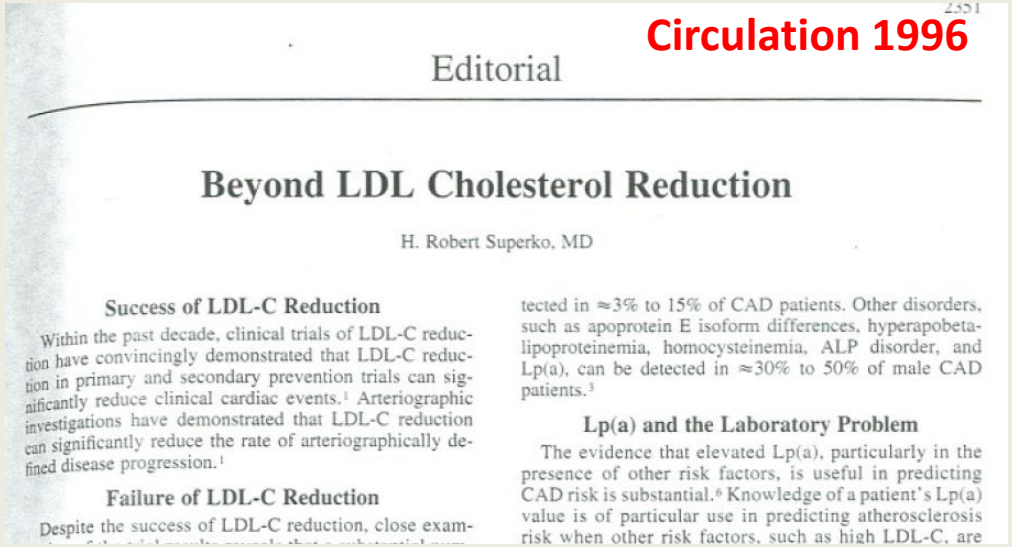
Beyond LDL-C

The Need for Advanced CVD Risk Testing

Residual Risk

Families

Show Me the EVIDENCE!



Circulation 1996

Editorial

Beyond LDL Cholesterol Reduction

H. Robert Superko, MD

Success of LDL-C Reduction

Within the past decade, clinical trials of LDL-C reduction have convincingly demonstrated that LDL-C reduction in primary and secondary prevention trials can significantly reduce clinical cardiac events.[1] Arteriographic investigations have demonstrated that LDL-C reduction can significantly reduce the rate of arteriographically defined disease progression.[1]

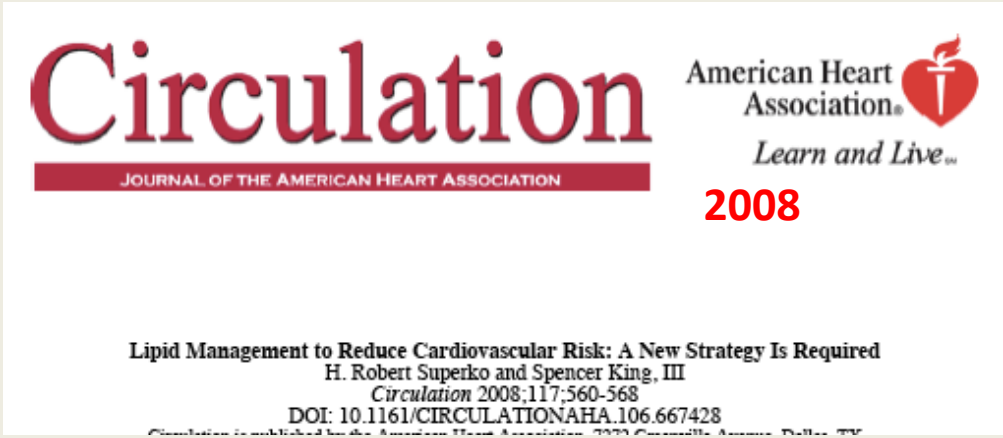
Failure of LDL-C Reduction

Despite the success of LDL-C reduction, close exam-

tected in ≈3% to 15% of CAD patients. Other disorders, such as apoprotein E isoform differences, hyperapobetalipoproteinemia, homocysteinemia, ALP disorder, and Lp(a), can be detected in ≈30% to 50% of male CAD patients.[3]

Lp(a) and the Laboratory Problem

The evidence that elevated Lp(a), particularly in the presence of other risk factors, is useful in predicting CAD risk is substantial.[6] Knowledge of a patient's Lp(a) value is of particular use in predicting atherosclerosis risk when other risk factors, such as high LDL-C, are



Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

2008

Lipid Management to Reduce Cardiovascular Risk: A New Strategy Is Required
H. Robert Superko and Spencer King, III
Circulation 2008;117;560-568
DOI: 10.1161/CIRCULATIONAHA.106.667428

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

President - Cholesterol, Genetics, and Heart Disease Institute – 21 yrs

- 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 Hospital1994-2004
- 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

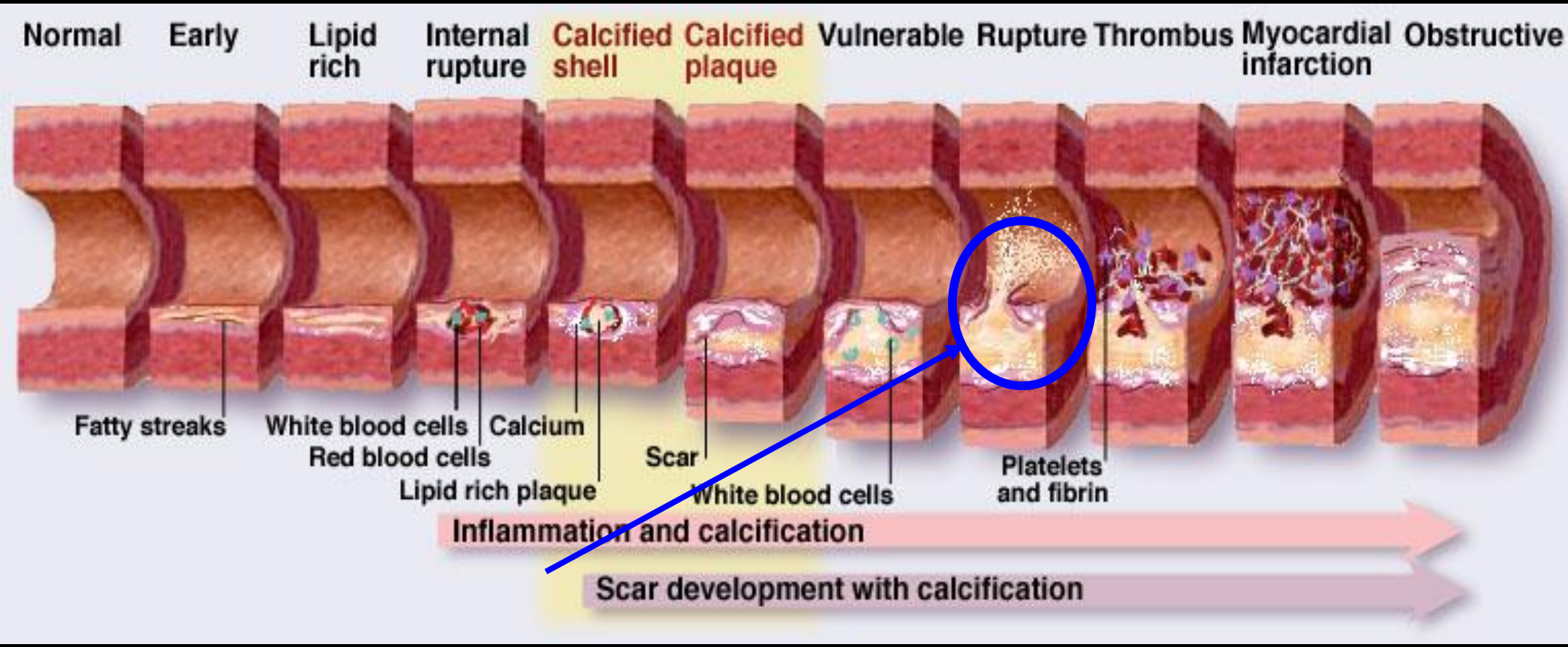
Agenda *(in 1 hour)*

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

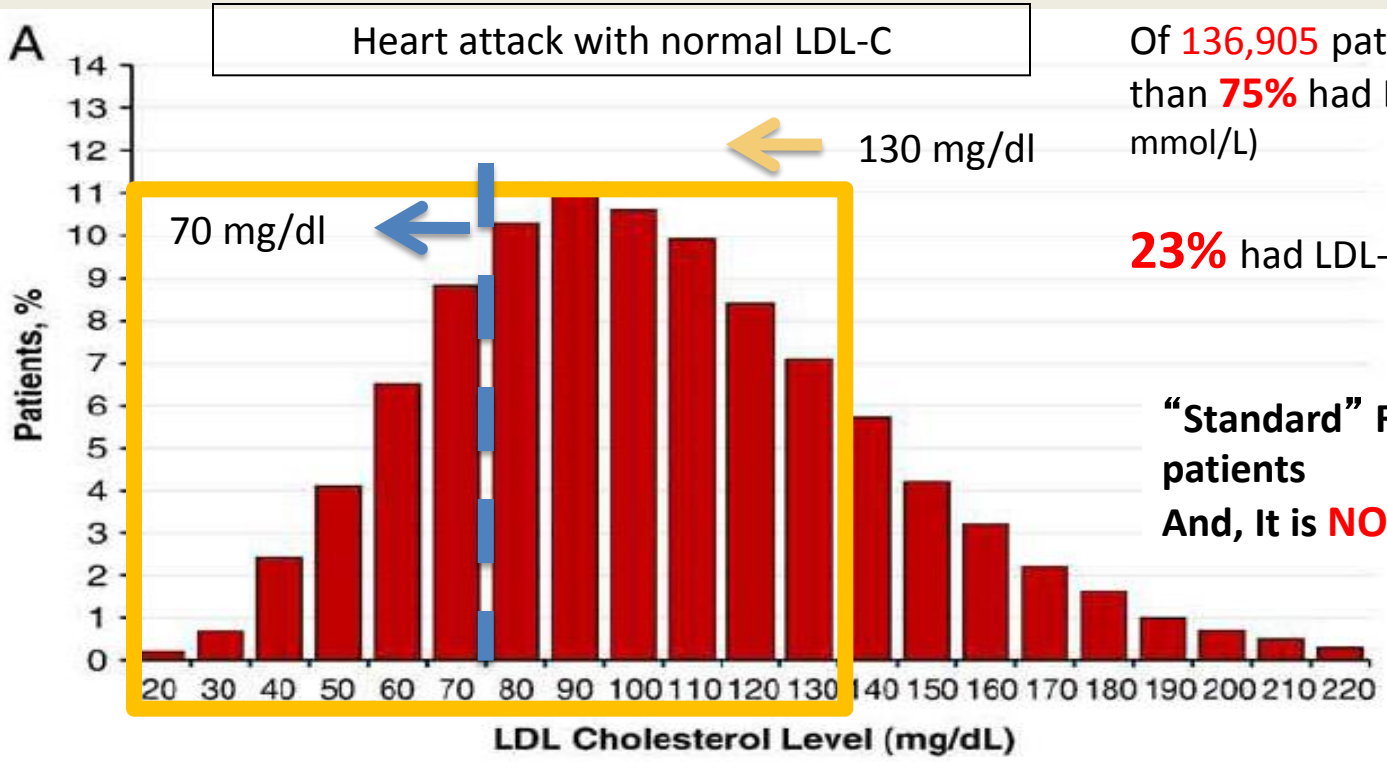
1. 50% of CHD diagnosis occurs at the time of **SUDDEN Death**
2. Most patients with CHD do **NOT** have a classic lipid disorder or elevated LDL-C
3. **More people** on a statin drug have a CHD event than the number prevented from having an event.
4. **25% RELATIVE** Risk Reduction is actually only 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**

ATHEROSCLEROSIS



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)

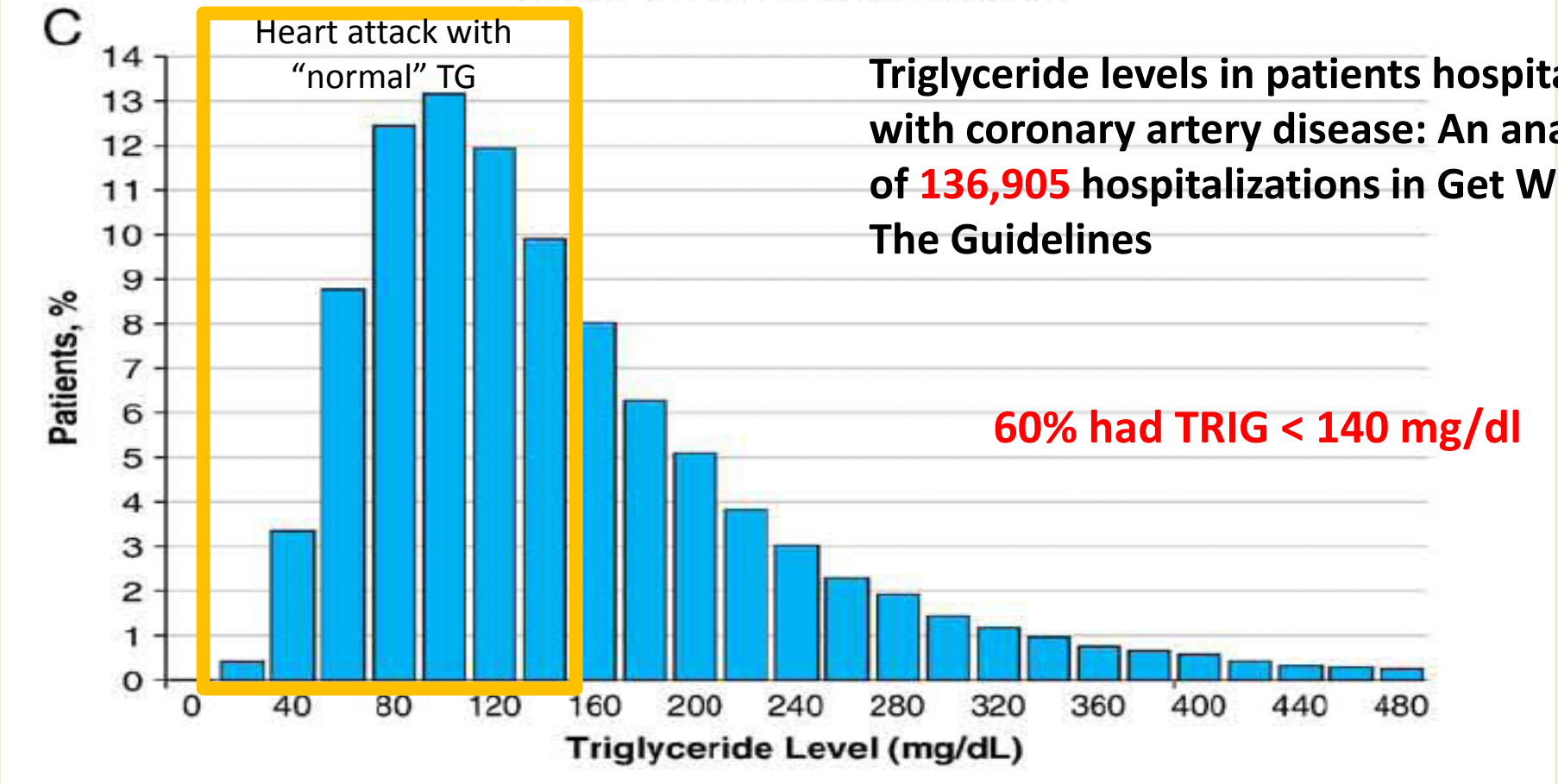
"Standard" Risk Evaluation misclassifies many patients
And, It is NOT PERSONAL

