Beyond LDL-C

The Need for Advanced CVD Risk Testing

Residual Risk

Families

Show Me the EVIDENCE!

H. Robert Superko, MD, FACC, FAHA, FAACVPR
PRIMA Heart Clinic
Cholesterol, Genetics, and Heart Disease Institute (501C3)
www.FamilyHeartFoundation.org
Robert Superko, MD, FACC, FAHA, FAACVPR

- Stanford University, Director Lipid Research Clinic CPPT 1980’s
- University of California, Lawrence Berkeley National Laboratory, Director Cholesterol Research Center 1990’s
- AHA – Lipid Disorders Training Center, Director 1990-1996
- Founder & Director of Research, Berkeley HeartLab 1996 – 2004
- MAMU Director Sequoia Hospital 1994-2004
- Chairman: Molecular, Genetic and Preventive Cardiology - Fuqua Heart Center Piedmont Hospital, 2004 - 2007
- Executive Director, Center for Genomics, St. Joseph’s Hospital (Atl) 2007 - 2009
- CMO & Vice President, Celera Genomics, Quest, 2009 – 2014
- President Cholesterol, Genetics, & Heart Disease Institute (501c3)
- PRIMA Heart Clinic, Monterey California 2014-Present
- NIH Clinical trials (~35 yrs)
- No Pharmaceutical or Device Company Conflicts
- Senior Scientific Medical Consultant – BostonHeart Dx

President - Cholesterol, Genetics, and Heart Disease Institute – 21 yrs
Agenda *(in 1 hour)*

1. **Why do we need to go “Beyond” LDL?**
   - Isn’t driving LDL-C down enough?
   - “Failure” of standard lipid criteria to identify risk
   - “Failure” of LDL-C reduction to eliminate risk
   - Relative Risk (RR) versus Absolute Risk (AR)

2. **sdLDL – 50+ years of NIH Research**
   - What’s New
   - The best Rx is the Least Expensive

3. **Lp(a) International Guidelines**
   - Just Follow them

4. **Fish Oil Controversy**
   - Importance of blood levels and who benefits

5. **Family Heart Disease Clinic**
   - Genetics

6. **Firefighters and Heart Disease**
   - A National Security threat and what U can do in Dallas
Why “Advanced” Tests are Useful

1. 50% of CHD diagnosis occurs at the time of SUDDEN Death
2. Most patients with CHD do NOT have a classic lipid disorder or elevated LDL-C
3. More people on a statin drug have a CHD event than the number prevented from having an event.
4. 25% RELATIVE Risk Reduction is actually only a 3% ABSOLUTE Risk Reduction with LDL-C reduction
5. “Advanced” Disorders are more common than high LDLC
6. “Advanced” tests explain a large portion of CHD etiology (differential diagnosis) and guide Treatment/Follow-up.
7. CHD is a Family Disease
2. Most patients with CHD do **NOT** have a classic lipid disorder or elevated LDL-C
Most People who Develop CHD Have “Normal” LDL-C

Of 136,905 patients hospitalized with CAD, more than 75% had LDL levels below 130 mg/dl (3.36 mmol/L)

23% had LDL-C ≤ 70 mg/dl (1.8 mmol/L)

“Standard” Risk Evaluation misclassifies many patients
And, It is NOT PERSONAL

Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get With The Guidelines

Sachdeva et al. AHJ, Vol 157, 111-117 Jan 2009
Most People who Develop CHD Have “Normal” Triglyceride Values

Heart attack with “normal” TG

Triglyceride levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get With The Guidelines

60% had TRIG < 140 mg/dl
Most People Who Develop CHD have “Normal” HDL-C values

Heart attack with “normal” HDL-C

52% had HDL-C > 40 mg/dl
3. **More people** on a statin drug have a CHD event than the number prevented from having an event.
More people on a statin drug have a CHD event than the number prevented from having an event.

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>Placebo</th>
<th>Treatment</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>186</td>
<td>622</td>
<td>431 (19.4%)</td>
<td>191 (8.6%)</td>
</tr>
<tr>
<td>CARE</td>
<td>139</td>
<td>207</td>
<td>157 (7.5%)</td>
<td>50 (2.4%)</td>
</tr>
<tr>
<td>CARDS</td>
<td>118</td>
<td>74</td>
<td>50 (3.5%)</td>
<td>24 (1.7%)</td>
</tr>
<tr>
<td>JUPITER</td>
<td>108</td>
<td>251</td>
<td>142 (2.8%)</td>
<td>109 (1.2%)</td>
</tr>
</tbody>
</table>

“Saved” from a CVD Event

Factors Other than LDL-C Must Contribute to CHD
Has Cholesterol Reduction been a SUCCESS?

or

Has Cholesterol Reduction been a FAILURE?
4. **25% RELATIVE** Risk Reduction is actually only a **3% ABSOLUTE** Risk Reduction with LDL-C reduction
Lipid Management to Reduce Cardiovascular Risk: A New Strategy is Required.
H. Robert Superko, MD, FAHA, FACC and Spencer King III, MD, MACC

Circulation 2008;117:560-568

BEYOND LDL-C Reduction
20-30% RR Reduction is Not Enough

Average of Clinical Trial Results

25% RRR = 3.4%
ARR

Patients on Statin Treatment experiencing CVD Events
Las estatinas no impidieron un ataque al corazón

LDL-C Reduction alone FAILS many people

% Subjects with CVD event

(Based on Superko HR & King S, Circulation 1996;94:2351-2354)

(Based on Superko HR & King S, Circulation 2008; ; Average of SSSS, PROVEIT, HPS, LIPID, CARE, TNT, AFTEXCAPS, WOSCOPS)
**Example**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>CVD Events</td>
<td>100</td>
<td>75 (difference – 25)</td>
</tr>
<tr>
<td>CVD Events %</td>
<td>10%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

**Relative Risk Reduction (RRR)**
- 25 relative to 100
- 25% RRR
- **NOT** 25% of 1,000

**Absolute Risk Reduction (ARR)**
- 2.5% (10% - 7.5%)

and the complications of heart disease pretty significantly. In fact, in a recent review of 19 clinical trials that examined how helpful statins were in preventing cardiovascular events in people who had never had an event before, statins were associated with a 31 percent reduction in the risk of dying from a cardiac event and a 36 percent reduction in risk of having a heart attack. **“RELATIVE”**
CV Events & Clinical Trials
20-30% RR Reduction is **Not** Enough

% Clinical Events in Large Trials
Control vs. Treatment Groups

**Many patients reduce LDL-C yet continue to have Events!**

**RELATIVE Risk Reduction ~25%**

**ABSOLUTE Risk Reduction ~3.4%**

Superko HR. Beyond LDL-C, Circ. **1996**;94:2351-2354
(Superko & King. 2008;117:560-568)

© 2008 CGHDI
What Does This MEAN Clinically?

The **SAME** Treatment is **NOT** the Best Treatment for **EVERYBODY**!

