnormal concentration in plasma of cholesterol, glycerides or a given class of the lipoproteins often raises questions of cause and relief that have no certain answer. These will not necessarily be forthcoming in this report. What will be attempted is the reduction of current information about fat transport and metabolism to the minimum terms needed by a physician to obtain a rational approach to the patient with hyperlipidemia and to keep abreast of new developments in this rapidly expanding field.

*From the Laboratory of Molecular Diseases, National Heart Institute.
†Diabetes and chief, Laboratory of Molecular Diseases, National Heart Institute.
‡Hilgard, Section on Lipoproteins, Laboratory of Molecular Diseases, National Heart Institute.
¶Assistant professor and associate physician, Rockefeller University.

The integration of information and concepts about normal mechanisms and clinical disorders will proceed from more theoretical to more practical grounds. The first part of the review will outline the normal tasks of fat transport and describe how the several plasma lipids and certain proteins interact in their performances. The proteins that have evolved mainly to participate in transport of esterified lipids and the lipoproteins that they form will be closely examined. This will include analysis of several inheritable diseases in which one of these proteins is deficient to gain perspective on the functions that they apparently serve.

A detailed discussion of hyperlipidemia will follow. This will be based on an approach developed primarily for the study of genetically determined abnormalities, but acquired or nonfamilial disorders, including changes in lipid concentrations secondary to other known disease, will be dealt with as well. All these disorders are translated into hyperlipoproteinemia on the premise — for which supporting evidence will be presented — that lipoprotein patterns offer necessary information not provided by analyses of plasma lipids alone. Some simple new nomenclature is offered since the older terminology

32
Sniderman Classification of Dyslipidemias
Classification Systems for Lipoprotein Phenotypes

Sniderman Classification

![Sniderman Classification Diagram](image)
Mondrian Inspirations

Composition II in Red, Blue, and Yellow, 1930

Piet Mondrian and Pétro (Nelly) van Doesburg in Mondrian’s Paris studio, 1923

VOGUE

Supplement

Collections

Hiver 65

200 Ideas

Choc
Classification Systems for Lipoprotein Phenotypes

Sniderman Classification

![Graph showing classification of lipoprotein phenotypes based on ApoB and TG levels.](image)
Correlation of apoB and NonHDL-C

![Graph showing the correlation between NonHDL-C and Apo B. The graph includes a regression line with the equation $y = 1.50x - 0.71$ and an $R^2$ value of 0.8616.](image)
Classification Systems for Lipoprotein Phenotypes

Sniderman Classification

NIH Classification
NIH Classification Systems for Lipoprotein Phenotypes
NIH Classification Systems for Lipoprotein Phenotypes
NIH Classification Systems for Lipoprotein Phenotypes
NIH Classification Systems for Lipoprotein Phenotypes
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NIH Classification Systems for Lipoprotein Phenotypes
NIH Classification Systems for Lipoprotein Phenotypes
NIH Classification Systems for Lipoprotein Phenotypes
NIH Classification Systems for Lipoprotein Phenotypes
Classification of Type III Hyperlipidemia
Classification of Type III Hyperlipidemia
Classification of Type III Hyperlipidemia
NMR Analysis of LDL Related Parameters by Phenotype
NMR Analysis of LDL Related Parameters by Phenotype
NMR Analysis of LDL Related Parameters by Phenotype
NMR Analysis of LDL Related Parameters by Phenotype
ASCVD Events by Phenotype in MESA
ASCVD Events by Phenotype in MESA
ASCVD Events by Phenotype in MESA

![Graphs showing ASCVD events by phenotype in MESA](image_url)
ASCVD Events by Phenotype in MESA
## Clinical Utility of Lipoprotein Phenotyping