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

Amit Sachdeva, MD,[a] Christopher P. Cannon, MD,[b] Prakash C. Deedwania, MD,[c] Kenneth A. LaBresh, MD,[d] Sidney C. Smith, Jr, MD,[e] David Dai, MS,[f] Adrian Hernandez, MD,[f] and Gregg C. Fonarow, MD [a] on behalf of the GWTG Steering Committee and Hospitals *Los Angeles and San Francisco, CA; Boston and Waltham, MA; and Chapel Hill and Durham, NC*

Sachdeva et al. AHJ, Vol 157, 111-117 Jan 2009

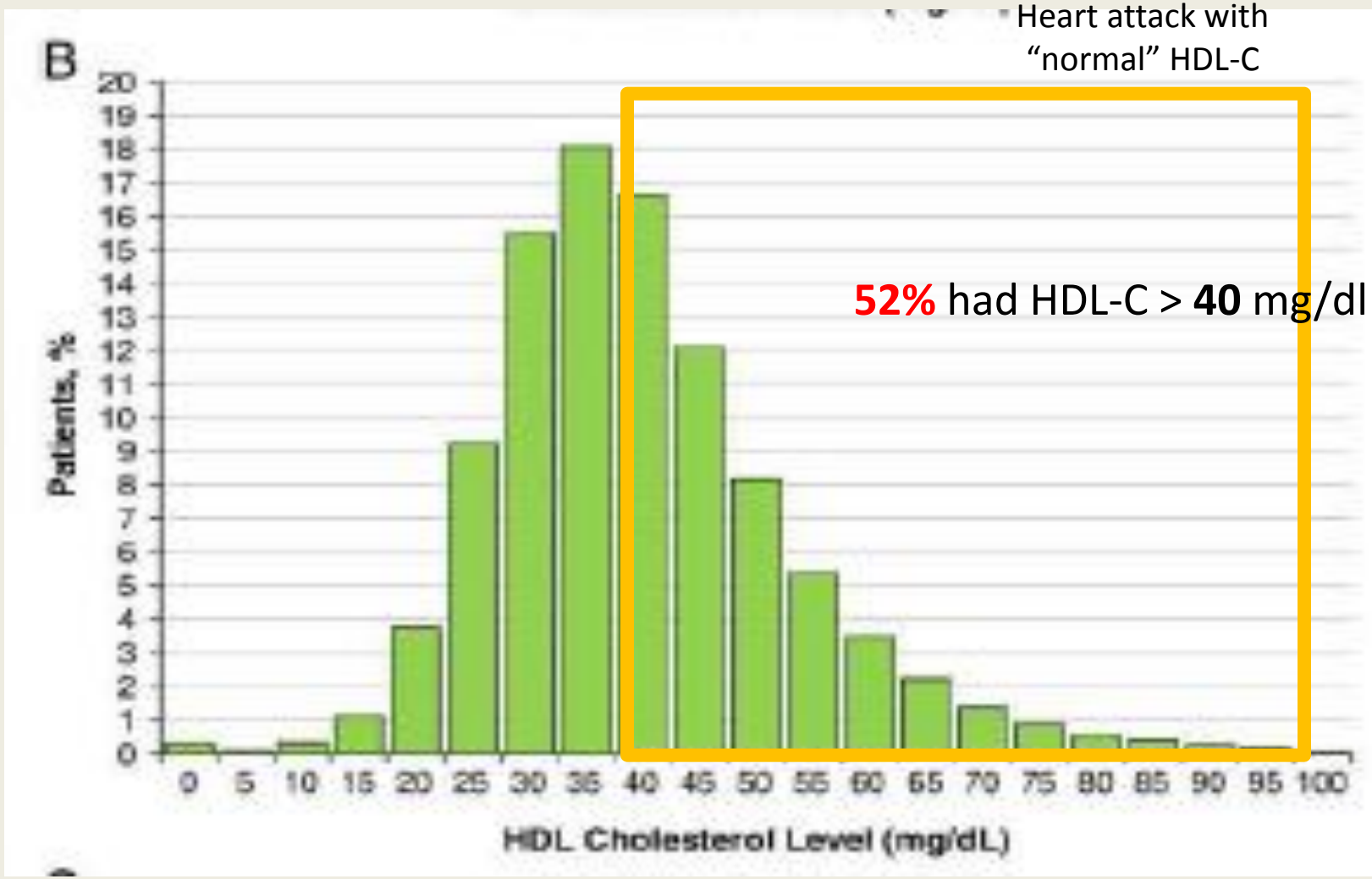
Most People who Develop CHD Have "Normal" Triglyceride Values



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



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.

"Saved" from a CVD Event

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

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

LDL-C Reduction alone FAILS many people

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Lipid Management to Reduce Cardiovascular Risk:
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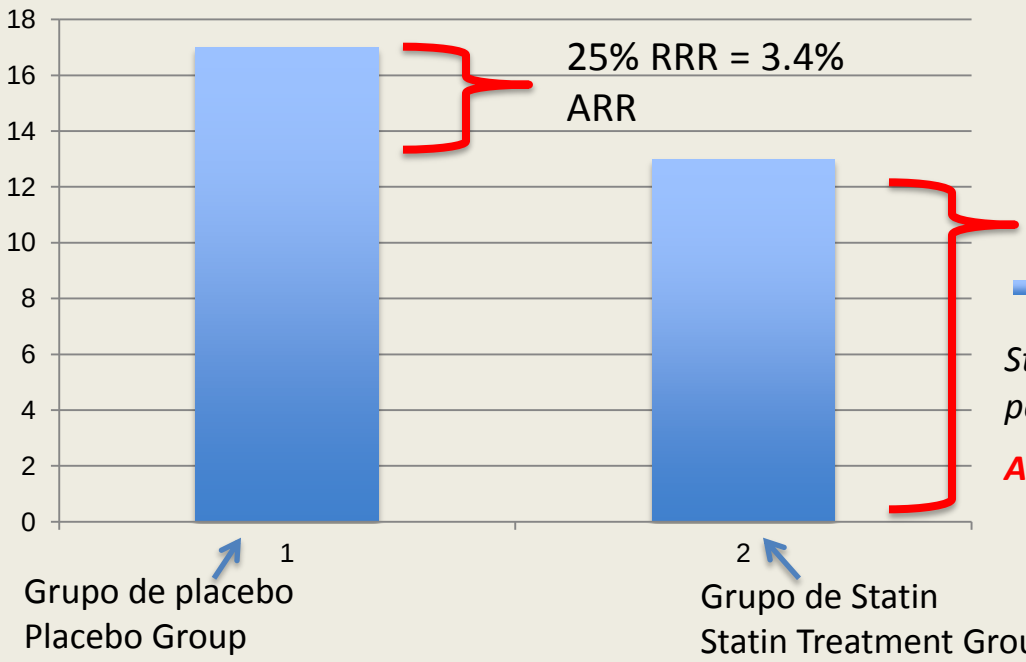
H. Robert Superko, MD, FAHA, FACC and
Spencer King III, MD, MACC

Circulation **2008**;117:560-568

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

(Superko HR. **Beyond LDL-C**, Circ. **1996**;94:2351-2354)

% Subjects with CVD event



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

Average of Studies

Statin ***RRR*** *(reducción del riesgo relativo) =* ***25%***
pero
ARR *(reducción del riesgo absoluto) =* ***3.4%***

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

Example

	Placebo	Treatment
N	1000	1000
CVD Events	100	75 (difference – 25)
CVD Events %	10%	7.5%
Relative Risk Reduction (RRR)		25 relative to 100 25% RRR NOT 25% of 1,000
Absolute Risk Reduction (ARR)		2.5% (10% - 7.5%)

U.S.News & World Report Health Care

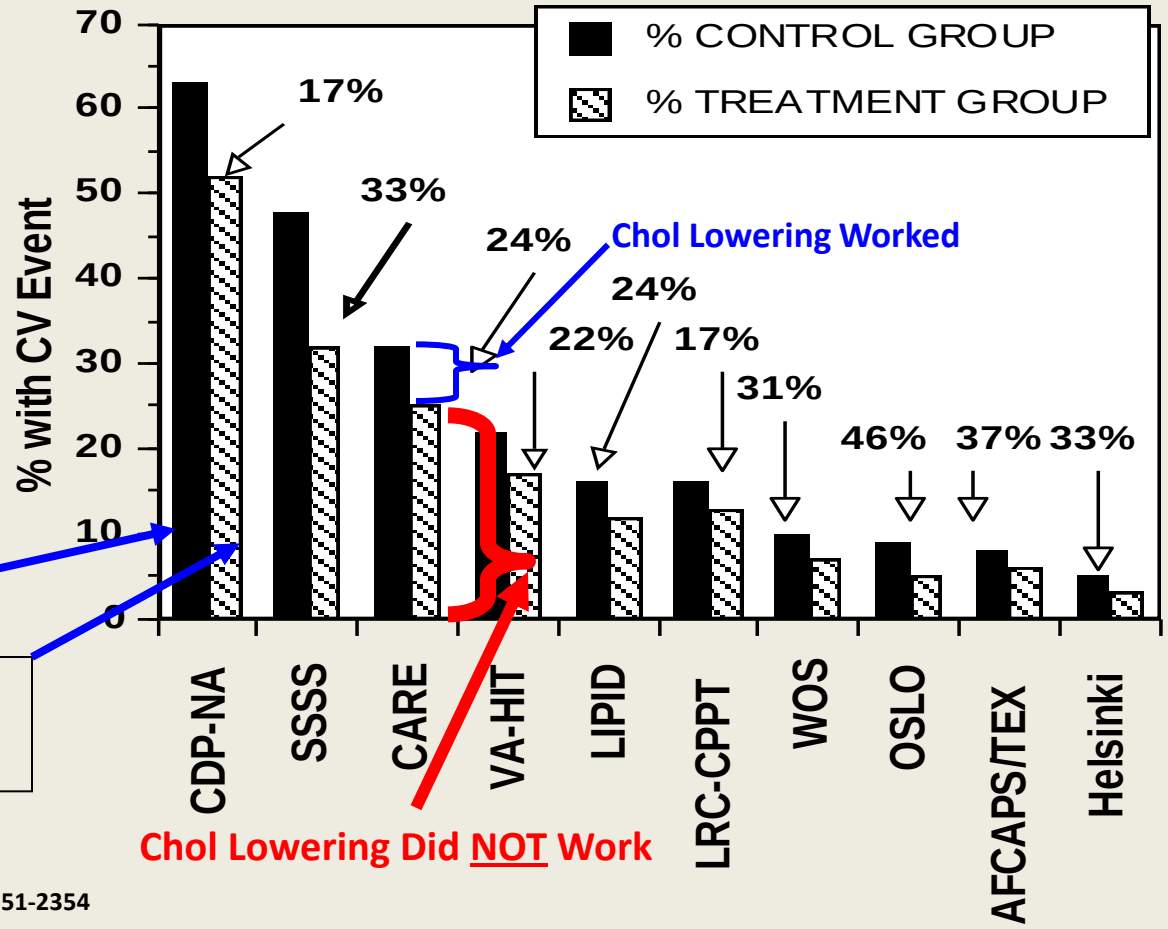
and the complications of heart disease pretty significantly. In fact, in a recent review of 19 clinical trials that examined how helpful statins were in preventing cardiovascular events in people who had never had an event before, statins were associated with a 31 percent reduction in the risk of dying 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

More LDL-C Reduction or SMARTER LDL-C Reduction?

% Clinical Events in Large Trials Control vs. Treatment Groups



Control group with events

Treatment group with events

Many patients reduce LDLC 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)

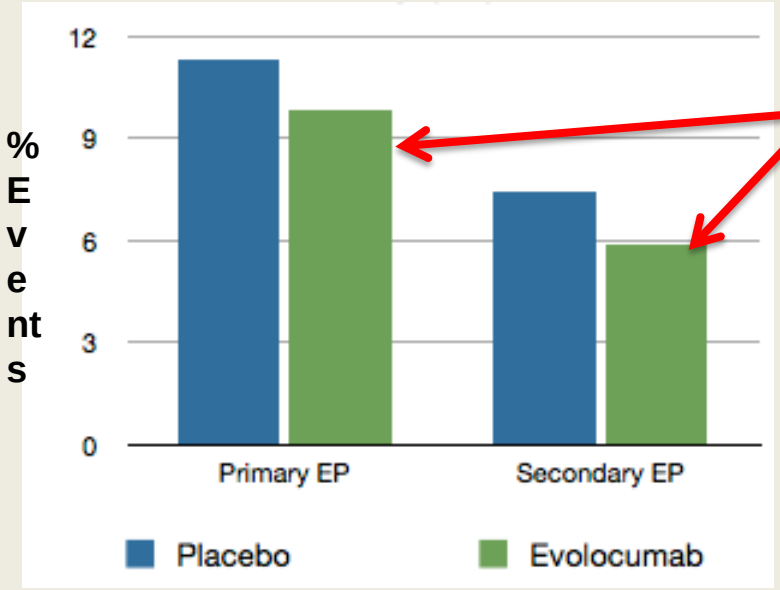
What Does This MEAN Clinically?

The SAME Treatment is NOT the Best Treatment for EVERYBODY!

Individualize Treatment based on the underlying Pathophysiology

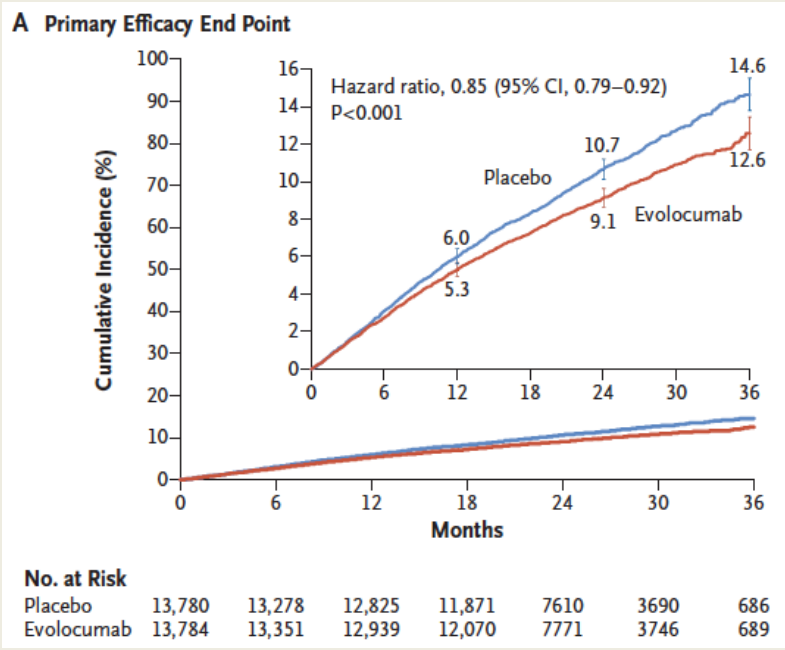
PCSK9 Results ACC 2017

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



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

N = 219 **"Saved"** from CV event

Sabatine et al NEJM 2017; DOI: 10.1056/NEJMoa1615664

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 LDLC < 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.