**Individualize** Treatment based on the underlying Pathophysiology
PCSK9 Results ACC 2017
FOURIER (Further CV Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk)

**Events in Evolocumab group**

**ARR = 1.5%**
(11.3-9.8%)
NNT ~60

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab</th>
<th>Placebo</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13,784</td>
<td>13,780</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LDLC</td>
<td>92 mg/dl</td>
<td>92 mg/dl</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>LDLC – Rx</td>
<td>30 mg/dl</td>
<td>~90 mg/dl</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Primary EP (all CV)</td>
<td>1344 (9.8%)</td>
<td>1563 (11.3%)</td>
<td>0.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary EP (select CV)</td>
<td>816 (5.9%)</td>
<td>1013 (7.4%)</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

N = 219 “Saved” from CV event
5. “Advanced” Disorders are more common than high LDLC

6. “Advanced” tests explain a large portion of CHD etiology (differential diagnosis) and guide Treatment/Follow-up.
The small LDL Problem is COMMON in CAD Patients even with LDL-C < 100 mg/dl

RESIDUAL RISK
30-40% Percent of CHD patients remain at risk due to small, dense LDL even with LDL-C < 100 mg/dl.

29% of Women and 44% of Men with CHD have high levels of sdLDL despite LDL-C < 100 mg/dl.
What Do Other Experts Think?
It is Difficult To Predict Whether an **INDIVIDUAL** Patient Will Have a Cardiovascular Event

“A majority of middle-aged patients who experienced a first myocardial infarction (MI) had a traditional risk factor profile which would **not have qualified them** for preventive medical therapy.” ¹

“Although current risk estimates work **very effectively in populations**, variation of estimated risk leads to **misclassification** of true risk in **individual** patients.” ²

“Even risk algorithms based on established risk factors are limited in predictive power for **individuals. More effective prediction tools are needed**.” ³

National Medical Group Advice on the Use of “Advanced Risk Markers”

“... the AHA and other national groups have recommended that the use of these novel modalities should be reserved for refining risk estimates in intermediate-risk patients when there is uncertainty about the need to start drug therapy (1-4).


(Mosca L et al. JACC 2011;57:1404-1423)
Indeed; High Blood Cholesterol reflects High Heart Disease Risk

However:

75% CAD pts have “normal” LDL-C Levels < 130 mg/dl (23% < 70 mg/dl)
60% of CAD patients have TRIG < 140 mg/dl
52% of CAD patients have HDL-C > 40 mg/dl

Most patients with CAD do NOT have a classic blood lipid disorder
CAD Risk is often Associated with non-traditional risk factors

~ 50% of Patients make the Diagnosis of CHD for the first time when they Suddenly Drop Dead

More patients have a CHD event on a statin than those in whom an event is prevented.

THUS: Disorders Other than classic lipid disorders Contribute to CHD
Agenda

1. **Why do we need to go “Beyond” LDL?**
   - Isn’t driving LDL-C down enough?
   - “Failure” of standard lipid criteria to identify risk
   - “Failure” of LDL-C reduction to eliminate risk
   - Relative Risk (RR) versus Absolute Risk (AR)

2. **sdLDL – 50+ years of NIH Research**
   - What’s New
   - The best Rx is the Least Expensive

3. **Lp(a) International Guidelines**
   - Just Follow them

4. **Fish Oil Controversy**
   - Importance of blood levels and who benefits

5. **Family Heart Disease Clinic**
   - Genetics

6. **Firefighters and Heart Disease**
   - A National Security threat and what U can do in Dallas
Important Points about Small, Dense LDL Phenotype

Atherogenic Lipoprotein Profile (ALP)

Atherosclerosis Susceptibility Trait (ATHS)

Metabolic Syndrome

1. **3-fold** increased CAD Risk Independent of LDL-C (Similar to cigarette smoking)
2. **Inherited** pattern (gene/environment chromosome 19 - ATHS)
3. Associated with moderate elevation in **Trig** and reduced **HDL-C** but can be present with “normal” Trig and HDL-C
4. Linked to **Insulin resistance (metabolic syndrome)**, rapid arterial wall infiltration, enhanced oxidation
5. Pathophysiology worked out in multiple **NIH** funded trials
6. Reduction in levels associated with **arteriographic** and **clinical event** benefit confirmed by 4 independent Laboratory methods
   
   Linked to CVD deaths even with **LDL-C 54 mg/dl** (JUPITER)
7. Evidence based on **NIH funded clinical trials**, not pharmaceutical trials
8. The best Rx is often the **LEAST EXPENSIVE**
   
   Fat weight loss, exercise, avoidance of simple carbohydrates, niacin, fibrates, OM3
Multiple Small LDLs with **No Change** in LDLC

<table>
<thead>
<tr>
<th>Patient #1</th>
<th>Patient #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>LVLC = 100</td>
<td>LVLC = 50</td>
</tr>
<tr>
<td></td>
<td>LVLC = 50</td>
</tr>
</tbody>
</table>

Total LDLC = **100** mg/dl

Whole plasma apo B reflects apo B on VLDL, IDL and LDL.

LDL particle number reflects LDL apo B not whole plasma apo B.
Atherogenic Lipoprotein Profile (ALP): Small Dense LDL (Pattern B) or Metabolic Syndrome

Incidence: 50% of Male and 20% of pre menopausal Female CAD pts (50% post meno not on HRT).

Increased Risk: 3 - fold.

What to Look for: Small LDL, slightly high TG, slightly low HDLC, insulin resistance, increased PPL, LDLC often normal, oxidation. (MetaSyn)

Inheritance: + Dominant mode. Linked to chromosome #19.

Other: Environmental interaction, weight, diet, exercise, medications. 2-fold greater arteriographic rate of progression, ‘better’ arteriographic outcome with Rx.
**John Gofman**, Wei Young, Robert Tandy; Ischemic Heart Disease, Atherosclerosis, and Longevity - *Circulation* 1966;34:679-697

**1950** analysis of Framingham data at Donner Laboratory (UCB); “Atherogenic Index”

**Ron Krauss** et. al. Lawrence Berkeley National Laboratory, University of California, Berkeley

**Robert Superko** et al. **1980-2010** Stanford Univ, Univ of California, Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Area Heart Project (UC Berkeley)</td>
<td>1987 NIH</td>
</tr>
<tr>
<td>Quebec CV Study</td>
<td>1997 Canada</td>
</tr>
<tr>
<td>Quebec CV 13 yr follow up</td>
<td>2005 Canada</td>
</tr>
<tr>
<td>Stanford Five City Project (UC Berkeley)</td>
<td>1996 NIH</td>
</tr>
<tr>
<td>Harvard Physicians Health Survey (UC Berkeley)</td>
<td>1996 NIH</td>
</tr>
<tr>
<td>Mellisa Austin AHA Epi meetings</td>
<td>1999</td>
</tr>
<tr>
<td>* independent of TG, HDLC, LDLC</td>
<td></td>
</tr>
<tr>
<td>NHLBI Type II (NHLBI + UC Berkeley)</td>
<td>1987 NIH</td>
</tr>
<tr>
<td>CLAS (TG break points) (USC + UC Berkeley)</td>
<td>1993 NIH</td>
</tr>
<tr>
<td>MARS (USC + UC Berkeley)</td>
<td>1994 NIH+Merck</td>
</tr>
<tr>
<td>SCRIP (Stanford + UC Berkeley)</td>
<td>1996 NIH</td>
</tr>
<tr>
<td>FATS (Univ. Washington)</td>
<td>1996 NIH</td>
</tr>
<tr>
<td>SCRIP (Stanford + UC Berkeley)</td>
<td>2000 NIH</td>
</tr>
<tr>
<td>EAST (Emory University + UC Berkeley)</td>
<td>2000 NIH</td>
</tr>
<tr>
<td>HATS (Univ. Washington)</td>
<td>2001 NIH</td>
</tr>
<tr>
<td>DAIS (Finland)</td>
<td>2003 Finland</td>
</tr>
<tr>
<td>Malmo (Sweden)</td>
<td>2009 NIH</td>
</tr>
<tr>
<td>Firefighters (SJH Atlanta)</td>
<td>2011 FEMA</td>
</tr>
<tr>
<td>HATS (Univ Washington, UC Berkeley)</td>
<td>2013 NIH</td>
</tr>
<tr>
<td>JUPITER</td>
<td>2016 NIH/Pharma</td>
</tr>
</tbody>
</table>

**Atherogenic Lipoprotein Profile (ALP)**

Major component of Metabolic Syndrome and Insulin resistance

If Trigs are (statistically significantly) related to LDL size, all I need to do is just measure Trig, Right?

