Cardiovascular Genetics Update: Implications of Personalized Testing Practical Examples

11th Annual Orange Co. Symposium on CVD Prevention November 09, 2019

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PRIMA Heart, Monterey, California
H. Robert Superko, MD, FACC, FAHA, FASPC

Background & Disclosures

• Stony Brook Medical School 1975
• University of California-Davis (Internship, Residence, Fellowship)
• 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
• Chairman: Molecular, Genetic and Preventive Cardiology - Fuqua Heart Center Piedmont Hospital, 2004 - 2007
• Executive Director, Center for Genomics, St. Jo’s Hospital (Atlanta) 2007-2009
• CMO & Vice President, Celera Genomics, Quest, 2009 – 2014
• President Cholesterol, Genetics, & Heart Disease Institute (501c3)
• Clinical Adjunct Professor, Mercer University School of Pharmaceutical Sciences
• Consultant – Select Labs

• **No Pharmaceutical or Device Company Conflicts**
Agenda:

1. What “Unmet Clinical Need” do Genetic Tests Fill?

2. Improved **CVD Risk Prediction**
   - CHD Risk Determination
   - Atrial Fibrillation

3. Improved **Drug Response** Identification
   - Aspirin and LPA
   - Omega-3 Blood Levels
   - Statin myopathy

4. **Family Heart Disease** Clinic
HI, NEIGHBOR BILL... HOW GOES IT?

GOOD. BEEN RUNNING LIKE CRAZY. ALL PART OF MY PLAN TO CONTROL THE RISK FACTORS FOR HEART DISEASE.

I DON'T DRINK. I DON'T SMOKE. I'M NOT OVERWEIGHT. I EAT A DIET LOW IN CHOLESTEROL.

PLUS, I DO THINGS TO KEEP MY BLOOD PRESSURE LOW. AND OF COURSE I EXERCISE RELIGIOUSLY.

ABOUT THE ONLY FACTOR I CAN'T CONTROL IS GENETICS, WHICH HOPEFULLY WON'T BE MUCH OF A FACTOR, GIVEN HOW HARD I WORK ON THESE OTHER

ACKK

LIFE IS TRICKY THAT WAY.
Beyond LDL-C
The Need for Advanced CVD Risk Testing
What’s New?

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. Arteriographic investigations have demonstrated that LDL-C reduction can significantly reduce the rate of arteriographically defined disease progression.

Failure of LDL-C Reduction
Despite the success of LDL-C reduction, close exami-
ted in ≈3% to 15% of CAD patients. Other disorders, such as apoprotein E isoform differences, hyperapo-
lipoproteinemia, homocysteinemia, ALP disorder, and
Lp(a), can be detected in ≈30% to 50% of male CAD
patients.

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. 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 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
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

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Why Genetic CVD 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. Genetic tests can help **explain** a large portion of CHD etiology (**differential diagnosis**) and guide **Treatment**/Follow-up.
6. CHD is a **Family Disease**
Most People who Develop CHD Have “Normal” Standard Lipid Values

• 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

Sachdeva et al. AHJ, Vol 157, 111-117 Jan 2009
Lipid Management to Reduce Cardiovascular Risk: 
A New Strategy is Required.
H. Robert Superko, MD, FAHA, FACC and 
Spencer King III, MD, MACC

LDL-C Reduction alone FAILS many people

Average of Clinical Trial Results

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

Statin RRR (reducción del riesgo relativo) = 25%

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)
**PCSK9 Results ACC 2017**

FOURIER (Further CV Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk)

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**Events in Evolocumab group**

![Graph showing events in Evolocumab group]

**ARR = 1.5%**

(11.3-9.8%)

NNT ~ 60

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**Table:**

<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>

Sabatine et al NEJM 2017; DOI: 10.1056/NEJMoa1615664

**N = 219 “Saved” from CV 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
Genetics
Nucleotides

DeoxyriboNucleic Acid (DNA). 4 sugars: A=adenine, C=cytosine, G=guanine, T=thymine
Speeding the Gene Hunt: High-Speed DNA Sequencing