Circulation 2008;117:560-568

Table 3. Mean (SD) Values for Standard Lipid Profile Measurements and the Percent of 2629 CHD Patients With Laboratory Values Outside the Noted Range Who Have LDL-C <100 mg/dL in Cardiology Practices That Embrace the ATP Prevention Concept

	Women	Men	*P*
n	1083	1546	
Total cholesterol, mg/dL	158 (24)	147 (23)	0.0001
LDL-C, mg/dL	79.7 (13.8)	77.7 (15.3)	0.0005
HDL-C, mg/dL	51.8 (16.3)	40.1 (11.7)	0.0001
Triglycerides, mg/dL	145 (109)	159 (188)	0.03
Prevalence of out-of-range laboratory values, %		%	
HDL-C <40 (men) or <50 (women) mg/dL	50.70	54.30	0.07
Triglycerides >150 mg/dL	33.50	32.90	0.75
LDL diameter <25.7 nm	29.10	44.00	0.0001
HDL2b <10 %	10.30	30.60	0.0001
Lp(a) >25 mg/dL	30.30	23.60	0.0002
Total homocysteine >14 mmol/L	15.20	12.00	0.73
Fibrinogen >400 mg/dL	57.00	43.50	0.0001
hs-CRP >4.0 mg/L	34.20	21.20	0.0001
Fasting insulin >12 μIU/mL	24.70	35.90	0.007

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]

1. Akosah KO, Schaper A, Cogbill C. *J Am Coll Cardiol*. 2003;41(9):1475-1479. **2.** Berman et al. *J Am Coll Cardiol.* 2004;44:923-30. **3.** Grundy SM, et al. *Circulation*. 2004;110:227-239 OR. Grundy SM et al. *Circulation*. 2005; 112:2735-2752. why cite two papers here?

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).

1. Pearson TA et al. Circulation 2003;107:499-511
2. Hlatky MA et al. Circulation 2009;119:2408-2416
3. Greenland P et al. Circulation 2007;115:402-426
4. Greenalnd P et al. Circulation 2010;122:e584-e636

(Mosca L et al. JACC 2011;57:1404-1423)

LESSON #1 – Need for "Advanced" Tests

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?
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   - 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**
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Important Points about Small, Dense LDL Phenotype

Atherogenic Lipoprotein Profile (ALP)

Atherosclerosis Susceptibility Trait (ATHS)

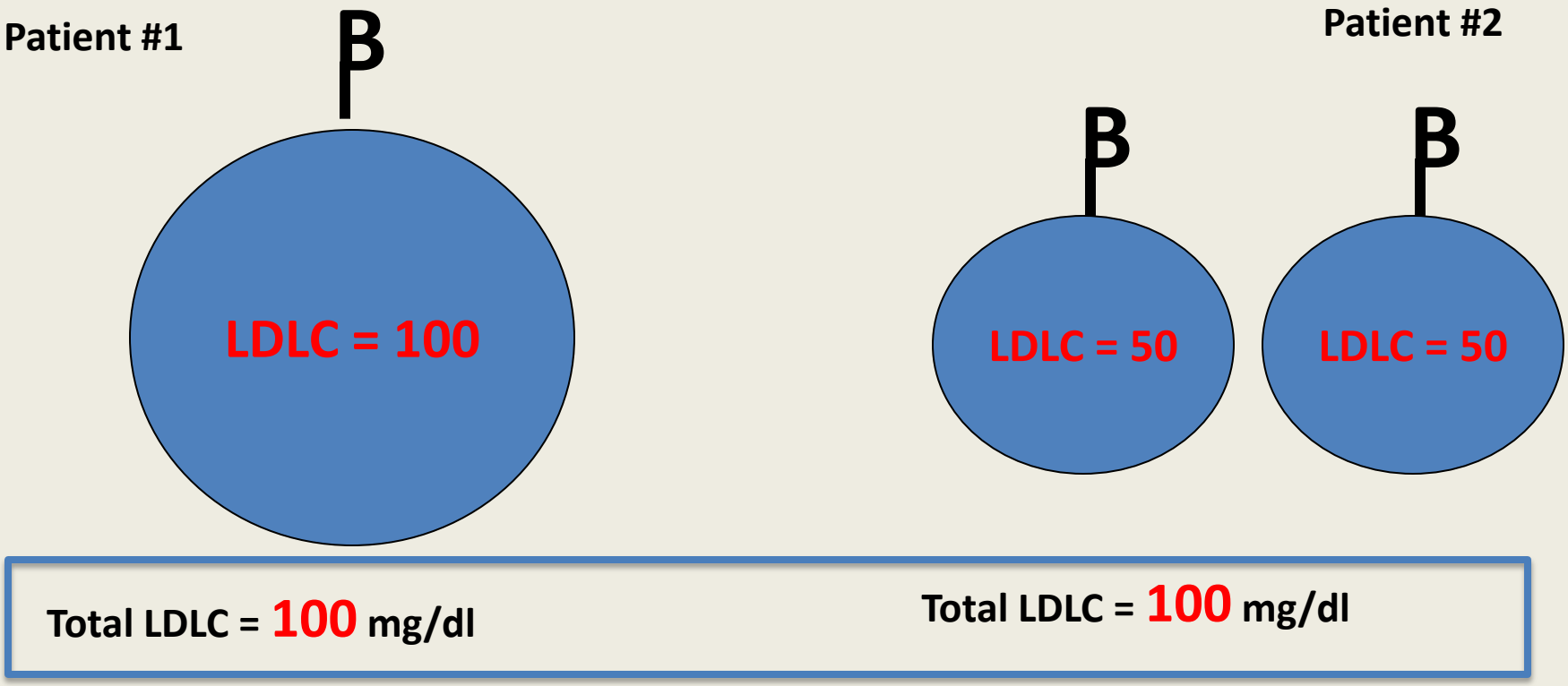
Metabolic Syndrome

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



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 **L**ipoprotein **P**rofile (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.**

LDL Subclasses - A 50+ Year History of Federal Research Funding (University of California)

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

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

Atherogenic Lipoprotein Profile (ALP)
Major component of Metabolic Syndrome and Insulin resistance

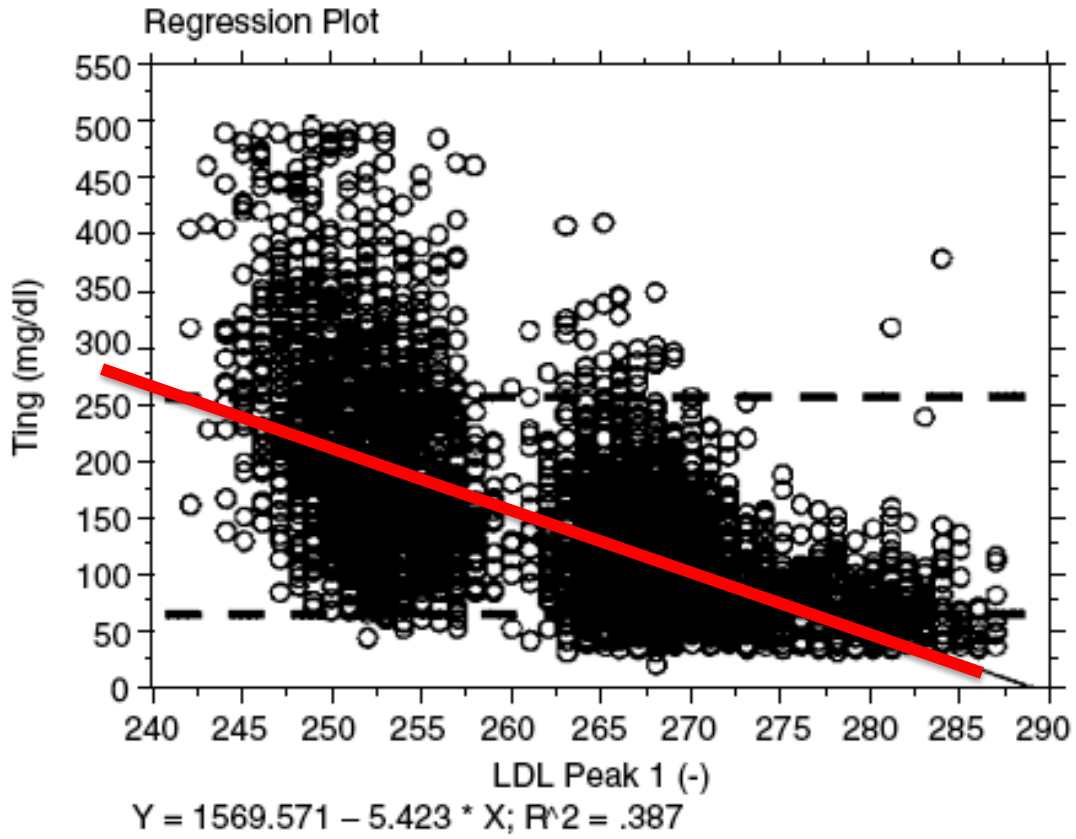
Gofman photo available at: http://ameblo.jp/yudaganka/entry-10836476300.html.

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 ShahTextbook)



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 ≥ 263 angstroms and small LDL particles a diameter ≤ 257 angstroms.

Triglycerides are Unreliable for Predicting LDL Subclass Pattern in Individual Patients

Trig Range

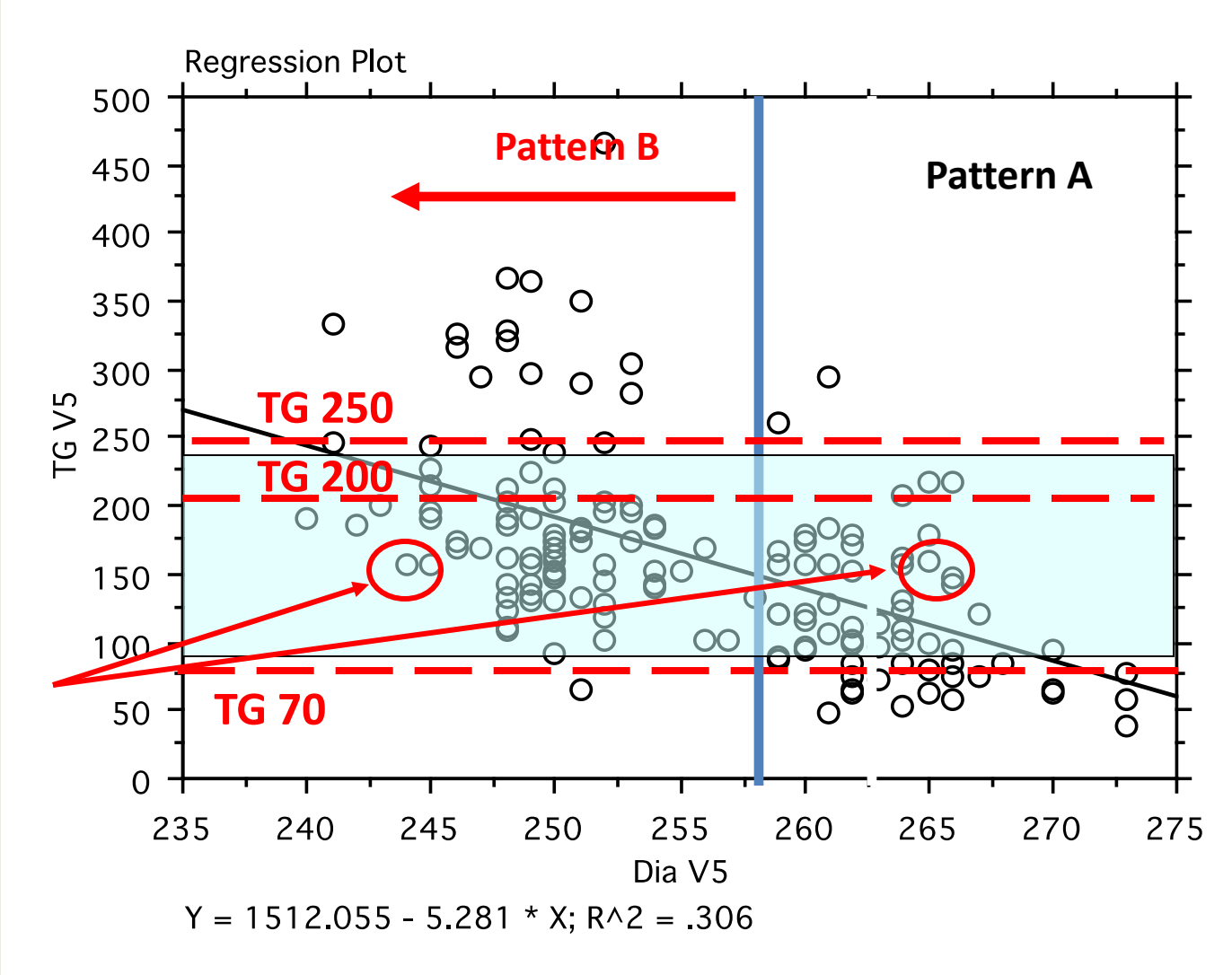
70 - 250 mg/dl

r=0.55

p<0.0001

A > 263 A

B < 257 A



Clinical Example: sdLDL **same** LDL-C Value

60 yo Male CAD

Lipid, Lipoprotein and Apolipoprotein Tests	Optimal	Borderline	High Risk
Total Cholesterol		219	
Range	<200	200-240	>240 mg/dL
Direct LDL-C			171
Range	<100	100-160	>160 mg/dL
HDL-C		44	
Range	>50	40-50	<40 mg/dL
Triglycerides	105		
Range	<150	150-200	>200 mg/dL
Non-HDL-C		175	
Range	<130	130-190	>190 mg/dL
sdLDL-C[1]		40	
Range	<20	20-40	>40 mg/dL
VLDL-C	4		
Range	<30	30-40	>40 mg/dL
Lp(a)	22		
Range	<30	30-50	>50 mg/dL
ApoA-I		144.9	
Range	>160	120-160	<120 mg/dL

Omega-3 FA Index			1.82
Range	>4.50	2.00–4.50	<2.00 %
EPA			7.1
Range	>50.0	14.0–50.0	<14.0 µg/mL
DHA		54.8	
Range	>100.0	45.0–100.0	<45.0 µg/mL
ALA		18.5	
Range	>30.0	14.0–30.0	<14.0 µg/mL