Trig – LDL size (n=5,366)
(Superko HR, King S, et al in PK Shah Textbook)

\[ r = 0.62 \]
\[ p < 0.0001 \]

**Figure 3** Scatter-plot of fasting triglycerides and LDL peak particle diameter in angstroms \( (r=0.62, p<0.0001) \) in 5366 CAD patients seen at the Fuqua Heart Center in Atlanta, Georgia. Large LDL particles have a diameter \( \geq 263 \) angstroms and small LDL particles a diameter \( \leq 257 \) angstroms.
Triglycerides are **Unreliable** for Predicting LDL Subclass Pattern in **Individual** Patients

**Trig Range**

70 - 250 mg/dl

r=0.55

p<0.0001

A > 263 A

B < 257 A

Y = 1512.055 - 5.281 * X; R^2 = .306
**Clinical Example: sdLDL same LDL-C Value**

**60 yo Male CAD**

- **LDLC** 171 mg/dl
- Trig = OK
- HDLC = OK
- sdLDL = 23%
- OM3 = Low
- **Rx:** Lifestyle, Statin, Ezetimibe, BABR, EPA

**49 yo Male CAD**

- **LDLC** 171 mg/dl
- Trig = OK
- HDLC = high
- sdLDL = 30%
- OM3 = Low
- **Rx:** Low CHO diet, Wgt control, NA+Statin, Ezetimibe, BABR, EPA

sdLDL test results ALTERS Rx
Small, Dense LDL (sdLDL) and Primary Prevention
**Small LDL Predicts CV Events**

<table>
<thead>
<tr>
<th>Study</th>
<th>Boston Area</th>
<th>Stanford</th>
<th>Harvard MD</th>
<th>Quebec</th>
<th>Women’s Health Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart</td>
<td>Five City</td>
<td>Health Study</td>
<td>CV Study</td>
<td>Health Study</td>
</tr>
<tr>
<td>Lab Method</td>
<td>ANUC</td>
<td>GGE</td>
<td>GGE</td>
<td>GGE</td>
<td>NMR</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>3.0</td>
<td>2.9</td>
<td>2.7</td>
<td>3.6</td>
<td>HR = 1.76</td>
</tr>
<tr>
<td>Covariant</td>
<td>TG, HDLC</td>
<td>TC/HDLC</td>
<td>non-fasting Trig (marginal)</td>
<td>Apo B</td>
<td>HR TC/HDLC=2.82, HR TG=2.58</td>
</tr>
</tbody>
</table>

* Austin AHA Epi 1999 - Small LDL predicts CAD risk INDEPENDENT of Trig, TC, LDLC, HDLC, BMI.

* Malmo Heart Study 2009: Small Medium LDL associated with CVD risk.

SFC = Stanford 5 Cities Project (Gardner et al., JAMA 1996;276:875-881.)
PHS = Physician’s Health Survey (Stampfer & Krauss et al. JAMA; 1996: 276;882-8.)
Quebec = Quebec Cardiovascular Study (Lamarche et al. Circ 1997;95:69-75)
Women’s Health = Mora et al Circ 2009;119:931-939
sdLDL-C and CHD Risk 2014 Primary Prevention

sdLDL-C is a better marker of CHD risk than LDL-C

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>sdLDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>MESA (n = 4,387)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Top quartile*</td>
<td>&gt;140 mg/dL</td>
<td>&gt;50 mg/dL</td>
</tr>
<tr>
<td>Hazard ratio (P), new CHD†</td>
<td>1.75 (0.019)</td>
<td>2.41 (0.0037)</td>
</tr>
<tr>
<td>ARIC (n = 11,419)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Top quartile</td>
<td>&gt;146 mg/dL</td>
<td>&gt;50 mg/dL‡</td>
</tr>
<tr>
<td>Hazard ratio (P), new CHD†</td>
<td>1.56 (&lt;0.0001)</td>
<td>2.0 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

* In MESA neither top quartile small LDL-P or total LDL-P was associated with new CHD (P >0.05) in normoglycemic, non-diabetic individuals in contrast to sdLDL-C.
† Top quartile compared with lowest quartile.
‡ In ARIC sdLDL-C levels > 50 mg/dL were predictive of risk even in individuals with LDL-C <100 mg/dL (HR 1.61).

1 Tsai MY et al. ATVB 2014; 34:196-201.
2 Hoogeveen RC et al. ATVB 2014; 34:1069-1077.
LDL-C and sdLDL Median (35 mg/dl) and Event Free Survival
sdLDL Better Predictor vs. LDL-C

sdLDL is a promising biomarker to predict future events for Secondary Prevention in
STABLE CAD Patients
sdLDL/LDL-C ratio had the highest HR (% small LDL)

(J Atheroscler Thromb 2014;21:755-767)
sdLDL and the Atherosclerosis Risk in Communities Study (ARIC) Small vs Large LDL and Risk

Mean
LDL-C 122 mg/dl
sdLDLC 43.5 mg/dl
%sdLDLC 35.7%

(Hoogeveen et al ATVB 2014;34:xxx)
If LDL-C is Low Enough, Is Small Dense LDL Still Important?

Atherogenic Lipoprotein Subfractions Determined by Ion Mobility and First Cardiovascular Events After Random Allocation to High-Intensity Statin or Placebo: The JUPITER Trial

Samia Mora¹; Michael P. Caulfield²; Jay Wohlgemuth²; Zhihong Chen²; H. Robert Superko³; Charles M. Rowland²; Robert J. Glynn¹; Paul M Ridker¹; Ronald M. Krauss⁴

CIRCULATIONAHA.115.016857
Published online before print September 25, 2015

© CGHDI 2016
Atherogenic Lipoprotein Subfractions Determined by Ion Mobility and First Cardiovascular Events After Random Allocation to High-Intensity Statin or Placebo: The JUPITER Trial
Samia Mora, Michael P. Caulfield, Jay Wohlgemuth, Zhihong Chen, H. Robert Superko, Charles M. Rowland, Robert J. Glynn, Paul M Ridker and Ronald M. Krauss

11,186 participants 1.9 yr

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5,600</td>
<td>4,597</td>
</tr>
<tr>
<td>CVD</td>
<td>199 (3.6%)</td>
<td>73 (1.6%)</td>
</tr>
<tr>
<td>CVD+</td>
<td>322 (5.8%)</td>
<td>108 (2.4%)</td>
</tr>
</tbody>
</table>

Supplemental Table 4. Baseline and on-treatment LDL subfractions (in clinical categories) in relation to incident CVD events