GWAS
Genome Wide Association Study

Figure 1. Computer-generated image of fluorescent bands after the fragments are detected by the laser.
Cost ($) of Genetic Testing
Cost of Sequencing Whole Genome (Celera)

- 2001: $100 Million
- 2007: $10 Million
- 2011: $0.04 Million
- 2015: $0.03 Million
- 2016: $1,000
- 2018: $700

www.genome.gov/sequencingcosts
CHD Risk Determination
Signal-Intensity Plots Showing the Association of Single-Nucleotide Polymorphisms (SNPs) with Coronary Artery Disease or Myocardial Infarction in the Genomewide Association Analysis

-Log p value

9p21

First CHD genetic risk factor INDEPENDENT of ALL Risk Factors

Robert Roberts and DeCode Genetics 2007

Samani NJ et al.
The 9p21 Variants are Associated with Early MI, AAA, and CHD 1.5 fold risk for heterozygous, 2.0 fold risk for homozygous

In Multiple Case-Control and Prospective Studies from leading groups around the world

• “Today, Chr9p21 is the most replicated genetic factor of human CAD and other forms of cardiovascular disease such as stroke, peripheral artery disease and arterial aneurysms.” - Holdt and Teupser et al. Arterioscler Thromb Vasc Biol. 2012;32:196

• “The fact that a major proportion of the susceptibility to CAD is due to genetic risk factors has been recognized for more than 5 decades. Thus, if this disease is to be markedly reduced or eliminated, comprehensive prevention will require knowledge of the genetic risk factors”

• “The 9p21 variant has now been established as an independent risk factor for CAD”² - Roberts and Stewart., Clin Chem. 012;58:104


p<0.000000000000000000000000000000000000000000000000000000000000001

Improved Risk Assessment

N = 9,998, 14.6 yr follow-up

<table>
<thead>
<tr>
<th>10 yr Risk</th>
<th>0-5%</th>
<th>5-10%</th>
<th>10-20%</th>
<th>&gt;20%</th>
<th>Reclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5%</td>
<td>97.7%</td>
<td>2.3%</td>
<td>0</td>
<td>0</td>
<td>110 (2.3%)</td>
</tr>
<tr>
<td>5-10%</td>
<td>6.0%</td>
<td>86.8%</td>
<td>7.2%</td>
<td>0</td>
<td>328 (13.2%)</td>
</tr>
<tr>
<td>10-20%</td>
<td>0</td>
<td>8.6%</td>
<td>86.5%</td>
<td>4.9%</td>
<td>292 (13.5%)</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>0</td>
<td>0</td>
<td>12.3%</td>
<td>87.7%</td>
<td>66 (10.5%)</td>
</tr>
<tr>
<td>N</td>
<td>4,648</td>
<td>2,746</td>
<td>1,953</td>
<td>651</td>
<td></td>
</tr>
</tbody>
</table>

- 17.1% of intermediate-low and 15.8% of intermediate-high FRS participants were reclassified, with potential changes in clinical management.
- Almost 90% of men and women in the two intermediate-risk categories had LDL-C levels of 100 mg/dL or higher (~ 55%-66% had levels > 130 mg/dL).
## Genetic Risk Score and Statin Response 2015

Populations: JUPITER & ASCOT (primary prevention), CARE & PROVE IT-TIMI22) (secondary prevention). N=48,421 subjects, 3,477 events. ~10 yr FU

Genetic Risk Score = **27 genetic variants**

<table>
<thead>
<tr>
<th></th>
<th>Quartile 1</th>
<th>Quartile 2-4</th>
<th>Quartile 5</th>
<th>p&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD HR</td>
<td>1.34</td>
<td>1.22-1.47</td>
<td>1.72</td>
<td></td>
</tr>
<tr>
<td>RRR</td>
<td>13%</td>
<td>29%</td>
<td><strong>48%</strong></td>
<td></td>
</tr>
<tr>
<td>NNT</td>
<td>66</td>
<td>42</td>
<td>25</td>
<td>JUPITER primary prevention</td>
</tr>
<tr>
<td>NNT</td>
<td><strong>57</strong></td>
<td>47</td>
<td><strong>20</strong></td>
<td>ASCOT primary prevention</td>
</tr>
</tbody>
</table>

**Interpretation:**
1. A genetic risk score identified **individuals** at increased risk for both incident and recurrent coronary heart disease events.
2. People with the highest burden of genetic risk derived the largest **RELATIVE and ABSOLUTE clinical benefit** from statin therapy.