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Signs and Symptoms</th>
<th>Diagnostic tests</th>
<th>Referrals</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pancreatitis, Lipemia Retinalis Eruptive Xanthomas</td>
<td>LPL Activity ± Apo C-II DNA Sequencing when TG&gt;880 mg/dL</td>
<td>Lipidologist Nutritionist</td>
<td>Diet, EPA Fibrates</td>
</tr>
<tr>
<td>IIa</td>
<td>Tuberous Xanthomas, Tendinous Xanthomas, Corneal Arcus</td>
<td>DNA Sequencing when LDL-C &gt;250 mg/dL</td>
<td>Lipidologist for refractory cases and homozygous FH</td>
<td>Statins</td>
</tr>
<tr>
<td>IIb</td>
<td>None</td>
<td>Apo B and ALT</td>
<td>Lipidologist for refractory cases</td>
<td>Statins, EPA Fibrates</td>
</tr>
<tr>
<td>III</td>
<td>Palmar Xanthomas, Tuberous Xanthomas</td>
<td>Apo B, Apo E2 isoforms, (\beta) quantification, Agarose gel electrophoresis</td>
<td>Lipidologist for refractory cases</td>
<td>Statins, EPA Fibrates</td>
</tr>
<tr>
<td>IV</td>
<td>Obesity, Insulin Resistance, Metabolic Syndrome</td>
<td>Apo B and ALT</td>
<td>Generally not needed</td>
<td>Statins, EPA Fibrates</td>
</tr>
<tr>
<td>V</td>
<td>Same as above</td>
<td>Apo B and ALT</td>
<td>Lipidologist Nutritionist</td>
<td>Diet, EPA Fibrates</td>
</tr>
<tr>
<td>VI</td>
<td>Malabsorption, Night Blindness, Ataxia</td>
<td>Apo B, Vitamin A&amp;E, PT INR</td>
<td>Lipidologist, Nutritionist Ophthalmologist, Neurologist</td>
<td>Diet Vitamins A&amp;E</td>
</tr>
</tbody>
</table>
Demystifying CVD Biomarkers

- Lipoprotein Metabolism
- New equation for LDL-C
- New algorithm for lipoprotein phenotyping
- New ASCVD risk score
Primary Prevention

Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia → statin

Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history, premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

Age 40-75 y and LDL-C ≥70 to <190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion

Diabetes mellitus and age 40-75 y
Moderate-intensity statin (Class I)

Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin (Class IIa)

Age >75 y
Clinical assessment, Risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity factors (e.g., South Asian ancestry)

Risk Discussion: Emphasize lifestyle to reduce risk factors Class (I)
Risk Discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy Class (IIb)
Risk Discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% Class (I)
Risk Discussion: Initiate statin to reduce LDL-C ≥50% Class (I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy
Primary Prevention

Assess ASCVD Risk in Each Age Group

- **Age 0-19 y**: Lifestyle to prevent or reduce ASCVD risk. Diagnosis of Familial Hypercholesterolemia → statin.
- **Age 20-39 y**: Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk. Consider statin if family history, premature ASCVD, and LDL-C ≥160 mg/dL (≥4.1 mmol/L).
- **Age 40-75 y**
  - LDL-C ≥190 mg/dL (≥4.9 mmol/L): No risk assessment; High-intensity statin (Class I).
  - Diabetes mellitus and age 40-75 y: Moderate-intensity statin (Class I).
  - 10-year ASCVD risk percent begins risk discussion.
- **Age >75 y**: Clinical assessment, Risk discussion.

**ASCVD Risk Enhancers**:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity factors (e.g., South Asian ancestry)

**Lipid/Biomarkers**:
- Persistently elevated triglycerides (≥175 mg/mL)

**If measured**:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apoB ≥1.30 mg/dL
- Ankle-brachial index (ABI) <0.9

**Risk Groups**

- **<5% “Low Risk”**
  - Risk Discussion: Emphasize lifestyle to reduce risk factors Class I.
- **5% - <7.5% “Borderline Risk”**
  - Risk Discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy Class IIb.
- **≥7.5% - <20% “Intermediate Risk”**
  - Risk Discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% Class I.
- **≥20% “High Risk”**
  - Risk Discussion: Initiate statin to reduce LDL-C ≥50% Class I.

**CAC**

- CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
- CAC = 1-99 favors statin (especially after age 55)
- CAC = 100+ and/or ≥75th percentile, initiate statin therapy
Primary Prevention: Assess ASCVD Risk in Each Age Group

Emphasize Adherence to Healthy Lifestyle

- **Age 0-19 y**
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → statin

- **Age 20-39 y**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history, premature ASCVD, and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- **Age 40-75 y**
  - LDL-C ≥190 mg/dL (≥4.9 mmol/L)
    - No risk assessment; High-intensity statin (Class I)
  - LDL-C 190 to <190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
    - 10-year ASCVD risk percent begins risk discussion

- **Age 40-75 y**
  - Diabetes mellitus and age 40-75 y
    - Moderate-intensity statin (Class I)

- **Age 40-75 y**
  - Risk assessment to consider high-intensity statin (Class IIa)

- **Age >75 y**
  - Clinical assessment, Risk discussion

**ASCVD Risk Enhancers:**
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity factors (e.g., South Asian ancestry)

**Lipid/Biomarkers:**
- Persistently elevated triglycerides (≥175 mg/mL)

- **In selected individuals if measured:**
  - hs-CRP ≥2.0 mg/L
  - Lp(a) levels >50 mg/dL or >125 nmol/L
  - apoB ≥1.30 mg/dL
  - Ankle-brachial index (ABI) <0.9