<table>
<thead>
<tr>
<th></th>
<th>CVD</th>
<th>CVD &amp; all-cause death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL particles, nmol/L</td>
<td>HR per SD higher*</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Large, I-IIa</td>
<td>1.08 (0.93-1.24)</td>
<td>0.32 †</td>
</tr>
<tr>
<td>Medium, IIb</td>
<td>1.22 (1.08-1.39)</td>
<td>0.002 †</td>
</tr>
<tr>
<td>Small, IIIa</td>
<td>1.32 (1.13-1.53)</td>
<td>&lt;0.001 †</td>
</tr>
<tr>
<td>Very small, IIIa-IVc</td>
<td>1.24 (1.07-1.42)</td>
<td>0.003</td>
</tr>
<tr>
<td>Rosuvastatin, on-treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL particles, nmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large, I-IIa</td>
<td>1.21 (0.89-1.66)</td>
<td>0.23</td>
</tr>
<tr>
<td>Medium, IIb</td>
<td>1.12 (0.85-1.49)</td>
<td>0.42</td>
</tr>
<tr>
<td>Small, IIIa</td>
<td>1.13 (0.86-1.48)</td>
<td>0.37</td>
</tr>
<tr>
<td>Very small, IIIa-IVc</td>
<td>0.94 (0.72-1.22)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**LDL-C = 110 mg/dl**

**LDL-C = 54 mg/dl**
Small, Dense LDL (sdLDL) and Secondary Prevention
sdLDL CHANGE and Multiple Clinical Trials

NHLBI-II  Greater Benefit with IDL and small LDL reduction

STARS  Dense LDL (LDL3) is the lipoprotein subfraction that exerts the single most powerful effect on the course of CAD

CLAS  Compared to controls, arteriographic improvement in pts with moderate Trig elevation but not in pts with “normal” Trig.

MARS  Arteriographic benefit in subset with medium density LDL but not dense or buoyant LDLs.

SCRIP  Arteriographic benefit in Dense LDL group and not in Buoyant LDL group.

FATS  Change in LDL density was the best predictor of arteriographic change. Better than LDL-C.

EAST  Small LDL significantly associated with NEW LESION formation in CABG patients

HATS  Small LDL reduction -> reduced progression and events

CARE  LDL size NOT different between cases and controls.

MALMO  Small/Medium LDL & Large HDL related to CVD Risk

MESA  sdLDL better predictor of risk than LDL-C

ARIC  sdLDL better predictor of risk than LDL-C even when LDL-C < 100 mg/dl

JUPITER  sdLDL relevant when LDLC~110 and even ~54 mg/dl for CHD+all mortality

Kim et al

© CGHDI 2016
**Secondary Prevention**: HATS, Small LDL, Regression, Events in Low HDL-C CAD Patients (2013)

**Odds Ratio for primary endpoints** (LDL IIIb = LDLIIIb% X LDL-C by ultracentrifuge)

<table>
<thead>
<tr>
<th></th>
<th>No Adjustment</th>
<th>Adjustment</th>
<th>Adjustment + Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL IIIb</td>
<td>1.73</td>
<td>1.56</td>
<td>1.77</td>
</tr>
<tr>
<td>P</td>
<td>0.01</td>
<td>0.06</td>
<td>0.03</td>
</tr>
</tbody>
</table>

“*When adjusted* for age, sex, baseline BMI and cigarette use, the odds for primary clinical endpoints (death from coronary causes, nonfatal myocardial infarction, stroke, or revascularization…) were significantly greater in subjects with higher on-study Small LDL (IIIb) levels both before (*P* = 0.01) and after (*P* = 0.03) adjustment for treatment group and the standard lipid values.”

- **Low levels** of cholesterol in small LDL particles associated with **reduced rate of atherosclerosis progression** & the primary clinical CV endpoint
- **Independent** of standard lipid levels
- The results **support the value** of assessing LDL subfractions for the management of cardiovascular disease risk.

Williams PT et al. PLOSone February 2013;Volume 8, Issue 2:e56782

© CGHDI 2016
sdLDL Treatment

**Diet:** Low simple sugar diets improve sdLDL. High CHO diets WORSEN sdLDL

**Exercise:** Endurance exercise can IMPROVE sdLDL

**Weight:** Excess body fat WORSENS sdLDL, loss of body fat IMPROVES sdLDL

**OM3:** Fish oils may improve sdLDL particularly if Trigs are elevated.

**Niacin:** Niacin can IMPROVE sdLDL

**Statins:** Statins lower both small and large LDL

**Statin + Niacin:** Used in several NIH Trials

**Fibrates:** Fibrates can IMPROVE sdLDL particularly if Trigs are elevated.

**Niacin+Fibrate:** The combination of niacin+fibrate can reduce sdLDL in appropriate patient populations.

**Thyroid replacement:** Thyroid replacement can improve sdLDL if the patient is hypothyroid.
Where are the Guidelines 2011?
National Lipid Association Panel & Statement

JCL 2011;5:338-367

“The recommendations of the panel should not be considered guidelines or official policy of the NLA. They represent the consensus of opinions of clinicians considered to be experts in the filed of clinical lipidology.”

Clinical utility of inflammatory markers and advanced lipoprotein testing: Advice from an expert panel of lipid specialists

Michael H. Davidson, MD, FNLA, Chair*, Christie M. Ballantyne, MD, FNLA, Co-Chair, Inflammatory Biomarkers Sub-group, Terry A. Jacobson, MD, FNLA, Co-Chair, Lipoprotein Biomarkers Sub-group, Vera A. Bittner, MD, MSPH, FNLA, Lynne T. Braun, PhD, CNP, FNLA, Alan S. Brown, MD, FNLA, W. Virgil Brown, MD, FNLA, William C. Cromwell, MD, FNLA, Ronald B. Goldberg, MD, FNLA, James M. McKenney, PharmD, FNLA, Alan T. Remaley, MD, PhD, Allan D. Sniderman, MD, Peter P. Toth, MD, PhD, FNLA, Sotirios Tsimikas, MD, Paul E. Ziajka, MD, PhD, FNLA

<table>
<thead>
<tr>
<th>LDL subfractions: initial clinical assessment and on-treatment management decisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In patients with low risk (&lt;5% 10-year CHD event risk), intermediate risk (5%–20% 10-year CHD event risk), CHD or CHD risk equivalent, premature family history of CHD in the absence of other risk factors, and in patients with established CHD who experience recurrent events despite appropriate therapy there is insufficient evidence to support LDL subfraction measurement for initial clinical assessment or on-treatment management decisions (rating: “not recommended”).</td>
</tr>
</tbody>
</table>
A new consensus statement on the clinical significance of LDL subclasses was published in 2011 authored by 18 lipoprotein and coronary heart disease experts.

The review of large, prospective epidemiologic studies of LDL heterogeneity noted that in respect to the Quebec Cardiovascular Study, “LDL size by GGE predicted the rate of CHD independent of LDL and HDL cholesterol, TGs, ApoB, and total cholesterol to HDL ratio.” In the Epic-Norfolk study it was noted that LDL size was inversely related to CHD (OR 0.60, CI 0.47-0.76), this relationship was abolished upon adjustment for LDL particle number. However, this is to be expected since the small LDL condition is associated with greater particle number (by definition) for any given level of LDL-C.
European *Consensus* Statement on LDL subclasses 2011


1.3. Genetic and Environmental Influences on LDL Heterogeneity

The predominance of sdLDL particles in plasma (phenotype B), is a feature characteristic of the *atherogenic lipoprotein phenotype* which is associated with increased risk for coronary heart disease (CHD). Other characteristics of the atherogenic lipoprotein phenotype include insulin resistance, high apo B concentrations, increased plasma levels of VLDL and TGs and reduced HDL cholesterol levels [41]. Accumulating evidence from various studies shows that there is a major genetic component that influences the LDL subclass profile [42-44].