LDLC **171** mg/dl
Trig = OK
HDLC = high
sdLDL=**30%**
OM3 = Low

Rx: Low CHO diet
Wgt control
NA+Statin
Ezetimibe
BABR
EPA

LDLC **171** mg/dl
Trig = OK
HDLC = OK
sdLDL=**23%**
OM3 = Low

Rx: Lifestyle
Statin
Ezetimibe
BABR
EPA

49 yo Male CAD

Lipid, Lipoprotein and Apolipoprotein Tests	Optimal	Borderline	High Risk
Total Cholesterol			248
Range	<200	200-240	>240 mg/dL
Direct LDL-C			171
Range	<100	100-160	>160 mg/dL
HDL-C	73		
Range	>50	40-50	<40 mg/dL
Triglycerides	116		
Range	<150	150-200	>200 mg/dL
Non-HDL-C		175	
Range	<130	130-190	>190 mg/dL
sdLDL-C[1]			50
Range	<20	20-40	>40 mg/dL
VLDL-C	4		
Range	<30	30-40	>40 mg/dL
Lp(a)	<15		
Range	<30	30-50	>50 mg/dL
ApoA-I	232.4		
Range	>160	120-160	<120 mg/dL

Omega-3 FA Index		2.21	
Range	>4.50	2.00–4.50	<2.00 %
EPA		21.4	
Range	>50.0	14.0–50.0	<14.0 µg/mL
DHA		68.8	
Range	>100.0	45.0–100.0	<45.0 µg/mL
ALA	30.7		
Range	>30.0	14.0–30.0	<14.0 µg/mL

sdLDL test results ALTERS Rx

Small, Dense LDL (sdLDL) and

Primary Prevention

Small LDL Predicts CV Events

Study	Boston Area Heart	Stanford Five City	Harvard MD Health Study	Quebec CV Study	Women's Health Study
Year	1988	1996	1996	1997	2009
Lab Method	ANUC	GGE	GGE	GGE	NMR
LDL gp	B=<257 A	1/5: < 260 A	1/5: < 250	1/3: < 256	1/5: NMR
Odds Ratio	3.0	2.9	2.7	3.6	HR = 1.76
Covariant	TG HDLC	TC/HDLC Trig	non-fasting (marginal)	Apo B	HR TC/HDLC=2.82 HR TG=2.58

* 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

Malmo Heart Study = Musunuru K, et al. ATVB. 2009;29:1975

sdLDL-C and CHD Risk **2014** *Primary Prevention*

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

	LDL-C	sdLDL-C
MESA (n = 4,387)[1]		
Top quartile*	>140 mg/dL	>50 mg/dL
Hazard ratio (*P*), new CHD†	1.75 (0.019)	2.41 (0.0037)
ARIC (n = 11,419)[2]		
Top quartile	>146 mg/dL	>50 mg/dL‡
Hazard ratio (*P*), new CHD†	1.56 (<0.0001)	2.0 (<0.0001)

sdLDL risk if
>50 mg/dl?
(36%)
>40 mg/dl?
>35 mg/dl?

* 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.

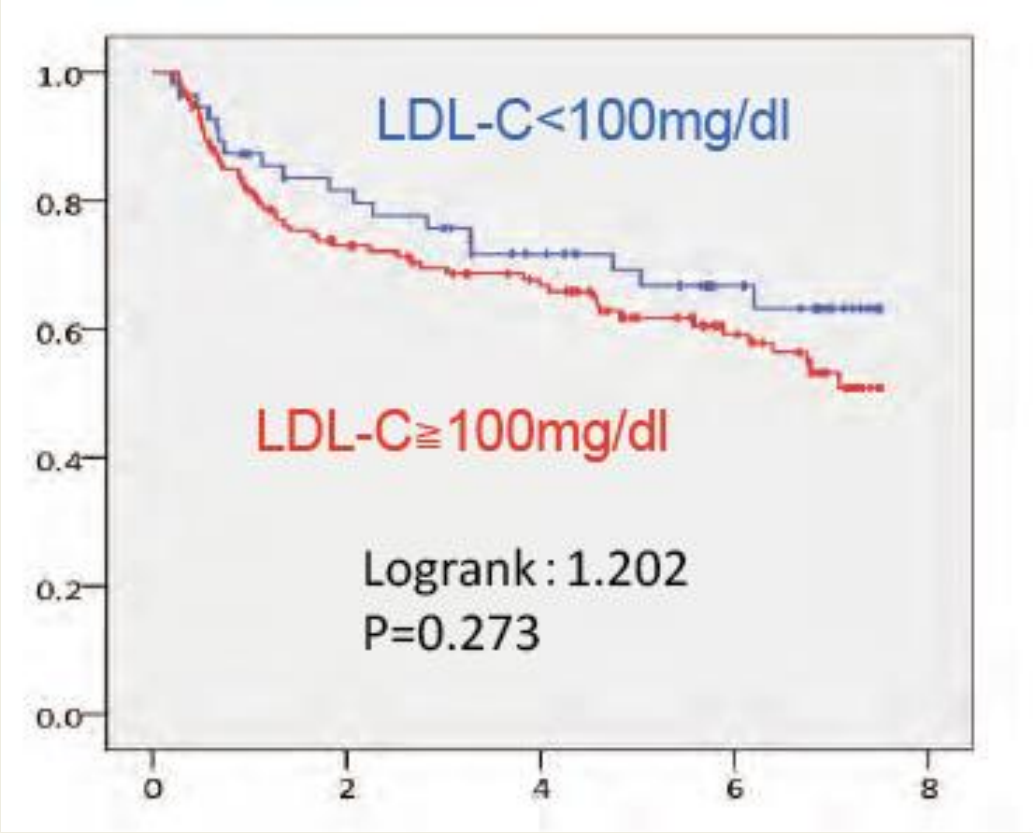
† Top quartile compared with lowest quartile.

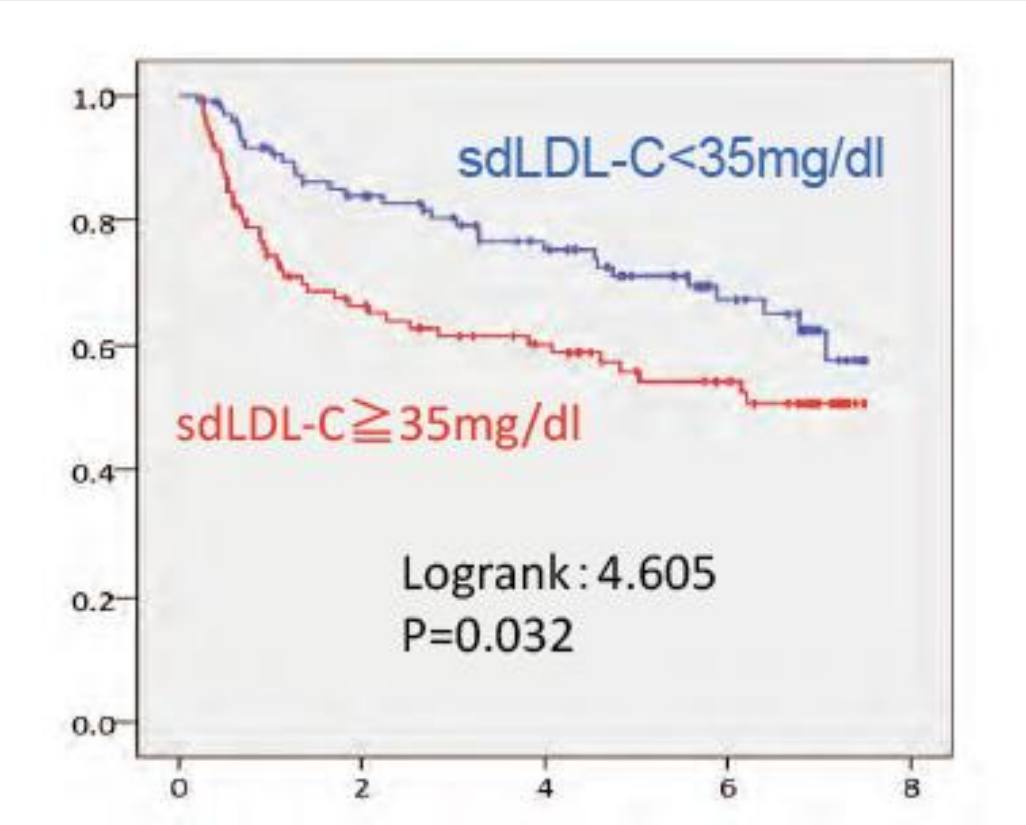
‡ In ARIC sdLDL-C levels > 50 mg/dL were predictive of **risk**

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



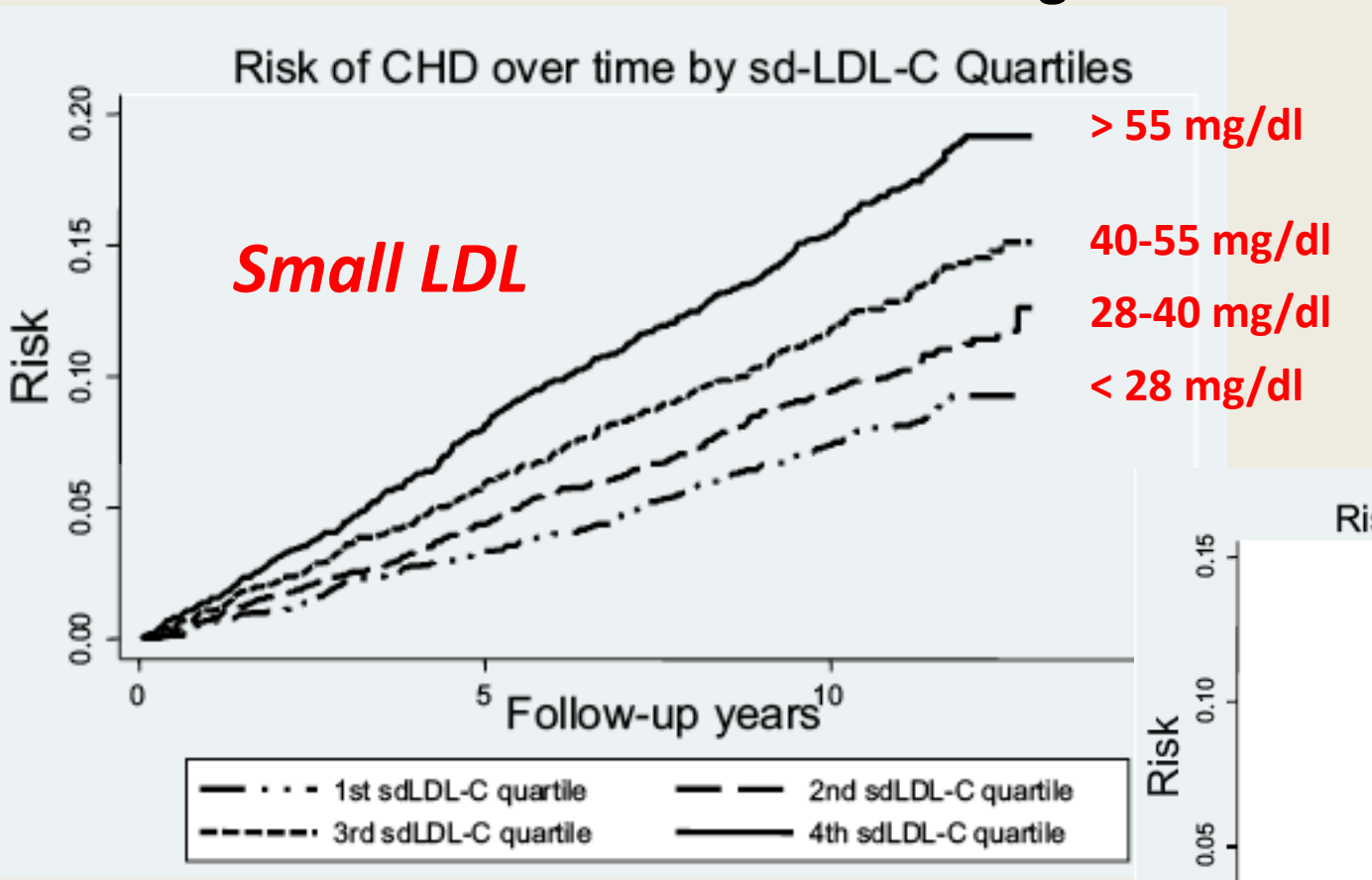


sdLDL is a promising biomarker to predict future events for Secondary Prevention in STABLE CAD Patients

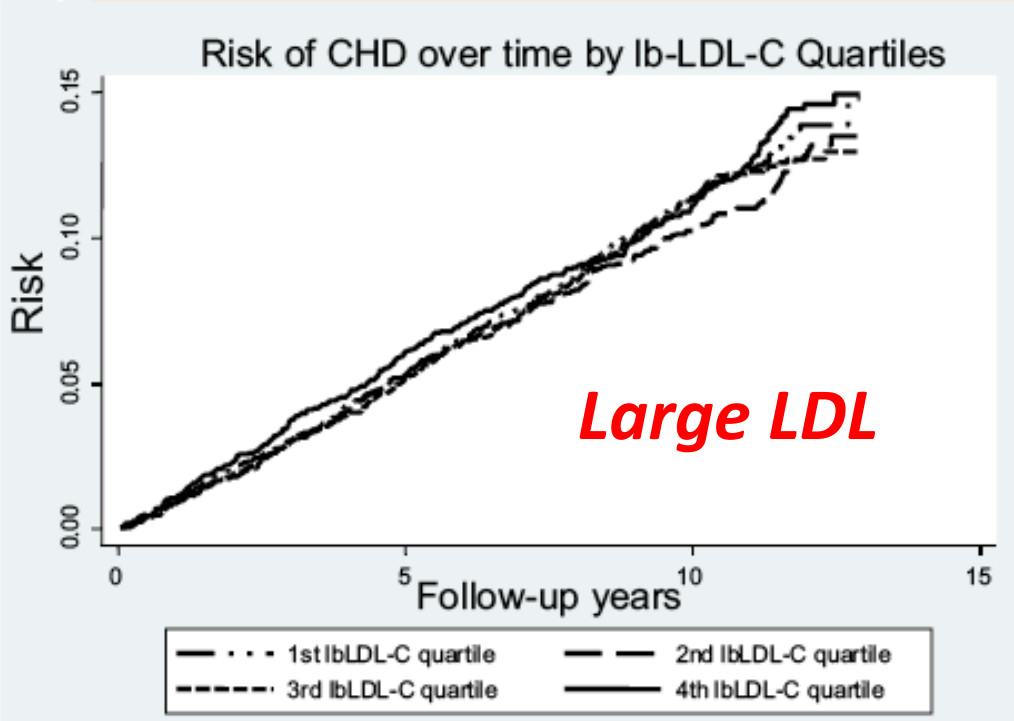
sdLDL/LDL-C ratio had the highest HR (% small LDL)

(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?