(Mega JL et al Lancet 2015;385:2264-2271)
New Paradigm

“The 9p21 risk is independent of known risk factors including diabetes, hypertension, cholesterol, and obesity. This implies a new mechanism for CAD previously unknown with respect to its molecular basis for vascular pathology.”

Application of genetic screening will be the beginning of a new paradigm in the prevention of heart disease. Genetic screening of those with a family history of heart disease or risk factors should occur in individuals at an age to enable early comprehensive prevention. In men it should occur in the second or third decade if not earlier and for women, before the fifth decade.”

Genetics and the Aspirin Controversy
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) as a cardiovascular risk factor: current status

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.
Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial.


**Abstract**

**BACKGROUND**: The use of aspirin in the primary prevention of cardiovascular events remains controversial. We aimed to assess the efficacy and safety of aspirin versus placebo in patients with a moderate estimated risk of a first cardiovascular event.

N = 12,546 men > 55 yr, women > 60 yr as “moderate” risk for CVD.

Randomized enteric coated ASA 100 mg/d or placebo. 2007-2016 mean F/U = 5 yr.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ASA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>4.48%</td>
<td>4.29%</td>
<td>0.60</td>
</tr>
<tr>
<td>GI bleed mile</td>
<td>0.46%</td>
<td>0.97%</td>
<td>0.0007</td>
</tr>
<tr>
<td>Serious adverse</td>
<td>20.9%</td>
<td>20.2%</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2.57%</td>
<td>2.55%</td>
<td></td>
</tr>
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</table>

**INTERPRETATION**: The event rate was much lower than expected, which is probably reflective of contemporary risk management strategies, making the study more representative of a low-risk population. The role of aspirin in primary prevention among patients at moderate risk could therefore not be addressed. Nonetheless, the findings with respect to aspirin’s effects are consistent with those observed in the previously published low-risk primary prevention studies.
3.5% of European Americans were carriers of the LPA variant.

Risk for CVD is increased by ~2 fold for carriers compared with noncarriers.

In WHS, this excess risk is ameliorated by low-dose aspirin therapy.

**P** interaction = 0.048 (SNP by treatment)

Chasman et al. *Atherosclerosis* 2009; 203:371
For *LPA* carriers, 5 events are prevented by low-dose aspirin treatment for every major bleed caused.

For *LPA* noncarriers, the number of major bleeds caused is greater than the number of events prevented by low-dose aspirin treatment.

*Unpublished data*
Genetics and Fish Oil Controversy
Omega-3 fatty acids
- Eicosapentaenoic acid: fish, shellfish
- Docosahexaenoic acid: fish, shellfish
- α Linolenic acid: Flaxseed, soybean, walnut, rapeseed oils

Polyunsaturated fatty acids

Omega-6 fatty acids
- Corn oil
- Safflower oil
- Sunflower oil

Monounsaturated fatty acids
- Omega-9 fatty acids
- Olive oil
- Avocados
- Peanuts
- Almonds

Controversy: Why have some fish oil trials FAILED and others have SUCCEEDED in reducing coronary events?
Fish Oils and CHD
Review of the Literature: 29 Studies Reporting Blood Levels of Omega3/6

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

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**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>
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<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>
<tr>
<td><strong>EPA/AA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itakura</td>
<td>&gt;0.75</td>
<td>Lower risk of MCE (suggested goal)</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>Matsuzaski</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)*
ABSTRACT

OBJECTIVE
To determine the longitudinal association between serial biomarker measures of circulating omega-3 polyunsaturated fatty acid (n3-PUFA) levels and healthy ageing.

DESIGN
Prospective cohort study.

SETTING
Four communities in the United States (Cardiovascular Health Study) from 1992 to 2015.

PARTICIPANTS
2622 adults with a mean (SD) age of 74.4 (4.8) and with successful healthy ageing at baseline in 1992-93.