... heritability of LDL particle size phenotypes ranges from 40- 60% [75, 76]. This is consistent with the strong influence of modifying (environmental) factors on the expression of LDL subclass phenotype B.

**Dietary intervention studies** have shown that the variation in dietary macronutrient composition (especially fats and carbohydrates) can strongly influence the expression of sdLDL phenotype [86, 87]
sdLDL Study Results After Consensus’ 2011

1. **ARIC 2014** – sdLDLC > 50 mg/dl (36%) associated with CHD events even with LDL < 100 mg/dl. (Primary Prevention) (p<0.0001)

2. **MESA 2014** – sdLDLC > 50 mg/dl (36%) associated with CHD events even with LDL < 100 mg/dl. (Primary Prevention) (p<0.004)

3. **JUPITER 2015** – small LDL predictive of CHD events and all cause mortality in control group with mean LDL = 110 mg/dl (p<0.001)
   
   Small LDL predictive of CHD+all cause mortality in treatment group with mean LDL = 54 mg/dl (p<0.03)

4. **Secondary Prevention 2014** – sdLDLC > 35 mg/dl predicts CHD events better than LDL < 100 mg/dl (p<0.03)

5. **HATS Secondary Prevention 2013** – Low levels of sdLDL associated with reduced progression INDEPENDENT of standard lipid measurements.

6. **HATS 4 Independent Lab Methods 2014** – 4 methods, same results
Indeed; High LDL-C reflects High Heart Disease Risk

However:

All LDLs are NOT alike

Small, dense LDL more dangerous than large LDL

Elevated small dense LDL is COMMON in the CAD population

50+ years of NIH funded research (unbiased)

Small LDL often, but not always, linked to Triglycerides

Small LDL linked to CAD progression and Events

Small LDL CHANGE linked to CAD Events

Small LDL TREATMENT often the LEAST Expensive

Supported by 2011 European Consensus Statement
1. **Why do we need to go “Beyond” LDL?**
   Isn’t driving LDL-C down enough?
   “Failure” of standard lipid criteria to identify risk
   “Failure” of LDL-C reduction to eliminate risk
   Relative Risk (RR) versus Absolute Risk (AR)

2. **sdLDL – 50+ years of NIH Research**
   What’s New
   The best Rx is the Least Expensive

3. **Lp(a) International Guidelines**
   Just Follow them

4. **Fish Oil Controversy**
   Importance of blood levels and who benefits

5. **Family Heart Disease Clinic**
   Genetics

6. **Firefighters and Heart Disease**
   A National Security threat and what U can do in Dallas
The Ile4399Met Variant of the *LPA* Gene

- *LPA* gene encodes the apo(a) component of Lp(a)
- High plasma levels of Lp(a) are associated with cardiovascular disease
- The Ile4399Met variant is located in the protease-like domain of apo(a)

Lipoprotein (a) (Lp(a))

What is it: Amino acid disorder (plasminogen look alike)
Inheritance: Median dominant (check family members)
Chromosome #6
Lab Defn: > 50 mg/dl (Laboratory Method Dependent)
Prevalence: ~33% CAD population
Clinical: Increases risk of other CAD RFs
Strong association with PVD (carotids)
Strong association with CAD
Associated with impaired vasoreactivity
+ associated with PTCA restenosis
Treatment: Nicotinic acid, estrogen, neomycin, apheresis, ASA
Caution: Lab methodology QC problems
Lp(a) and TC/HDL in Women
Elevated Lp(a) Compounds Risk

(Solymoss, AJC, 1994;72:1215)
2013 Lp(a) Update from JUPITER
Is Lp(a) still important if LDLC reduced with a Statin?

On-treatment Lp(a) associated with **RESIDUAL RISK**
HR 1.3 for each SD change

**RECLASSIFICATION** into higher risk group and thus more aggressive Treatment?
Elevated Lp(a) in numerous studies is associated with and causally linked to coronary heart disease, ischemic heart disease, and stroke. Meta-analysis of 36 studies demonstrates that elevated Lp(a) confers increased risk for CV events.

Lp(a) is an independent risk factor, and provides clinical information distinct from HDL-C, LDL-C, and TG.
In our study, high Lp(a) level ≥ 50 mg/dL in angina pectoris patients undergoing elective PCI with DES was significantly associated with binary restenosis and 3-year adverse clinical outcomes in an Asian population.

Patients with elevated Lp(a) and LDLC > 70 mg/dl may benefit from further LDLC reduction.

Lp(a) Level Associated with Stent Restenosis – Meta Analysis

9 cohort studies, n = 1,834 (600 ISR, 1234 no-ISR) BMS and DES

Baseline Lp(a) associated with ISR (p=0.003) (Qin et al Atherosclerosis 2013;227:360-366)
Physician Obligation to a Patient: **DIFFERENTIAL DIAGNOSIS**

46 yo Female: premature CHD, Family Hx CHD

**Why does she have CHD?**

**Why is CHD prevalent in her FAMILY?**

LDLC – not too high at 122 mg/dl

HDLC – good at 71 mg/dl

TC/HDL-C = 2.9

Trig – good at 98 mg/dl

sdLDL – not really high (18%)

Lp(a) – **Very Elevated**

Screen First degree relatives
LESSON #3 – Lp(a) is Important

Indeed; High LDL-C reflects High Heart Disease Risk

However:

Elevated Lp(a) increases CHD risk 3-Fold

Inherited in Dominant fashion

Compounds other risk factors

Explains Residual Risk when LDLC = 54 mg/dl

Treatment exists, oligonucleotides on their way

Guidelines Exist – Follow them
Agenda

1. Why do we need to go “Beyond” LDL?
   - Isn’t driving LDL-C down enough?
   - “Failure” of standard lipid criteria to identify risk
   - “Failure” of LDL-C reduction to eliminate risk
   - Relative Risk (RR) versus Absolute Risk (AR)

2. sdLDL – 50+ years of NIH Research
   - What’s New
   - The best Rx is the Least Expensive

3. Lp(a) International Guidelines
   - Just Follow them

4. Fish Oil Controversy
   - Importance of blood levels and who benefits

5. Family Heart Disease Clinic
   - Genetics

6. Firefighters and Heart Disease
   - A National Security threat and what U can do in Dallas
Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events: A Systematic Review and Meta-analysis

**Context** Considerable controversy exists regarding the association of omega-3 polyunsaturated fatty acids (PUFAs) and major cardiovascular end points.

**Objective** To assess the role of omega-3 supplementation on major cardiovascular outcomes.

**Data Sources** MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through August 2012.

**Study Selection** Randomized clinical trials evaluating the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke.

**Data Extraction** Description and relative risk (RR) estimates for the presence of blinding of participants and personnel, randomization, and allocation concealment were extracted from eligible studies.

**Data Synthesis** Of the 3635 citations retrieved, 20 studies of 68,680 patients were included, reporting 7044 deaths, 3993 cardiac deaths, 1150 sudden deaths, 1837 myocardial infarctions, and 1490 strokes. No statistically significant association was observed with all-cause mortality (RR, 0.96; 95% CI, 0.91 to 1.02; risk reduction [RD] -0.004; 95% CI, -0.01 to 0.02), cardiac death (RR, 0.91; 95% CI, 0.85 to 0.98; RD, -0.01; 95% CI, -0.02 to 0.00), sudden death (RR, 0.87; 95% CI, 0.75 to 1.01; RD, -0.003; 95% CI, -0.012 to 0.006), myocardial infarction (RR, 0.89; 95% CI, 0.76 to 1.04; RD, -0.002; 95% CI, -0.007 to 0.002), and stroke (RR, 1.05; 95% CI, 0.93 to 1.18; RD, 0.001; 95% CI, -0.002 to 0.004) when all supplement studies were considered.