Circulation

Original Article

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[1]*; Michael P. Caulfield[2]; Jay Wohlgemuth[2]; Zhihong Chen[2]; H. Robert Superko[3]; Charles M. Rowland[2]; Robert J. Glynn[1]; Paul M Ridker[1]; Ronald M. Krauss[4]

CIRCULATIONAHA.115.016857
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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

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

Circulation. published online September 25, 2015;
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

11,186 participants 1.9 yr

	Placebo	Statin
N	5,600	4,597
CVD	199 (3.6%)	73 (1.6%)
CVD+	322 (5.8%)	108 (2.4%)

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

	CVD HR per SD higher* (95% CI)	P	CVD & all-cause death HR per SD higher* (95% CI)	P
Placebo, baseline				
LDL particles, nmol/L				
Large, I-IIa	1.08 (0.93-1.24)	0.32 ‡	0.96 (0.85-1.08)	0.51
Medium, IIb	1.22 (1.08-1.39)	0.002 ‡	1.06 (0.95-1.18)	0.30
Small, IIIa	1.32 (1.13-1.53)	<0.001 ‡	1.15 (1.02-1.30)	0.018
Very small, IIIb-IVc	1.24 (1.07-1.42)	0.003	1.21 (1.09-1.35)	<0.001 ‡
Rosuvastatin, on-treatment				
LDL particles, nmol/L				
Large, I-IIa	1.21 (0.89-1.66)	0.23	1.30 (1.01-1.66)	0.040
Medium, IIb	1.12 (0.85-1.49)	0.42	1.31 (1.03-1.66)	0.029
Small, IIIa	1.13 (0.86-1.48)	0.37	1.25 (1.00-1.57)	0.050
Very small, IIIb-IVc	0.94 (0.72-1.22)	0.64	1.06 (0.84-1.34)	0.60

LDL-C = 110 mg/dl

LDL-C = 54 mg/dl

Small, Dense LDL (sdLDL) and

Secondary Prevention

sdLDL CHANGE and Multiple Clinical Trials

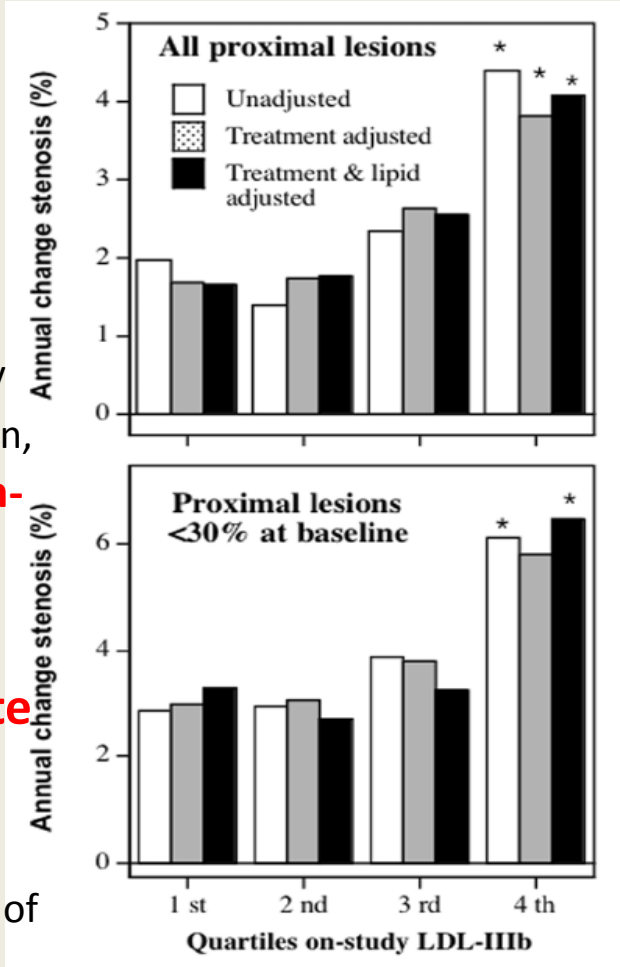
NHLBI-II	Greater Benefit with **IDL** and **small LDL** reduction
STARS	**Dense LDL** (LDL3) is the lipoprotein subfraction that exerts the **single most powerful** effect on the course of CAD
CLAS	Compared to controls, arteriographic improvement in pts with **moderate Trig elevation** but not in pts 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	In stent restenosis linked to small LDL

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)

	No Adjustment	Adjustment	Adjustment + Lipids
LDL IIIb	1.73	1.56	1.77
P	0.01	0.06	0.03

"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

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

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

"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."

	Initial Clinical Assessment					
	CRP	Lp-PLA$_2$	Apo B	LDL-P	Lp(a)	HDL or LDL Subfractions
Low risk (<5% 10-year CHD event risk)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommende
Intermediate risk (5-20% 10-year CHD event risk)	Recommended for routine measurement	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommende
CHD or CHD Equivalent	Consider for selected patients	Consider for selected patients	Consider for selected patients	Consider for selected patients	Consider for selected patients	Not recommende
Family History	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommende
Recurrent Events	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommende

LDL subfractions: initial clinical assessment and on-treatment management decisions

1. In patients with low risk (<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"**).

European *Consensus* Statement on LDL subclasses 2011

(Mikhailidis DP, Elisaf M, Rizzo M, et al. European panel on low density lipoprotein (LDL) subclasses: A statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. Current Vascular Pharmacology **2011**;9:531-571)

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

(Mikhailidis DP, Elisaf M, Rizzo M, et al. European panel on low density lipoprotein (LDL) subclasses: A statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. Current Vascular Pharmacology **2011**;9:531-571)

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 LDLC < 100 mg/dl. (Primary Prevention) ($p<0.0001$)
2. **MESA 2014** – sdLDLC > 50 mg/dl (36%) associated with CHD events even with LDLC < 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 LDLC = 110 mg/dl ($p<0.001$)

   Small LDL predictive of CHD+all cause mortality in treatment group with mean LDLC = 54 mg/dl ($p<0.03$)
4. **Secondary Prevention 2014** – sdLDLC > 35 mg/dl predicts CHD events better than LDLC < 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

Tsai MY et al. ATVB 2014; 34:196-201.
Hoogeveen RC et al. ATVB 2014; 34:1069-1077
Mora S et al Circ 2015

J Atheroscler Thromb 2014;21:755-767
Williams PT et al. Atherosclerosis 2014;233:713-720)

LESSON #2 – Small, Dense LDL (sdLDL)

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

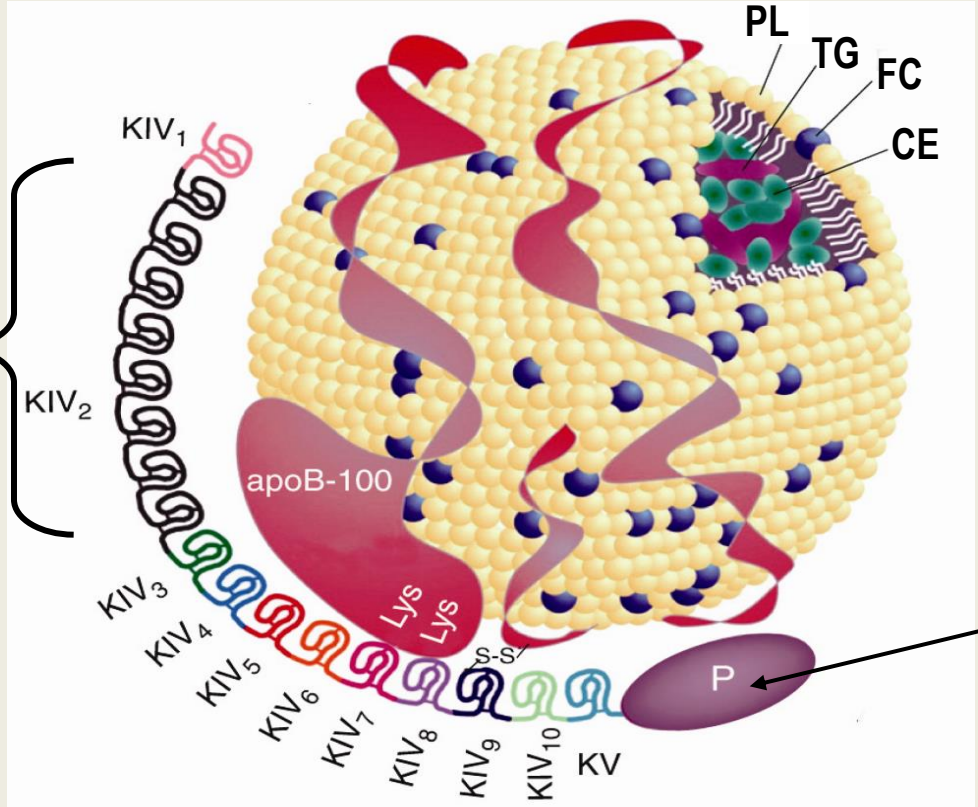
Supported by 2011 European Consensus Statement

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

The Ile4399Met Variant of the *LPA* Gene

Variable number of kringle repeats



Ile4399Met (rs3798220)

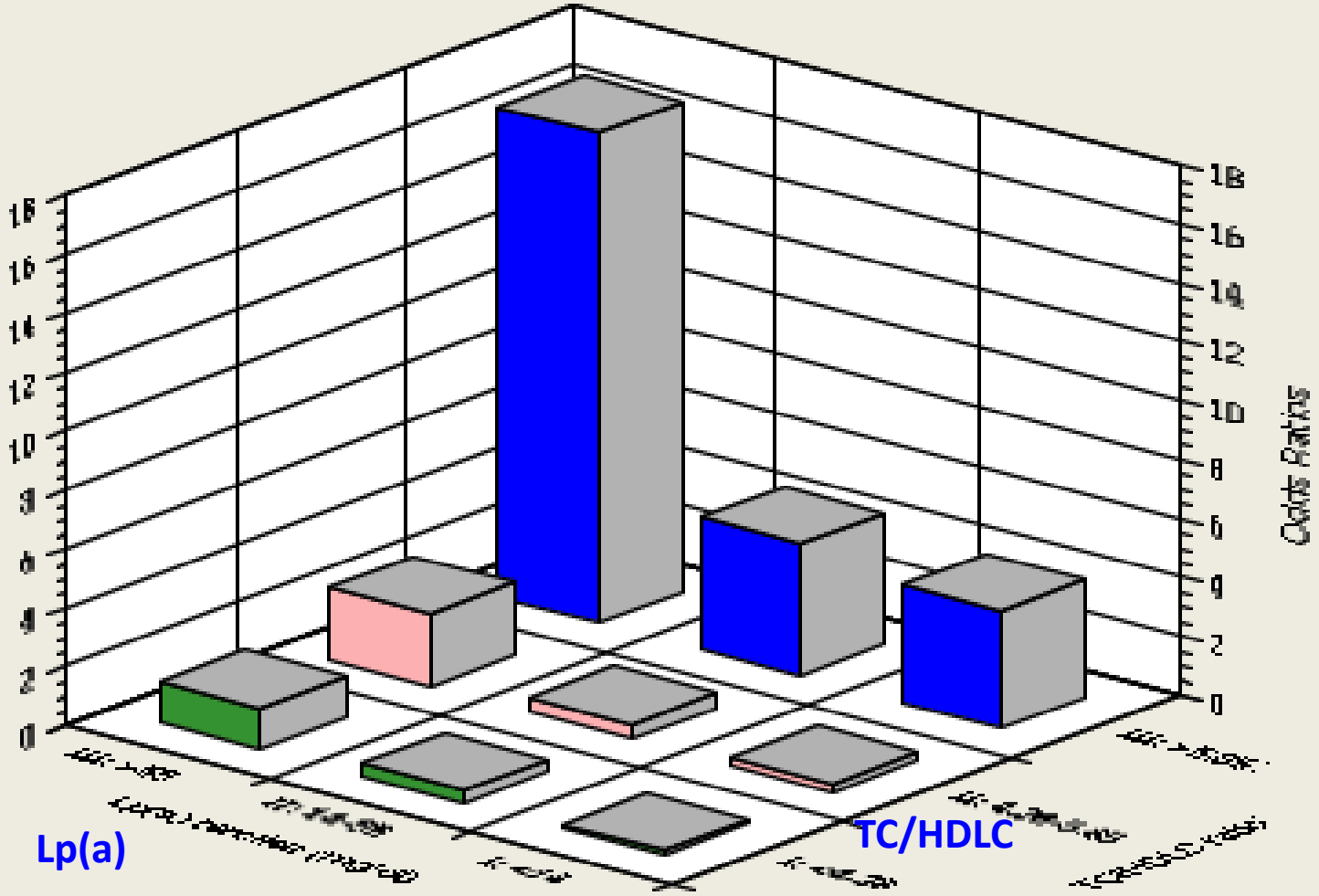
- *LPA* gene encodes the apo(a) component of Lp(a)
- High plasma levels of Lp(a) are associated with cardiovascular disease
- The Ile4399Met variant is located in the protease-like domain of apo(a)

Image: Albers, Koschinsky & Marcovina. *Kidney International* 2007; **71**:961

Lipoprotein (a) (Lp(a))

What is it:	**Amino acid disorder (plasminogen look alike)**
Inheriteance:	**Medlian 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?

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Lipoprotein(a) Concentrations, Rosuvastatin Therapy, and Residual Vascular Risk: An Analysis from the JUPITER Trial

Amit V. Khera, Brendan M. Everett, Michael P. Caulfield, Feras M. Hantash, Jay Wohlgemuth, Paul M Ridker and Samia Mora

Circulation. published online November 17, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

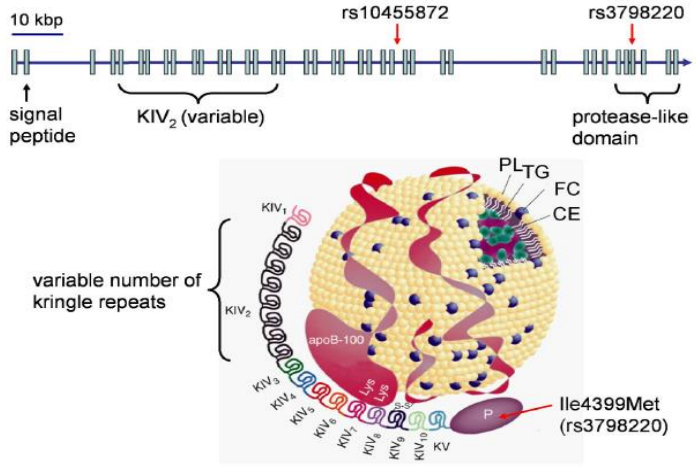
Conclusions—Among white JUPITER participants treated with potent statin therapy, Lp(a) was a significant determinant of residual risk. The magnitude of relative risk reduction with rosuvastatin was similar among participants with high or low Lp(a).

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?

European Lp(a) Guidelines 2010 – Borge Nordestgaard, MD



European Heart Journal (2010) 31, 2844–2853
doi:10.1093/eurheartj/ehq386

CURRENT OPINION

Lipoprotein(a) as a cardiovascular risk factor: current status

Børge G. Nordestgaard[1]*, M. John Chapman[2], Kausik Ray[3], Jan Borén[4], Felicita Andreotti[5], Gerald F. Watts[6], Henry Ginsberg[7], Pierre Alberico Catapano[9], Olivier S. Descamps[10], Edward Fisher[11], P Jan Albert Kuivenhoven[13], Philippe Lesnik[2], Luis Masana[14], Zelj Marja-Riitta Taskinen[16], Lale Tokgözoglu[17], and Anne Tybjærg- European Atherosclerosis Society Consensus Panel†

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.