**Risk Discussion:**
- If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

**Risk Decision:**
- If risk decision is uncertain:
  - Consider measuring CAC in selected adults:
    - CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
    - CAC = 1-99 favors statin (especially after age 55)
    - CAC = 100+ and/or ≥75th percentile, initiate statin therapy
Pooled Cohort Risk Equations

\[ 1 - S_{10} e^{(\text{Ind}X'B - \text{Mean}X'B)} \]

African American Females
African American Males
Non-Hispanic White Females
Non-Hispanic White Males
Predictive Value of LDL-C

Low Risk

High Risk

Frequency

Frequency

Percent

Percent

Sensitivity  Specificity  Positive Predictive Value  Negative Predictive Value

Sensitivity  Specificity  Positive Predictive Value  Negative Predictive Value
ASCVD Risk by Lipids

65-yo White Male
ASCVD Risk by Lipids

65-yo White Male
ASCVD Risk by Lipids

PC Risk

[Graphs showing risk assessment by lipids]
ASCVD Risk by Lipids
ASCVD Risk by Lipids

- LDL
- non-HDL-C
- PC Risk

100-Percentile HDLC

Percentile TC

100-Percentile HDLC
ASCVD Risk by Lipids

PC Risk
## ROC Analysis of Lipids

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Pooled Cohort Risk Equations

1 - S_{10} e^{(IndX'B - MeanX'B)}

### African American Females

#### Non-Hispanic White Females

| Men (Example: 55 years of age with Hg, nonsmoker, and without diabetes) |
|-----------------------------|------------------|
| Ln Age (y)                  | 12.344           |
| Ln Total Cholesterol (mg/dL)| 11.853           |
| Ln Age×Ln Total Cholesterol | -2.664           |
| Ln HDL–C (mg/dL)            | -7.990           |
| Ln Age×Ln HDL–C             | 1.769            |
| Ln Treated Systolic BP (mm Hg) | 1.797         |
| Ln Untreated Systolic BP (mm Hg) | 1.764       |
| Current Smoker (1=Yes, 0=No)   | 7.837            |
| Ln Age×Current Smoker       | -1.795           |
| Diabetes (1=Yes, 0=No)      | 0.658            |

### African American Males

#### Non-Hispanic White Males
### Fitting of Truncated Pooled Cohort Risk Equations

#### AA Females

**Equation:**
\[ Y = -0.3758 + 0.0567 X^2 \]
\[ Y = 0.2016 + 0.0668 X^2 \]
\[ Y = -0.0490 + 0.0001 X^2 \]
\[ Y = -0.0767 + 0.0891 X^2 \]

#### AA Males

**Equation:**
\[ Y = -0.2708 \]
\[ Y = 0.2146 \]
\[ Y = -0.0654 \]
\[ Y = -0.0767 \]

#### White Females

**Equation:**
\[ Y = -29.799 \]
\[ Y = 17.114 \]
\[ Y = 12.344 \]
\[ Y = 2.469 \]

#### White Males

**Equation:**
\[ Y = 13.540 \]
\[ Y = 0.940 \]
\[ Y = 11.853 \]
\[ Y = 0.302 \]

#### Summary of Results

<table>
<thead>
<tr>
<th>Category</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tbody>
<tr>
<td>Black Female</td>
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<td>Black Male</td>
<td>3.263406</td>
<td>0.9665</td>
<td>0.9665</td>
<td>0.9665</td>
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</tbody>
</table>

#### Model Terms

- **Intercept:**
  - White Female: 4.404577
  - Black Female: 1.307477
  - White Male: 4.712263
  - Black Male: 3.263406

- **Ln Age:**
  - White Female: -29.799
  - Black Female: 17.114
  - White Male: 12.344
  - Black Male: 2.469

- **Ln Age Squared:**
  - White Female: 13.540
  - Black Female: 0.940
  - White Male: 11.853
  - Black Male: 0.302

- **Ln Total Cholesterol:**
  - White Female: -13.578
  - Black Female: -18.920
  - White Male: -7.990
  - Black Male: -0.307

- **Ln Age * Ln Total Cholesterol:**
  - White Female: -3.114
  - Black Female: 0.0
  - White Male: -2.664
  - Black Male: 0.0

- **Ln HDL:**
  - White Female: -13.578
  - Black Female: -18.920
  - White Male: -7.990
  - Black Male: -0.307

- **Ln Age * Ln HDL:**
  - White Female: 1.957
  - Black Female: -6.432
  - White Male: 2.780
  - Black Male: 1.764

- **Ln Treated Systolic BP:**
  - White Female: 2.019
  - Black Female: -29.291
  - White Male: 1.797
  - Black Male: 1.916

- **Ln Untreated Systolic BP:**
  - White Female: 1.957
  - Black Female: -6.087
  - White Male: 2.780
  - Black Male: 1.764