**Conclusion** Overall, omega-3 PUFA supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association.

---

**Trial populations** were heterogeneous
- JELIS: favored omega-3 (pure EPA) over placebo; 14,981 patients with hypercholesterol; endpoint: major coronary events; not significant for all-cause mortality
- ORIGIN: no effect (47%EPA, 1 g/d omega-3); 12,536 patients with impaired fasting glucose, impaired glucose tolerance, or diabetes; endpoint: cardiovascular mortality
- GISSI: favored omega-3; 11,324 patients surviving a recent (<3 months) MI; endpoint: mortality/cardiovascular mortality
- GISSI-HF: favored omega-3: 6,975 patients heart failure; endpoint:

**What is Missing from Analysis? Blood Omega-3 Levels!**

- **Composition of omega-3** could affect therapeutic outcomes
  - Amarin’s Vascepa (100% EPA): lowers triglyceride; lowers LDL-C
  - GSK’s Lovaza (38% DHA, 47% EPA): lowers triglyceride; raises LDL-C by 40% to 50%
  - For treatment of depression, supplement with EPA>60% was effective while <60% was not

- **Concomitant cardioprotective therapies** could have masked effect of omega-3
  - e.g. statin use was high for JELIS (~100%), ORIGIN (~50%)
Fish Oils and CHD
Review of the Literature: 29 Studies Reporting Blood Levels of Omega3/6

American Heart Association Omega-3/6 Symposium at 2013 Annual Scientific Sessions

H. Robert Superko, MD, FAHA – Chairman
Spencer King III, MD, FACC – Co-Chairman
Michael Davidson, MD, FAHA
Carl Lavie, MD, FAHA
Jyrki Virtanen, MD
Fish Oil Blood Levels in Populations

“OM3 Index” = %EPA + %DHA

<table>
<thead>
<tr>
<th>Country</th>
<th>Disorder</th>
<th>EPA%</th>
<th>DHA%</th>
<th><strong>EPA+DHA%</strong></th>
<th>EPA/AA</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>CABG</td>
<td>2.9</td>
<td></td>
<td></td>
<td></td>
<td>Sandesara 2012</td>
</tr>
<tr>
<td>USA</td>
<td>ACS</td>
<td>3.4</td>
<td></td>
<td></td>
<td></td>
<td>Block 2008</td>
</tr>
<tr>
<td>Germany</td>
<td>“Healthy”</td>
<td>0.6%</td>
<td>2.9%</td>
<td>3.5</td>
<td>0.05</td>
<td>Rupp 2004</td>
</tr>
<tr>
<td>USA</td>
<td>MD sudden death</td>
<td>1.7%</td>
<td>2.1%</td>
<td>3.8</td>
<td>0.16</td>
<td>Albert 2002</td>
</tr>
<tr>
<td>USA(RBC)</td>
<td>Controls ACS</td>
<td></td>
<td></td>
<td>4.3</td>
<td></td>
<td>Block 2008</td>
</tr>
<tr>
<td>USA</td>
<td>“Healthy”</td>
<td>0.49%</td>
<td>3.97%</td>
<td>4.46</td>
<td></td>
<td>Skulas-Ray 2011</td>
</tr>
<tr>
<td>USA</td>
<td>Nephropathy</td>
<td>0.8%</td>
<td>3.7%</td>
<td>4.5</td>
<td>0.09</td>
<td>Donadio 2001</td>
</tr>
<tr>
<td>USA</td>
<td>AMI</td>
<td></td>
<td></td>
<td>5.0</td>
<td></td>
<td>Salisbury 2011</td>
</tr>
<tr>
<td>Sweden</td>
<td>Alzheimer’s</td>
<td>2.1%</td>
<td>4.6%</td>
<td>6.7</td>
<td></td>
<td>Vedin 2011</td>
</tr>
<tr>
<td>Japan</td>
<td>JELIS Study</td>
<td>3.0%</td>
<td>5.4%</td>
<td><strong>8.4</strong></td>
<td>0.57</td>
<td>Itakura 2011</td>
</tr>
<tr>
<td>Alaska(USA)</td>
<td>Eskimos</td>
<td>2.2%</td>
<td>6.7%</td>
<td>8.9</td>
<td>0.49</td>
<td>Ebbesson 2011</td>
</tr>
<tr>
<td>Japan</td>
<td>CHD lesions JELIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hayakawa 2012</td>
</tr>
</tbody>
</table>

© 2014 CGHDI
What is the Optimal OM3 Blood Level? Omega-3 Blood Level Index (EPA+DHA%): Estimates Based on Studies

### Table 2. Baseline Blood Fatty-Acid Levels of Study Participants Who Died Suddenly from Cardiac Causes Without Evidence of Cardiovascular Disease and Controls Matched for Age and Smoking Status.*

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>Group with Sudden Death from Cardiac Causes (N=94)</th>
<th>Control Group (N=184)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total saturated</td>
<td>31.6±1.88</td>
<td>31.3±1.80</td>
<td>0.21</td>
</tr>
<tr>
<td>Palmitic</td>
<td>19.2±2.16</td>
<td>18.8±2.00</td>
<td>0.16</td>
</tr>
<tr>
<td>Stearic</td>
<td>10.6±1.02</td>
<td>10.6±0.91</td>
<td>0.75</td>
</tr>
<tr>
<td>Total monounsaturated</td>
<td>19.8±3.25</td>
<td>19.5±2.69</td>
<td>0.72</td>
</tr>
<tr>
<td>Oleic</td>
<td>17.2±2.69</td>
<td>17.0±2.28</td>
<td>0.89</td>
</tr>
<tr>
<td>Total n−6 polyunsaturated</td>
<td>38.1±3.81</td>
<td>38.3±3.49</td>
<td>0.65</td>
</tr>
<tr>
<td>Linoleic</td>
<td>24.0±3.31</td>
<td>24.2±3.61</td>
<td>0.56</td>
</tr>
<tr>
<td>Arachidonic</td>
<td>10.6±1.88</td>
<td>10.6±1.75</td>
<td>0.93</td>
</tr>
<tr>
<td>Total long-chain n−3 polyunsaturated</td>
<td>4.82±1.31</td>
<td>5.24±1.32</td>
<td>0.01</td>
</tr>
<tr>
<td>Eicosapentaenoic</td>
<td>1.72±0.59</td>
<td>1.84±0.53</td>
<td>0.06</td>
</tr>
<tr>
<td>Docosahexaenoic</td>
<td>2.12±0.65</td>
<td>2.38±0.78</td>
<td>0.005</td>
</tr>
<tr>
<td>Docosapentaenoic</td>
<td>0.98±0.23</td>
<td>1.01±0.21</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Note:** The highlighted values (3.84 and 4.22) refer to the differences in EPA and DHA percentages between the groups, possibly indicating a cut-point for risk assessment.
Lowest Omega-3 blood level quartile had OBSERVED 90% higher risk for sudden coronary death

Relative Risk of Sudden Cardiac Death and Blood Omega-3 Levels: *Physicians’ Health Study*