Whom to screen

We suggest that Lp(a) should be measured once in all subjects at intermediate or high risk of CVD/CHD who present with:

(i) premature CVD,
(ii) familial hypercholesterolaemia,
(iii) a family history of premature CVD and/or elevated Lp(a),
(iv) recurrent CVD despite statin treatment,
(v) ≥3% 10-year risk of fatal CVD according to the European guidelines,[35] and
(vi) ≥10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines[36]

Repeat measurement is only necessary if treatment for high Lp(a) levels is initiated in order to evaluate therapeutic response.

Research Article

Baseline LDL-C and Lp(a) Elevations Portend a High Risk of Coronary Revascularization in Patients after Stent Placement

Anping Cai,[1] Liwen Li,[1] Ying Zhang,[1] Yujin Mo,[1] Zhigen Li,[1] Weiyi Mai,[2] and Yingling Zhou[1]

Disease Markers 2003;35:857

		Lp(a) <30	Lp(a) >30	p
N		n=552	n=280 (34%)	
LDLC<70				
46%	MACE	18.5%	16.3%	0.78
	Revasc	13%	8.7%	0.16
LDLC>70				
54%	MACE	16.6%	26.1%	**0.02**
	Revasc	7.5%	15.4%	**0.006**

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

Park SH et al. Clin Exp Pharmacol Physiol. 2015 Jun;42(6):588-95

N=595 consecutive patients with PCI and DES.
High Lp(a) -> >50 mg/dl n=111, 19%) 6-9 month cath, 3 yr events

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.

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

Lipid, Lipoprotein and Apolipoprotein Tests			
	Optimal	Borderline	High Risk
Total Cholesterol		203	
Range	<200	200-240	>240 mg/dL
Direct LDL-C		122	
Range	<100	100-160	>160 mg/dL
HDL-C	71		
Range	>60	50-60	<50 mg/dL
Triglycerides	98		
Range	<150	150-200	>200 mg/dL
Non-HDL-C		132	
Range	<130	130-190	>190 mg/dL
sdLDL-C[1]		22	
Range	<20	20-40	>40 mg/dL
VLDL-C	10		
Range	<30	30-40	>40 mg/dL
Lp(a)			135
Range	<30	30-50	>50 mg/dL
ApoA-I	185.2		
Range	>180	140-180	<140 mg/dL

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 Descripti
and relative risk (RR) estimate
geneity was assessed using t
for the presence of blinding
cardioverter-defibrillators, and
dose. A statistical significanc
multiple comparisons.

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.

(Rizos et al. JAMA 2012;308:1024-1033)

- 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:
  - Amarin's Vascepa (100% EPA): lowers triglyceride 21.5% and 10.1% for the 4 and 2 g/d groups
  - 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%)

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

Fish Oils and CHD

Review of the Literature: 29 Studies Reporting Blood Levels of Omega3/6

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Omega-3 Fatty Acid Blood Levels: Clinical Significance and Controversy

H. Robert Superko, Scott M. Superko, Khurram Nasir, Arthur Agatston and Brenda C. Garrett

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Circulation
Volume 128(19):2154-2161
November 5, **2013**

***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

American Heart Association
Learn and Live

Table 1. Investigations Reporting Plasma, Serum, or Whole Blood Measurements of Omega-3 Fatty Acids

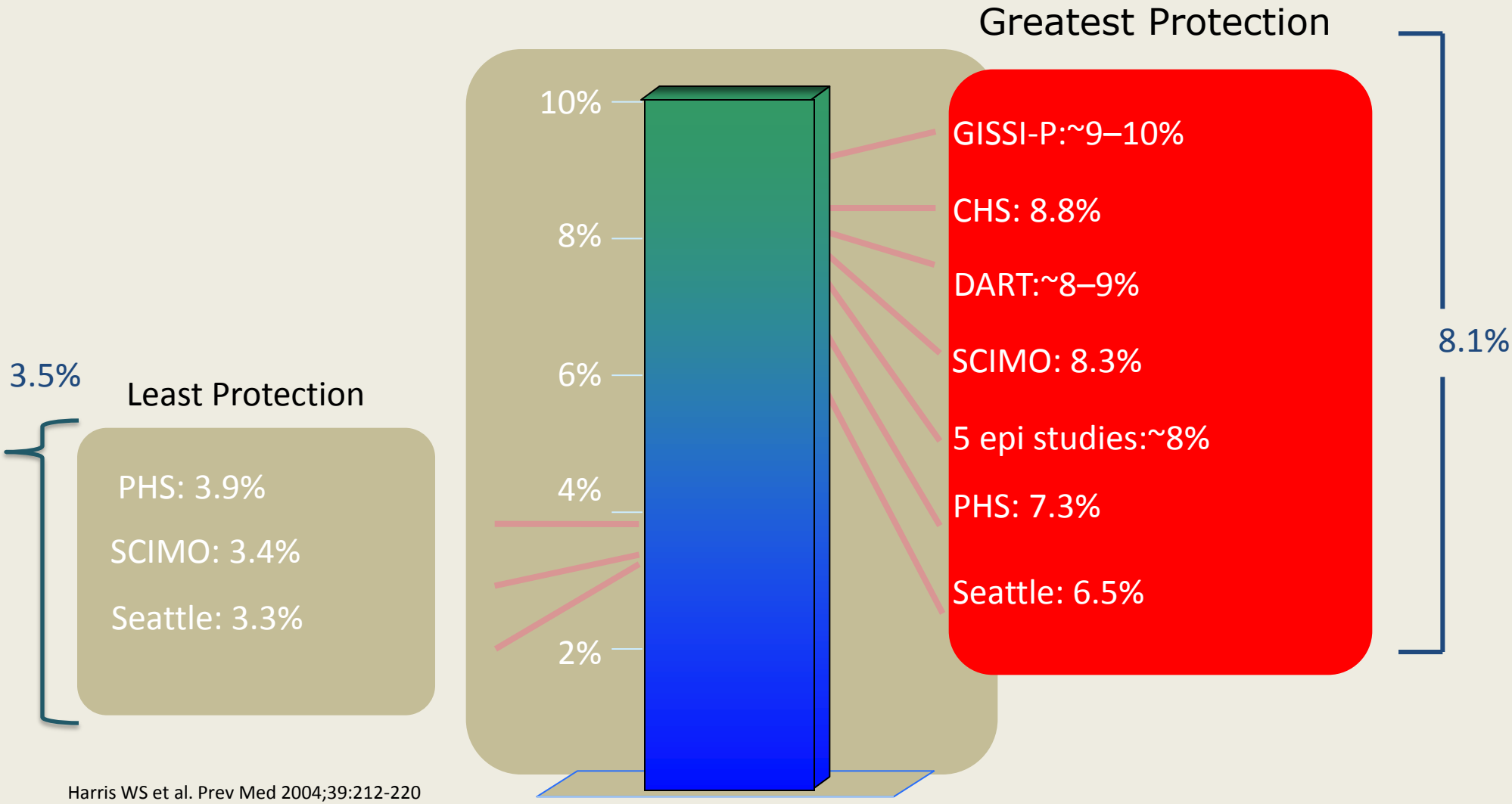
Author (ref)	n	Subjects	Study Method	Sample Type	Findings
Anderson[10]	174	Random population without DM	Follow-up study	Plasma	Omega-3 fatty acids predict CV mortality independent of pulse wave velocity.
Albert[14]	261	Healthy men 17-y follow-up	Observational	Blood	Reduction in sudden death related to EPA+DHA+DSA%
Baylin[15]	3338	MI vs control	Case control genetic study	Plasma	EPA and DHA higher in carriers of *FADS2* 7 allele but not related to CHD status.
Chung[16]	900	MESA study	Observational	Blood	EPA and DHA correlated with nonfried fish consumption
DiStasio[18]	36	Healthy subjects	Dosing study	Plasma	1 g/d omega-3 increases blood levels 2- to 3-fold in 1 wk
Donadio[17]	73	IgA nephropathy	Randomized, open label, 2 y, 2 doses 3.35 or 6.70 g/d	Plasma	3.35 g/d increased EPA from 0.8% to 3.6% and DHA from 3.7% to 6.7% 6.7 g/d increased EPA from 0.9% to 4.9% and DHA from 3.5% to 7.4%
Donadio[19]	73	IgA nephropathy	Randomized open label, 2 y, 2 doses 3.35 or 6.70 g/d	Plasma	Omega-3 supplementation slowed the rate of renal loss
Hayakawa[20]	206	Stable angina pectoris	Observational	Plasma	Complex coronary lesions associated with lower plasma EPA/AA
Hogg[21]	96	IgA nephropathy	Randomized, double-blind 12-mo trial	Plasma	Superiority of omega-3 fatty acids over placebo in slowing progression of renal disease
Itakura[1]	16397	TC >250 mg/dL	JELIS. Low-dose statin, then randomized to omega-3 or not.	Plasma	Coronary event risk reduced when plasma EPA >150 μg/mL or EPA/AA >0.75
Khaw[22]	3841	EPIC-Norfolk	Nested case control	Plasma	Omega-3 plasma fatty acids inversely related to CHD but no longer significant after multivariate adjustment
Laidlaw[23]	31	Healthy women	Randomized trial	Serum	4 g EPA+DHA per day increased omega-3 fatty acids 5.6% to 14.4% fatty acids by weight and the EPA/AA from 0.12 to 0.88
Lockyer[24]	100	Free living	Genetic diet and supplement intervention study	Plasma	Increase in EPA but no difference based on ApoE genotype
Lindberg[25]	254	Acutely ill elderly	Follow-up study	Plasma	Mortality higher in patients with EPA in lowest quartile
Matsuzaki[26]	3664	MI, AP, or PCI with LDL-C >170 mg/dL	JELIS. Low-dose statin, then randomized to omega-3 or not.	Plasma	Cardiac death or MI was significantly lower in the group with the highest EPA/AA ratio vs the lowest ratio
Meyers[28]	992	VA hospital	Observational Heart & Soul Study	Whole blood	EPA+DHA associated with exercise capacity and HR recovery
Mozaffarian[27]	2692	Older healthy	Prospective cohort	Plasma	Omega-3 fatty acids associated with lower CV events
Nigam[29]	734	Acute coronary syndrome	Observational	Plasma	Metabolic syndrome patients had lower EPA and DHA levels vs those without the metabolic syndrome
Poppitt[31]	95	Ischemic stroke patients	Randomized, double-blind trial omega-3 and CVD and mood	Serum	Following a 30% increase in omega-3 fatty acids for 12 wk, no effect was seen
Portale[30]	956	CHD in older men, Heart & Soul Study	Observational	Blood	EPA+DHA <3.6% revealed greater mortality $P=.002$
Raatz[32]	10	Healthy adults	Randomized, crossover 48-h absorption study	Plasma	Emulsified fish oil had enhanced absorption compared with capsular fish oil
Rupp[33]	11	Healthy	Dosing study	Whole blood	EPA 0.6% to 1.4% within 10 days, DHA 2.9% to >4.3%, after withdrawal returned to baseline in 10 days
Schaeffer[34]	727	German Health Survey	Genetic study	Serum	FADS polymorphisms associated with AA, EPA, and DPA
Shintani[35]	43	JELIS CAD patients with angiography	Abstract 2012 ACC Randomized to EPA or ezetimibe	Blood	Reduction in soft plaque when EPA/AA increased from 0.40 to 1.34
Simon[36]	188 men	Multiple Risk Factor Intervention Trial	Nested case control	Serum	DPA inversely associated with CHD risk
Vedin[40]	16	Alzheimer's disease patients	Genetic study	Plasma	Omega-3 supplementation affects expression of genes influencing inflammation.
Virtanen[37]	1857	No CHD, Kuopio Ischaemic Heart Disease Risk Factor Study	Observational	Serum	DHA associated with sudden cardiac death but only in subjects with lower hair mercury content
Virtanen[38]	2174	Kuopio Ischaemic Heart Disease Risk Factor Study	Observational	Serum	DHA associated with reduced AF risk
Wang[2]	2909	Atherosclerosis Risk in Communities Study	Observational	Plasma	Incidence of DM positively associated with palmitic, palmitoleic, and dihomo-g-linolenic acids and inversely with linoleic acid
Wu[39]	3326	Free of CHD and >65 y of age	Observational	Plasma	Higher levels of DHA associated with lower AF risk

Fish Oil Blood Levels in Populations

"OM3 Index" = %EPA + %DHA

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

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



Harris WS et al. Prev Med 2004;39:212-220

Harvard Physician's Health Study and EPA+DHA %

Is there a CUT-POINT?

TABLE 2. BASE-LINE 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.*

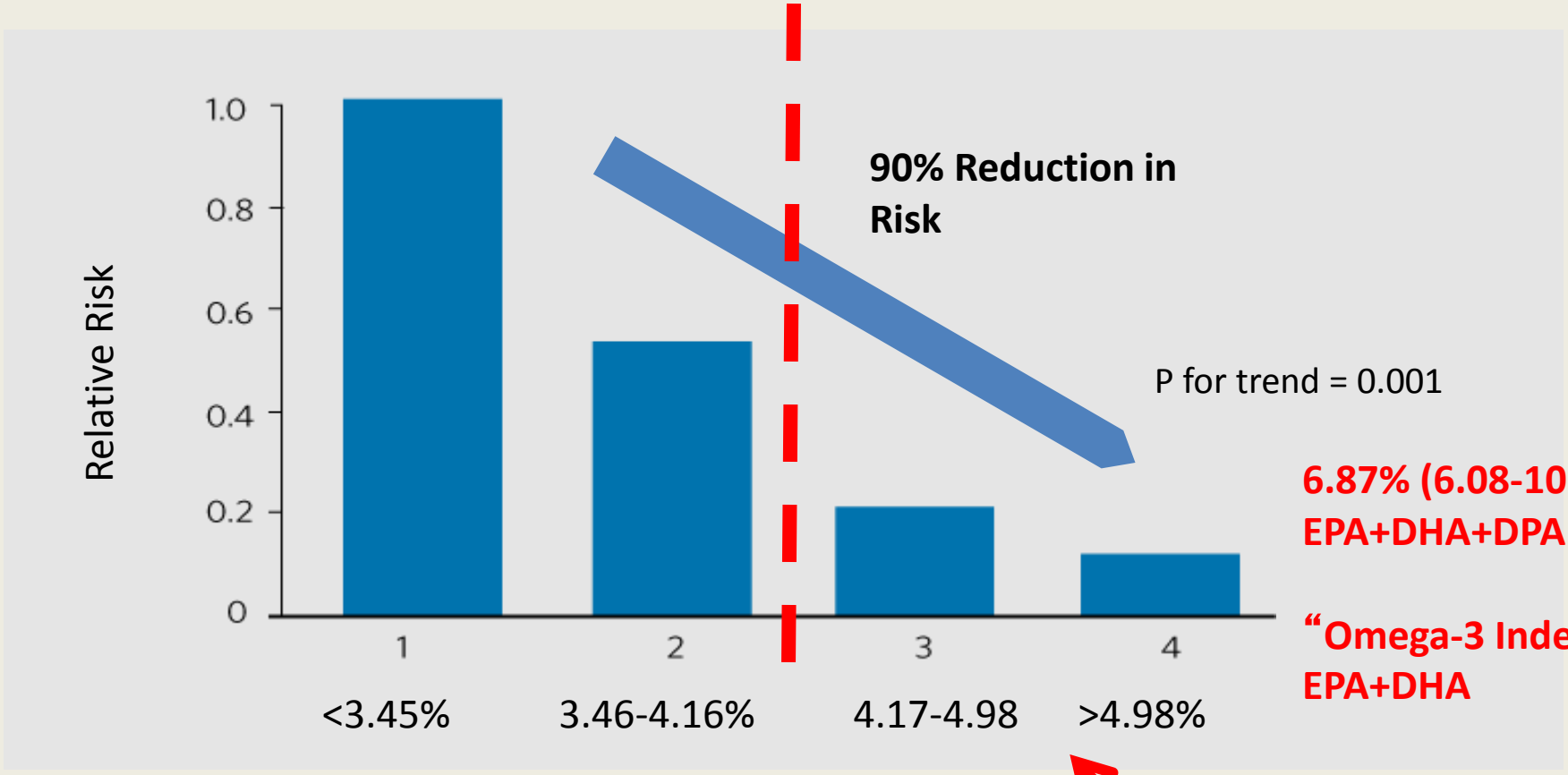
FATTY ACID	GROUP WITH SUDDEN DEATH FROM CARDIAC CAUSES (N=94)	CONTROL GROUP (N=184)	P VALUE
	percentage of total fatty acids		
Total saturated	31.6±1.88	31.3±1.80	0.21
Palmitic	19.2±2.16	18.8±2.00	0.16
Stearic	10.6±1.02	10.6±0.91	0.75
Total monounsaturated	19.8±3.25	19.5±2.69	0.72
Oleic	17.2±2.69	17.0±2.28	0.89
Total n−6 polyunsaturated	38.1±3.81	38.3±3.49	0.65
Linoleic	24.0±3.31	24.2±3.61	0.56
Arachidonic	10.6±1.88	10.6±1.75	0.93
Total long-chain n−3 polyunsaturated	4.82±1.31	5.24±1.32	0.01
Eicosapentaenoic	1.72±0.59	1.84±0.53	0.06
Docosahexaenoic	2.12±0.65	2.38±0.78	0.005
Docosapentaenoic	0.98±0.23	1.01±0.21	0.25