- **Current Smoker:**
  - White Female: 7.574
  - Black Female: 0.691
  - White Male: 7.837
  - Black Male: 0.549

- **Diabetes:**
  - White Female: 0.661
  - Black Female: 0.874
  - White Male: 0.658
  - Black Male: 0.645

**Mean coefficient values:**
- White Female: -29.18
- Black Female: 86.61
- White Male: 61.18
- Black Male: 19.54

**Final results:**
- Whites true blacks forced
- no lipid meds data mixed no risk

---

*Note: The diagrams illustrate the NIH risk score and PC risk score for different categories.*
Survival Analysis by Quartiles in MESA

Full ASCVD Risk

ASCVD-Lipid Risk

Time to event: time to all CVD or last followup
Censor Code 1
Grouped by PC groups

Summary

<table>
<thead>
<tr>
<th>Group</th>
<th>Number failed</th>
<th>Number censored</th>
<th>Mean</th>
<th>Std Error</th>
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<tbody>
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<td>Combined</td>
<td>416</td>
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Quantiles

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<tr>
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<th>Upper 95%</th>
<th>Failures</th>
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<th>DF</th>
<th>Prob&gt;ChiSq</th>
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Effect of Non-Lipid Risks on ASCVD-Lipid Score

Diabetes

Smoking

BP Meds

SBP
ROC Analysis of ASCVD-Lipid Score

Low Risk

High Risk
YOU’LL NEVER FIND THE RIGHT ANSWERS IF YOU’RE ASKING THE WRONG QUESTIONS
Population Test Distributions

Full ASCVD Risk

Diagram showing distributions for TN (True Negative) and TP (True Positive).
Population Test Distributions

Full ASCVD Risk

TP

TN

Full ASCVD Risk

TN

Full ASCVD Risk

TP
Population Test Distributions

Full ASCVD Risk

ASCVD-Lipid Risk
5 DAY FORECAST

TUE
PRETTY SURE

WED
IFFY

THU
NOT A CLUE

FRI
WILD GUESS

SAT
?
ROC Analysis at 7.5% ASCVD Risk

Population Distribution

ROC Analysis

- TN
- TP

7.5%
Predictive Value of ASCVD-Lipid Risk Score

<table>
<thead>
<tr>
<th>ASCVD-Lipid Score</th>
<th>PPV</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>99.0</td>
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<tr>
<td>2</td>
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- PPV: Positive Predictive Value
- NPV: Negative Predictive Value
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### Statin Eligibility

- **Highly Unlikely**
- **Unlikely**
- **Possible**
- **Highly Likely**
- **Definite**

### % Total Population

- 40.9
- 21.7
- 19.9
- 16.7
- 0.8

### % Statin Eligible

- 1.3
- 10.7
- 34.9
- 50.5
- 2.5
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#### Statin Eligibility
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#### PPV and NPV
- **PPV**
  - Highly Unlikely: 99.0
  - Unlikely: 84.0
  - Possible: 43.1
  - Highly Likely: 98.7
  - Definite: -
- **NPV**
  - Highly Unlikely: -
  - Unlikely: -
  - Possible: -
  - Highly Likely: -
  - Definite: -

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WE'RE GOING TO BE TORTURED

ALRIGHT... AND IT LOOKS LIKE

THE WORST KIND.
Summary

• Using just results from the standard lipid panel, but using higher order terms, it is possible to more accurately calculated LDL-C up to TG of 800 mg/dL.

• Using just results from the standard lipid panel, it is possible to phenotype patients for lipoprotein disorders, except for Type III, and can be used as a decision aid in the clinical management of patients.

• Using just results from the standard lipid panel, an ASCVD-Lipid risk score can be used to detect the great majority of statin eligible patients and increase compliance with our current guidelines.
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Low Bar for Implementation
THE NUDGE CONTINUUM

FEATHER OF STATISTICAL INSIGNIFICANCE

BAT OF PATERNALISTIC OVERREACH
THE NUDGE CONTINUUM

FEATHER of STATISTICAL INSIGNIFICANCE

GENTLE TAP of GOOD SENSE

BAT of PATERNALISTIC OVERREACH
Acknowledgments

Roa Harb
Clarence Ling
Qian Sun
Ania Wolska
Sierra Wilson
Rami Ballout
Marcelo Amar
Bob Shamburek
Jeff Meeussen
Jim Otvos
Maureen Sampson
Acknowledgments

Maureen Sampson
WE SHALL NOT CEASE
FROM EXPLORATION,
AND THE END OF ALL OUR EXPLORING
WILL BE TO ARRIVE WHERE WE STARTED
AND KNOW THE PLACE FOR THE FIRST TIME.

— T.S. ELIOT