- **Physicians’ Health Study**

  - **P for trend = 0.001**

  - **90% Reduction in Risk**

  - **6.87% (6.08-10.2)**

  - **EPA+DHA+DPA**

  - **“Omega-3 Index” = EPA+DHA**

  - Range by personal communications with authors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control</th>
<th>EPA</th>
<th>p</th>
<th>CHANGE</th>
<th>Control</th>
<th>EPA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61</td>
<td>61</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD%</td>
<td>19.2%</td>
<td>19.0%</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker%</td>
<td>18.2%</td>
<td>19.8%</td>
<td>0.01</td>
<td>LDL-C (mg/dl)</td>
<td>-46</td>
<td>-45</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes%</td>
<td>16.4%</td>
<td>16.3%</td>
<td>NS</td>
<td>HDL-C (mg/dl)</td>
<td>1</td>
<td>0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>182</td>
<td>182</td>
<td>NS</td>
<td>Trig (mg/dl)</td>
<td>-31</td>
<td>-37</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>58</td>
<td>59</td>
<td>NS</td>
<td>N-6 Linoleic acid</td>
<td>10</td>
<td>-38</td>
<td>0.001</td>
</tr>
<tr>
<td>Trig (mg/dl)</td>
<td>190</td>
<td>188</td>
<td>NS</td>
<td>n-3 EPA (ug/ml)</td>
<td>2</td>
<td>69</td>
<td>0.001 (+71% increase)</td>
</tr>
<tr>
<td>EPA (ug/ml)</td>
<td>93</td>
<td>97</td>
<td>NS</td>
<td>n-3 DHA</td>
<td>-2</td>
<td>-14</td>
<td>0.001</td>
</tr>
<tr>
<td>DHA (ug/ml)</td>
<td>169</td>
<td>170</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Criticism:
1. High LDL-C
2. Done in Japan (Land of Sushi)
<table>
<thead>
<tr>
<th></th>
<th>Statin</th>
<th>S+EPA</th>
<th>p</th>
<th>HazRatio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>9,319</td>
<td>9,326</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td><strong>All Events</strong></td>
<td>324</td>
<td>262</td>
<td>0.01</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Nonfatal MI</strong></td>
<td>297</td>
<td>240</td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td><strong>All cause mortality</strong></td>
<td>no difference</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Primary Prevention**

All Events (-18%)

- Statin: 127 (1.4%)
- S+EPA: 104 (1.1%)
- p: 0.13

**Secondary Prevention**

N

- Statin: 1,841
- S+EPA: 1,823
- UAP (unstable angina)
  - Statin: 123
  - S+EPA: 88
- p: 0.02

NNT statin studies = 40-60

(Yokoyama M. AHA Late Breaking Nov. 2005)
OM3 Benefit in CHD patient with Prior Intervention (JELIS)

(Matsuzaki et al. Circ J 2009;73:1283-1290)
Incremental Effects of EPA on CV Events in Statin-Treated Patients with CAD (JELIS)

Stable Angina + Intervention

(Matsuzaki et al. Circ J 2009;73:1283-1290)
### Area for Intervention

#### Lipid management cont'd

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. <em>(Level of Evidence: C)</em></td>
</tr>
<tr>
<td>2. For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy <em>(Level of Evidence: B)</em> or fish oil <em>(Level of Evidence: C)</em> may be reasonable.</td>
</tr>
<tr>
<td>3. For all patients, it may be reasonable to recommend omega-3 fatty acids from fish oil or fish oil capsules (1 g/d) for cardiovascular disease risk reduction. <em>(Level of Evidence: B)</em></td>
</tr>
</tbody>
</table>
Supplementation with marine-based omega-3 polyunsaturated fatty acids (PUFAs) remains "reasonable" for secondary prevention in patients with cardiovascular disease (CVD) and specific clinical indications, according to an American Heart Association science advisory statement.

Even a modest 10% reduction in heart disease mortality in this group "would justify treatment with a relatively safe therapy," stated advisory committee chair David S. Siscovick, MD, of the New York Academy of Medicine in New York City, and colleagues.

However, people in the general population who choose to take omega-3 fish oil supplements are doing so "in the absence of scientific data that shows any benefit of the supplements in preventing heart attacks, stroke, heart failure or death for people who do not have a diagnosis of cardiovascular disease," Siscovick noted in a news release. "We cannot make a recommendation to use omega-3 fish oil supplements for primary prevention of cardiovascular disease at this time."

The update to prior recommendations also states that clinicians should consider the use of omega-3 PUFA supplementation in patients with heart failure. This new recommendation is based on evidence from the 2008 GISSI-HF trial, which reported that supplementation reduced mortality and hospitalizations by 9% in patients with a left ventricular ejection fraction of less than 40%. 
## Blood or Plasma Fatty Acids and Ranges Associated with Clinical Benefit in Primary and Secondary Prevention

### Primary Prevention

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>Range</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itakura</td>
<td>&gt;150 ug/ml</td>
<td>Lower risk (suggested goal)</td>
</tr>
<tr>
<td><strong>DHA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sekikawa</td>
<td>&lt;1.0%</td>
<td>Highest IMT thickness in US Whites</td>
</tr>
<tr>
<td></td>
<td>&lt;4.0%</td>
<td>Highest IMT thickness in Japanese</td>
</tr>
<tr>
<td>Virtanen</td>
<td>&gt;2.66%</td>
<td>Reduced SCD risk</td>
</tr>
<tr>
<td>Virtanen</td>
<td>&gt;2.85%</td>
<td>Reduced AF risk</td>
</tr>
<tr>
<td>Wu</td>
<td>&gt;3.54%</td>
<td>Reduced AF risk</td>
</tr>
<tr>
<td><strong>EPA+DHA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albert</td>
<td>&lt;3.45%</td>
<td>High risk (lowest quartile)</td>
</tr>
<tr>
<td>Sekikawa</td>
<td>&gt;12.3%</td>
<td>Less CAC in Japanese (in Japan)</td>
</tr>
<tr>
<td></td>
<td>&gt;6.49%</td>
<td>Less CAC in Japanese Americans</td>
</tr>
<tr>
<td></td>
<td>&gt;5.23%</td>
<td>Less coronary calcium in Whites</td>
</tr>
<tr>
<td>Sandesara</td>
<td>4.35%</td>
<td>Achieving EPA+DHA level did not prevent post CABG surgery AF.</td>
</tr>
</tbody>
</table>

### Secondary Prevention

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>Range</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee</td>
<td>&lt;1.26%</td>
<td>High risk</td>
</tr>
<tr>
<td>Hayakawa</td>
<td>&gt;111 ug/ml</td>
<td>Least complex coronary lesions</td>
</tr>
<tr>
<td>Ishikawa</td>
<td>5.6%</td>
<td>Mean EPA% in Rx group and associated with reduced MCE.</td>
</tr>
<tr>
<td><strong>EPA+DHA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pottala</td>
<td>&gt;3.6%</td>
<td>Reduced all-cause mortality</td>
</tr>
<tr>
<td>Lee</td>
<td>&gt;4.74%</td>
<td>Reduced all cause and CVD mortality</td>
</tr>
<tr>
<td><strong>EPA/AA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayakawa</td>
<td>&gt;0.88</td>
<td>Least complex coronary lesions</td>
</tr>
<tr>
<td>Matsuzaki</td>
<td>&gt;1.06</td>
<td>Lowest cardiac death or MI</td>
</tr>
</tbody>
</table>

**AHA/ACCF 2011 Guidelines**: OM3 Class IIb for treatment (1 g/d) of dyslipidemia (secondary prevention) ([Circ 2011;124:2458](http://example.com))

_Superko HR, et al. 2013_
Agenda

1. Why do we need to go “Beyond” LDL?
   Isn’t driving LDL-C down enough?
   “Failure” of standard lipid criteria to identify risk
   “Failure” of LDL-C reduction to eliminate risk
   Relative Risk (RR) versus Absolute Risk (AR)

2. sdLDL – 50+ years of NIH Research
   What’s New
   The best Rx is the Least Expensive

3. Lp(a) International Guidelines
   Just Follow them

4. Fish Oil Controversy
   Importance of blood levels and who benefits

5. Family Heart Disease Clinic
   Genetics

6. Firefighters and Heart Disease
   A National Security threat and what U can do in Dallas
“Entire families sometimes show this tendency to early arteriosclerosis. A tendency which cannot be explained in any other way than that in the make-up of the machine bad material was used for the tubing.”