3.84 = 1.72 + 2.12 (Eicosapentaenoic + Docosahexaenoic, Group with Sudden Death)

4.22 = 1.84 + 2.38 (Eicosapentaenoic + Docosahexaenoic, Control Group)

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



Range by personal communications with authors

Source: Albert et al. N Engl J Med (2002) 346:1113

JELIS – Baseline

Japanese EPA Lipid Intervention Study (2011)

N = 16,397 Japanese (~61 yo), elevated LDL-C **1,800 mg EPA/day** (>98% EPA methyl ester) **for 4.6 yrs**

	Control	EPA	p
Age (yr)	61	61	NS
CHD%	19.2%	19.0%	NS
Smoker%	18.2%	19.8%	0.01
Diabetes%	16.4%	16.3%	NS
LDL-C (mg/dl)	**182**	**182**	NS
HDL-C (mg/dl)	58	59	NS
Trig (mg/dl)	**190**	**188**	NS
EPA (ug/ml)	93	97	NS
DHA (ug/ml)	169	170	NS

CHANGE	Control	EPA	p
LDL-C (mg/dl)	-46	-45	NS
HDL-C (mg/dl)	1	0.3	0.001
Trig (mg/dl)	-31	-37	0.001
N-6 Linoleic acid	10	-38	0.001
n-3 EPA (ug/ml)	**2**	**69**	**0.001** (+71% increase)
n-3 DHA	-2	-14	0.001

Criticism:

1. High LDL-C
2. Done in Japan (Land of Sushi)

Itakura H et al. J Athero and Thrombo 2011;18:99-107

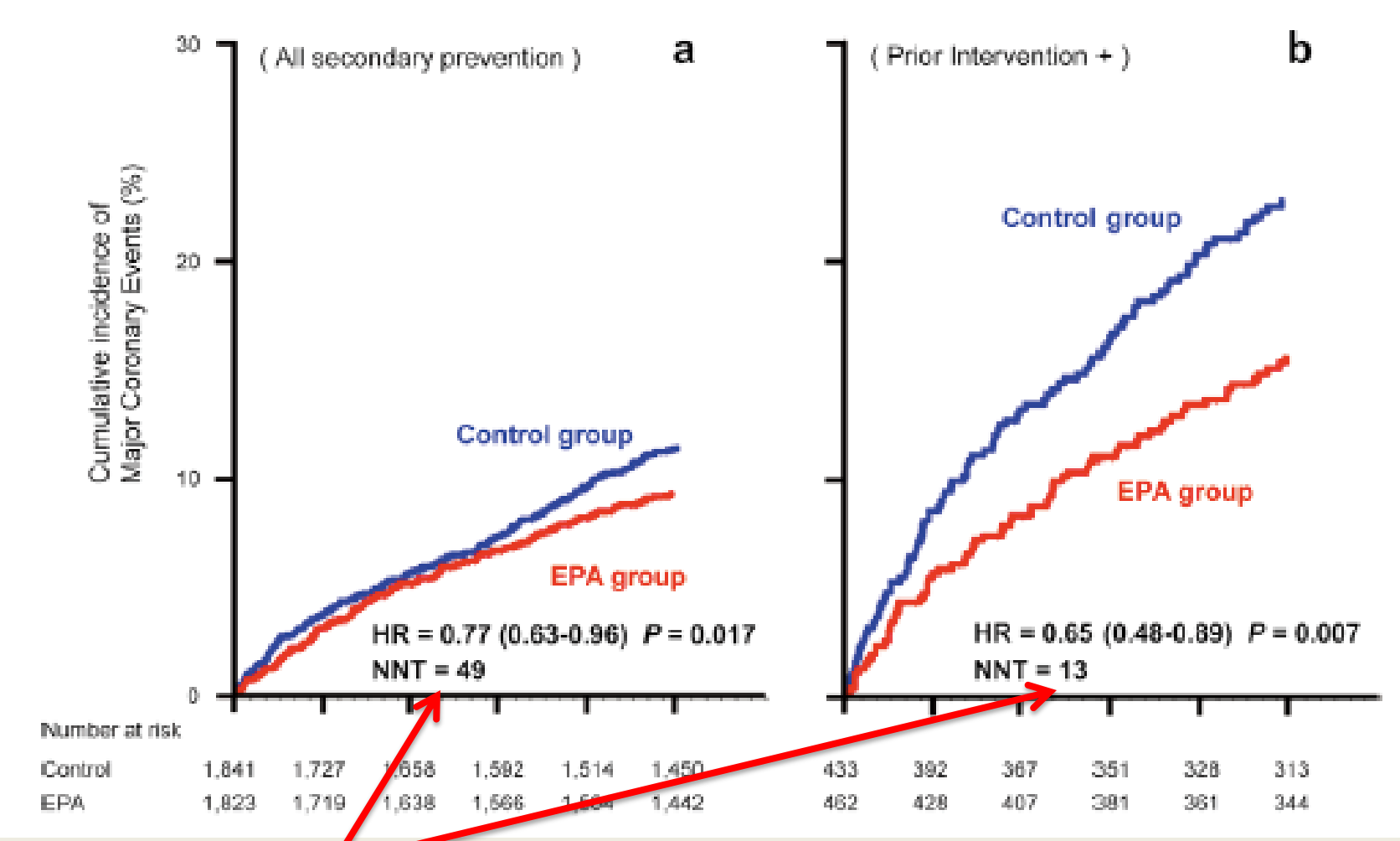
JELIS - AHA 2005 – Secondary Prevention

	Statin	S+EPA	p	HazRatio
N	9,319	9,326		
All Events	324	262	0.01	NNT = 150
Nonfatal MI	297	240		
All cause mortality		no difference		
Primary Prevention				
All Events (-18%)	127 (1.4%)	104 (1.1%)	0.13	NNT = 405
Secondary Prevention				
N	1,841	1,823		
All Events (-19%)	197(10.7%)	158(8.7%)	0.05	NNT = 47
UAP (unstable angina)	123	88	0.02	

NNT statin studies = 40-60

(Yokoyama M. AHA Late Breaking Nov. 2005)

OM3 Benefit in CHD patient with Prior Intervention (JELIS)

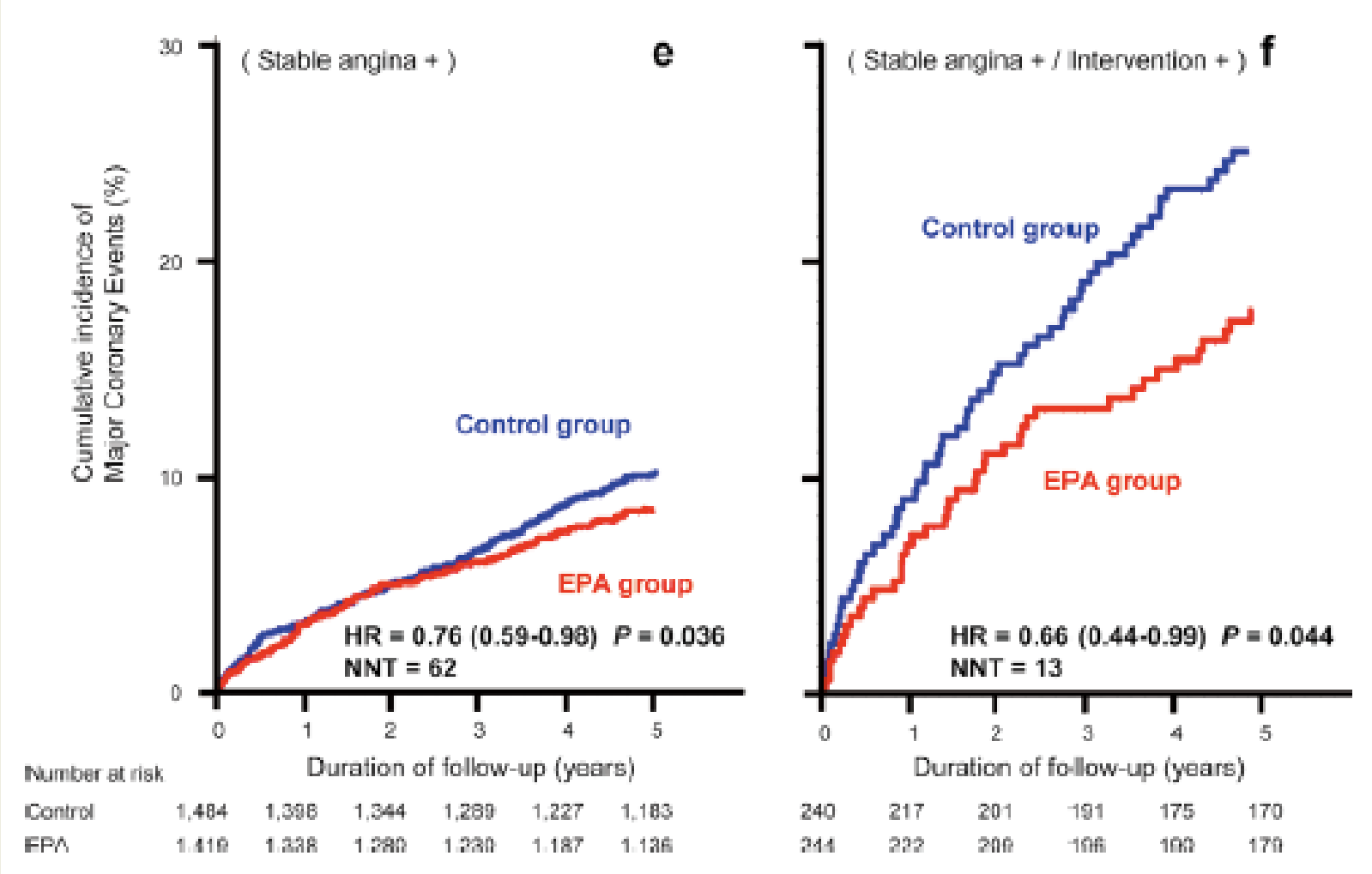


NNT

(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)

AHA/ACCF Guideline

AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update

A Guideline From the American Heart Association and American College of Cardiology Foundation

Endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association

Sidney C. Smith, Jr, MD, FAHA, FACC, Chair; Emelia J. Benjamin, MD, ScM, FAHA, FACC; Robert O. Bonow, MD, FAHA, FACC; Lynne T. Braun, PhD, ANP, FAHA; Mark A. Creager, MD, FAHA, FACC; Barry A. Franklin, PhD, FAHA; Raymond J. Gibbons, MD, FAHA, FACC; Scott M. Grundy, MD, PhD, FAHA; Loren F. Hiratzka, MD, FAHA, FACC; Daniel W. Jones, MD, FAHA; Donald M. Lloyd-Jones, MD, ScM, FAHA, FACC; Margo Minissian, ACNP, AACC, FAHA; Lori Mosca, MD, PhD, MPH, FAHA; Eric D. Peterson, MD, MPH, FAHA, FACC; Ralph L. Sacco, MD, MS, FAHA; John Spertus, MD, MPH, FAHA, FACC; James H. Stein, MD, FAHA, FACC; Kathryn A. Taubert, PhD, FAHA

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit — is not recommended; is not indicated; should not be COR III: Harm — potentially harmful; causes harm; associated with

Area for Intervention	Recommendations
Lipid management cont'd	**Class IIb** 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.§ ***(Level of Evidence: C)*** 2. For patients who continue to have an elevated non–HDL-C while on adequate statin therapy, niacin§ or fibrate‖ therapy[32,35,41] ***(Level of Evidence: B)*** or fish oil ***(Level of Evidence: C)*** may be reasonable. 3. For all patients, it may be reasonable to recommend omega-3 fatty acids from fish¶ or fish oil capsules (1 g/d) for cardiovascular disease risk reduction.[44–46] ***(Level of Evidence: B)***

March 14, 2017

Cardiology CME/CE

AHA: Fish Oil OK After Heart Attack, Heart Failure

— But no new evidence for use in primary prevention of CVD

Action Points

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

Fatty Acid	Range	Risk
EPA		
Itakura	>150 ug/ml	Lower risk (suggested goal)
DHA		
Sekikawa	<1.0%	Highest IMT thickness in US Whites
	<4.0%	Highest IMT thickness in Japanese
Virtanen	>2.66%	Reduced SCD risk
Virtanen	>2.85%	Reduced AF risk
Wu	>3.54%	Reduced AF risk
EPA+DHA		
Albert	**<3.45%**	High risk (lowest quartile)
Sekikawa	>12.3%	Less CAC in Japanese (in Japan)
	>6.49%	Less CAC in Japanese Americans
	>5.23%	Less coronary calcium in Whites
Sandesara	4.35%	Achieving EPA+DHA level did not prevent post CABG surgery AF.
EPA/AA		
Itakura	>0.75	Lower risk of MCE (suggested goal)

Secondary Prevention

Fatty Acid	Range	Risk
EPA		
Lee	<1.26%	High risk
Hayakawa	> 111 ug/ml	Least complex coronary lesions
Ishikawa	5.6%	Mean EPA% in Rx group and associated with reduced MCE.
EPA+DHA		
Pottala	>3.6%	Reduced all-cause mortality
Lee	>4.74%	Reduced all cause and CVD mortality
EPA/AA		
Hayakawa	>0.88	Least complex coronary lesions
Matsuzaski	≥1.06	Lowest cardiac death or MI

AHA/ACCF 2011 Guidelines: OM3 Class IIb for treatment (1 g/d) of dyslipidemia (secondary prevention) (Circ 2011;124:2458)

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

History: Families and Heart Disease

"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."