“Knowledge of genetic factors in the etiology of coronary heart disease has not so far been adequately utilized in attempts to combat premature CHD. The time has now come to utilize genetic information in a setting of family-oriented preventive medicine. This approach would greatly improve the efficiency of preventive efforts, utilizing predictive genetic testing and targeting counseling on those who need it most.”

“The link between CHD and inheritance is indisputable and the evidence strong and consistent. For clinicians, the question is how to utilize this information, in an efficient manner, in order to improve patient care and detection of high-risk family members.”

(Clin Chem. 2008;33 E1-E6)
Grandfather deceased
MI age 62 yr

Father 62 yo
MI

Brother asymptomatic
90% LAD

Son 1
25 yo

Son 2
23 yo

Daughter 1
20 yo

Wife
50 yo

PATIENT
54 yo
MI age 53

+GXT, 90% LAD

Brother 2
58 yo

Brother 1
56 yo

Mother 78 yo

Father 62 yo
MI

Mother 78 yo

Father MI age 53 yrs
Cost of Sequencing Whole Genome (Celera)

- 2001: $100 Million
- 2007: $10 Million
- 2011: $0.04 Million
- 2015: $3,000
- 2016: $1,000

Agenda

1. **Why do we need to go “Beyond” LDL?**
   - Isn’t driving LDL-C down enough?
   - “Failure” of standard lipid criteria to identify risk
   - “Failure” of LDL-C reduction to eliminate risk
   - Relative Risk (RR) versus Absolute Risk (AR)

2. **sdLDL – 50+ years of NIH Research**
   - What’s New
   - The best Rx is the Least Expensive

3. **Lp(a) International Guidelines**
   - Just Follow them

4. **Fish Oil Controversy**
   - Importance of blood levels and who benefits

5. **Family Heart Disease Clinic**
   - Genetics

6. **Firefighters and Heart Disease**
   - A National Security threat and what U can do
The Problem

Firefighters have **200-300%** more heart disease than other professions (US dept Labor).

The **prevalence** of undiagnosed heart disease is **unknown**.

The **cause** is **unknown**.

Hidden Heart Disease in Firefighters is a threat to National Security

Prevention strategies can not be designed without this knowledge.

If a Firefighter comes to help YOU and he has a MI,

**YOU are OUT OF LUCK!**
When do Firefighter Heart Attacks Occur?

- Heart attacks are the most frequent cause of death in firefighters
- 29.1% of these heart attacks occurred at the scene of a fire or incident
- 32.7% after an incident
- 10.9% responding
- 10.9% while training
- 12.7% during other duty

(Federal Emergency Management Agency records of deaths of all on-duty firefighters)
Deaths from Heart Disease among Firefighters During Activities

Compared to odds of death from CHD during non emergency duties, odds for CHD death during activities were:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Odds of Deaths from CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fire suppression</td>
<td>12.1 to 136 fold increase</td>
</tr>
<tr>
<td>Alarm response</td>
<td>2.8 to 14.1 fold increase</td>
</tr>
<tr>
<td>Returning from alarm</td>
<td>2.2 to 10.5 fold increase</td>
</tr>
<tr>
<td>Physical training</td>
<td>2.9-6.6 fold increase</td>
</tr>
</tbody>
</table>

(Kales S  NEJM 2007;356:1207-1215)
CHD Death Risk by Age and Duty
Original Article

Firefighters, Heart Disease, and Aspects of Insulin Resistance
The FEMA Firefighter Heart Disease Prevention Study

H. Robert Superko, MD, Kathryn M. Momary, PharmD, Lakshmana K. Pendyala, MD, Paul T. Williams, PhD, Steven Frohwein, MD, Brenda C. Garrett, RN, Cathy Skrifvars, RN, Radhika Gadesam, MD, Spencer B. King, III, MD, Steve Rolader, Bill Meyers, David Dusik, and Stoney Polite

A study describing the prevalence of CHD risk factors among 200 firefighters has reported that the prevalence of obesity, elevated blood cholesterol, and elevated blood pressure exceeded the healthy people 2010 targets and were higher than the general population.2

In the Firefighter Heart Disease Prevention (FHDP) study, we investigated the relationship between noninvasive coronary artery calcium (CAC) lesions and fasting insulin as a predictor of total coronary artery calcium burden. Association of cardiovascular risk markers was evaluated in the study. Methods: Cross-sectional, noninvasive, and longitudinal assessments. Results: Total coronary artery calcium burden was related to fasting insulin levels (p = 0.001), and a positive association was found between fasting insulin and total coronary artery calcium burden. This association was independent of other risk factors.
Atlanta Community Experience

- ~800 First Responders Screened (self pay)
  * Conducted through SJH Cardiac Rehabilitation Program – Debriefing RD
  * Offered directly to First Responders
  * One county provided grant support
Monterey Firefighter Heart Disease Prevention Program

Testing consisted of:

**Cardiac CT** to determine if coronary calcium was present and quantify the amount and location.

**Blood Tests** (donated by Boston Heart Diagnostics)
- Lipid panel (TC, LDLC, HDLC, TG)
- sdLDL
- HDL subclasses
- Lp(a)
- Apo A1
- Fatty acid balance test
- Omega-3 test
- Cholesterol absorption/production
- Fibrinogen
- Hs-CRP
- LpPLA2
- MPO
- Pre-diabetes assessment
- Fasting glucose
- Fasting insulin (insulin resistance test)

**Genetic Tests** (donated by Boston Heart Diagnostics):
- SLCO1B1
- Apo E
- Prothrombin G20210B
- Factor V Leiden

Chief Gaudenz Panholzer (Monterey Fire)
Spencer Reade (Monterey Fire)
Brenda Garrett, RN (CGHDI)
Robert Superko, MD (CGHDI)
Thank You Firefighters

Our Lives Depend on Your Health

www.FamilyHeartFoundation.org

© CGHDI 2016
Lecture Summary

1. We need to go “Beyond” LDL because LDL reduction is not enough

2. sdLDL – increases risk 3-fold, is common, treatment is cheap

3. Lp(a) International Guidelines exist – Follow Them

4. Fish Oil Controversy – Blood levels linked to CVD benefit and variation in individual response to a given dose

5. Family Heart Disease Clinic – Consider this if you are not already doing it.

6. Firefighters and Heart Disease – Consider a community screening program to identify the “VULNERABLE” Firefighter and initiate personalized preventive treatment. They will Thank You