Osler W. *The Principles and Practice of Medicine*. New York: D. Appleton & Co.: **1892**:664

"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."

(Berg K. Clin Genet **1989**; 36:299-312)

Special Article

Family Coronary Heart Disease: A Call to Action

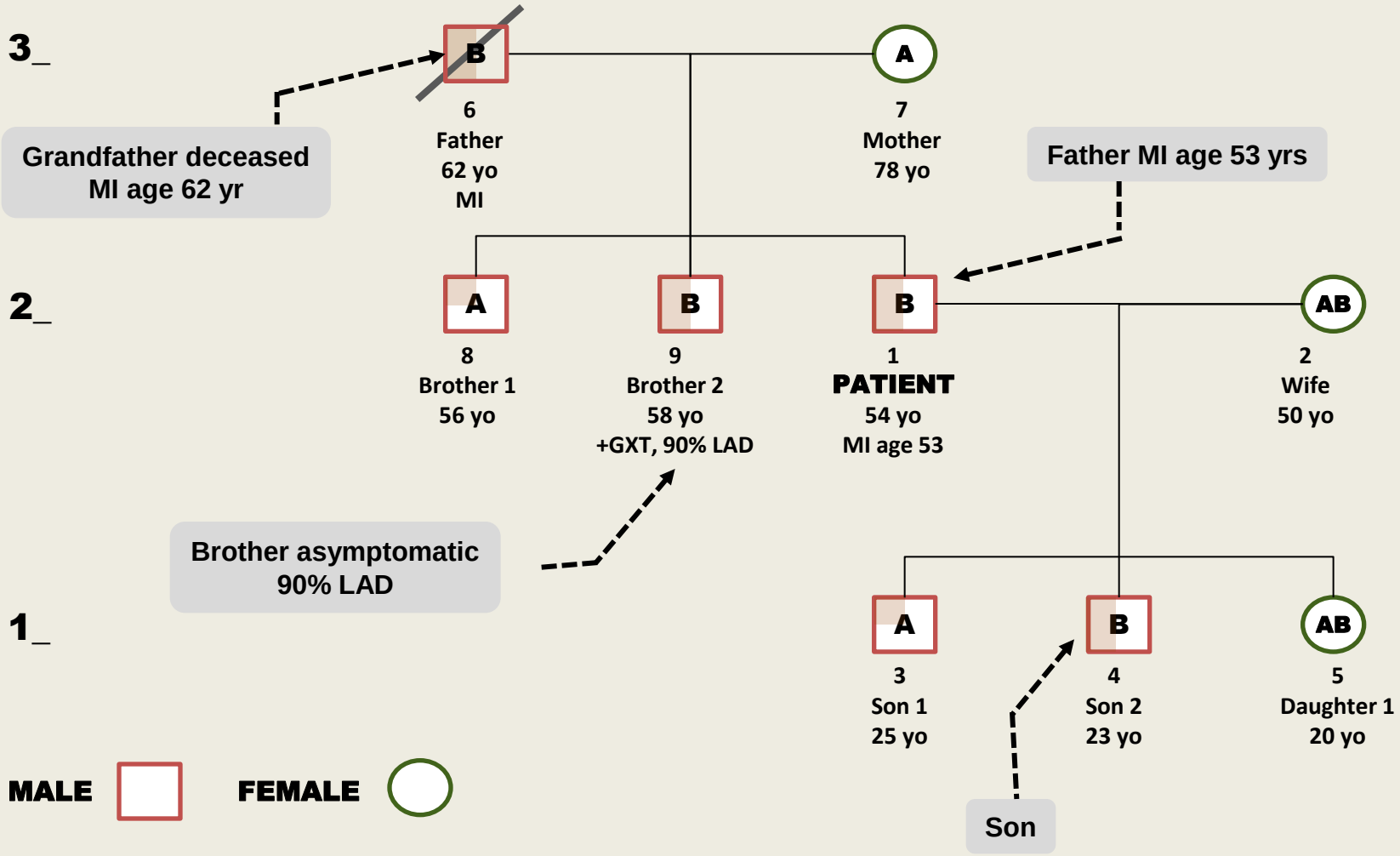
H. Robert Superko, MD, FACC; Robert Roberts, MD, MACC; Brenda Garrett, RN; Lakshmana Pendyala, MD; Spencer King III, MD, MACC

Center for Genomics and Human Health (Superko, Garrett, Pendyala, King), Saint Joseph's

"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)

Family Pedigree Example



Cost of Sequencing Whole Genome (Celera)

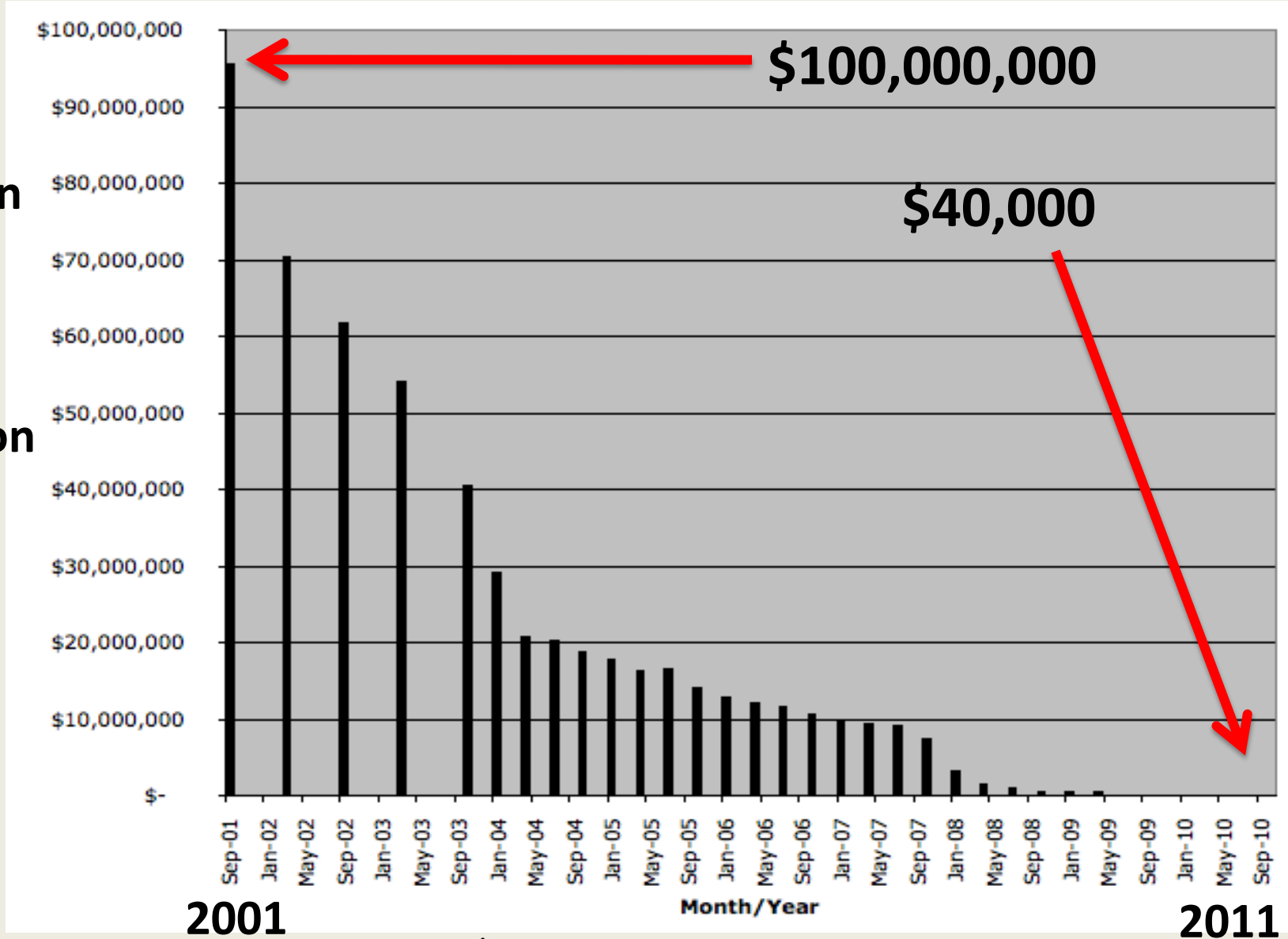
2001 $100 Million

2007 $10 Million

2011 $0.04 Million

2015 $3,000

2016 $1,000



(Mardis E. Nature 2011;470:198-203) (www.genome.gov/sequencingcosts)

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   - 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

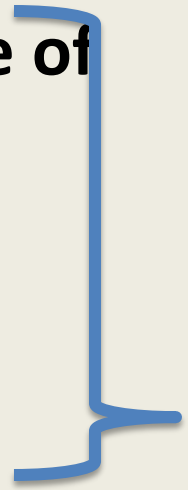
Prevention strategies can not be designed without this knowledge.

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



73%
Firefighting Activities

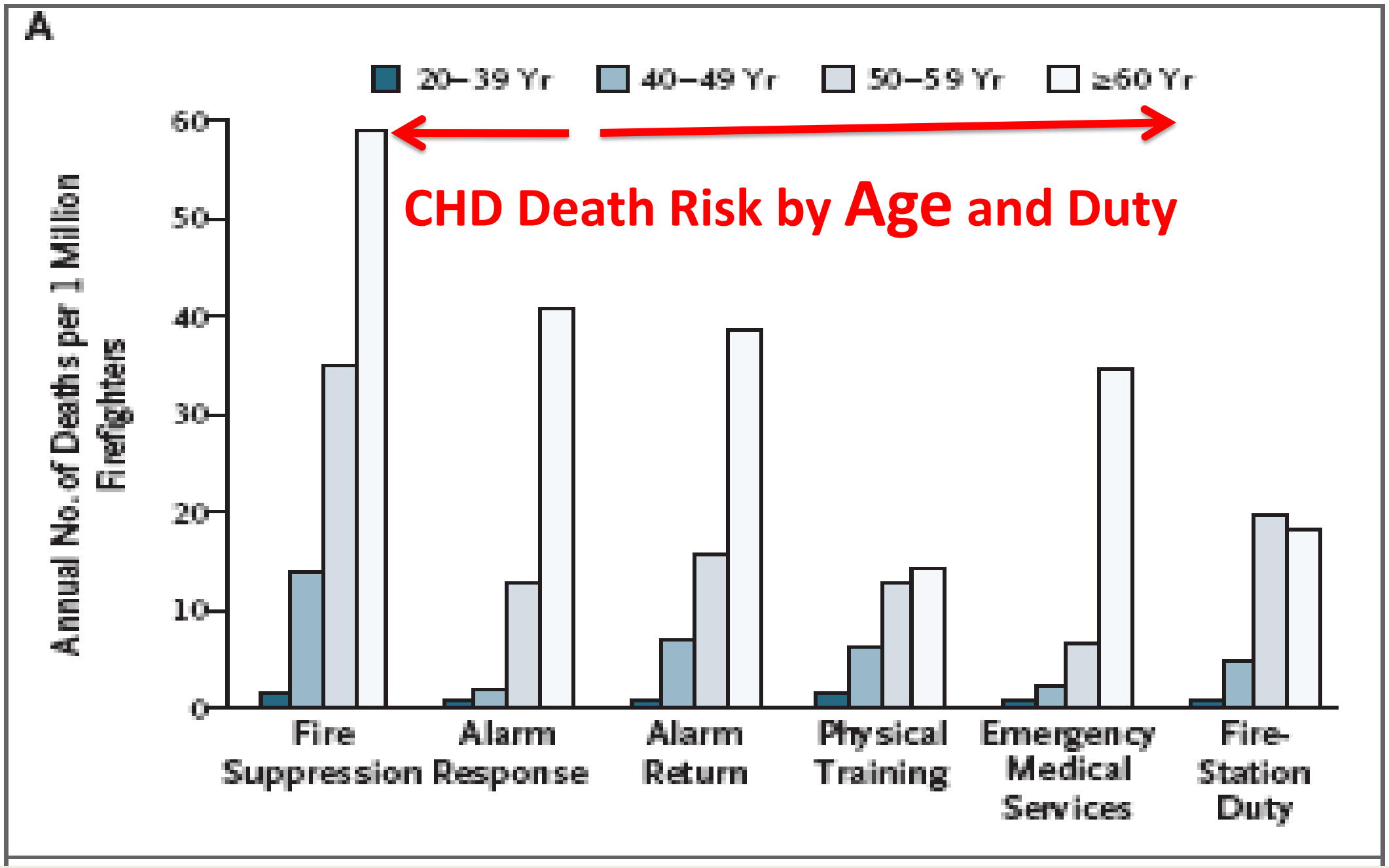
(Federal Emergency Management Agency records of deaths of all on-duty firefighters)

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:

	Odds of Deaths from CHD
Fire suppression	12.1 to 136 fold increase
Alarm response	2.8 to 14.1 fold increase
Returning from alarm	2.2 to 10.5 fold increase
Physical training	2.9-6.6 fold increase

(Kales S NEJM 2007;356:1207-1215)


A
20–39 Yr
40–49 Yr
50–59 Yr
≥60 Yr
CHD Death Risk by Age and Duty
Annual No. of Deaths per 1 Million Firefighters
60
50
40
30
20
10
0
Fire Suppression
Alarm Response
Alarm Return
Physical Training
Emergency Medical Services
Fire-Station Duty

Kales et al

EVIDENCE BASED APPROACH

Tax $ Funded FEMA 2011

WWW.FamilyHeartFoundation.org

Presented at:
AHA
ACC
International Fire Chiefs

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

association of cardiovascular risk markers
erosclerosis in firefighters. **Methods:** Cross-
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rs. **Results:**
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assessments.
re related to
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CAC lesions
d fasting in-
predictor of
f total coro-

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.[4]

In the Firefighter Heart Disease Prevention (FHDP) study we investigated the relationship between noninvasi
atherosclerosis to phenotypic and genotypic markers
sis risk in asymptomatic professional firefighters to d
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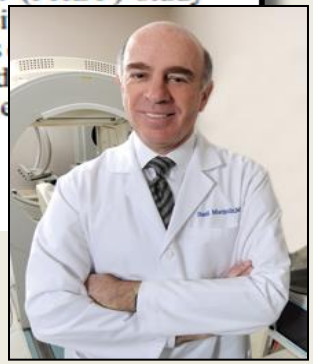
thus, increas

Dr Robert Superko

Brenda Garrett, RN



Dr Basil Margolis

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

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

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

Thank You Firefighters

Our Lives Depend on Your Health

www.FamilyHeartFoundation.org

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


Mahalo