EXPOSURE
Cumulative levels of plasma phospholipid n3-PUFAs were measured using gas chromatography in 1992-93, 1998-99, and 2005-06, expressed as percentage of total fatty acids, including \( \alpha \)-linolenic acid from plants and eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid from seafood.

MAIN OUTCOME MEASURE
Healthy ageing defined as survival without chronic diseases (ie, cardiovascular disease, cancer, lung disease, and severe chronic kidney disease), the absence of cognitive and physical dysfunction, or death from other causes not part of the healthy ageing outcome after age 65. Events were centrally adjudicated or determined from medical records and diagnostic tests.

RESULTS
Higher levels of long chain n3-PUFAs were associated with an 18% lower risk (95% confidence interval 7% to 28%) of unhealthy ageing per interquintile OM3 Supplements NOT given
Participants in the highest group consumed about one additional weekly serving of fish compared with the lowest group.


DHA was associated with healthy aging after adjustment for total fish intake.

EPA+DHA Group 5 (OM3) = 5.36%
The human FADS gene cluster located on chromosome 11 with exon/intron organization and location of some published SNPs shown to be associated with fatty acid and phospholipid levels. SNP rs174537 is located 13.7 kb upstream of FADS1 (//indicates change of scaling).

**FADS**, fatty acid desaturase; SNPs, single nucleotide polymorphisms; **FADS1**, fatty acid desaturase 1; **FADS2**, fatty acid desaturase 2; **FADS3**, fatty acid desaturase 3.

The omega-9, omega-6, and omega-3 fatty acid metabolism pathways. *FADS1*, fatty acid desaturase 1; *FADS2*, fatty acid desaturase 2; SCD, stearoyl-CoA desaturase; D5D, delta-5 desaturase; D6D, delta-6 desaturase; D8D, delta-8 desaturase; D9D, delta-9 desaturase.

Clinical Trials and OM3 Genetics

**MARINA** Clinical Trial OM3 effect on endothelial function
Three doses of EPA+DHA 0.45 gm/d, 0.9 gm/d, 1.8 gm/d

**FADS** variants in response to supplementation showed **NO** response difference to EPA & DHA (low power?)

**ELOV2** SNPs (elongase) modulated TG response and minor allele carriers had **30% higher EPA** and 9% high DHA

Minor allele carriers could therefore **particularly benefit** from a high intake of EPA and DHA in maintaining high levels of plasma n-3 PUFA conducive to protection from CVD.

Minor **ELOV12** alleles % Population
Rs3734398       32%
Rs2236212        32%
Rs953413         28%
Identifying genetic adaptations to local environment, including historical diets, and elucidating their implication in human health and disease are of central interest in human evolutionary genomics. The fatty acid desaturase (FADS) gene family consists of FADS1, FADS2 and FADS3, which evolved by gene duplication. FADS1 and FADS2 encode rate-limiting enzymes for the biosynthesis of omega-3 and omega-6 long-chain polyunsaturated fatty acids (LCPUFAs) from plant-sourced shorter-chain precursors.

These varying selection patterns concur with anthropological evidence of varying diets, and with the association of farming-adaptive alleles with higher FADS1 expression and thus enhanced LCPUFAs biosynthesis. Genome-wide association studies reveal that farming-adaptive alleles not only increase LCPUFAs, but also affect other lipid levels and protect against several inflammatory diseases.
Background: The -5 and -6 desaturases, encoded by FADS1 and FADS2 genes, are key enzymes in polyunsaturated fatty acid (PUFA) metabolism that catalyze the conversion of linoleic acid (LA) into arachidonic acid (AA) and that of α-linolenic acid (ALA) into eicosapentaenoic acid (EPA).

Single-nucleotide polymorphisms (SNPs) in FADS1 and FADS2 have been associated with different concentrations of AA and LA, and those associations have possible functional consequences for desaturase activity.

Conclusion: In populations following a Western diet, subjects carrying FADS haplotypes that are associated with higher desaturase activity may be prone to a proinflammatory response favoring atherosclerotic vascular damage.

**VASCEPA: Exploratory effects on inflammatory markers**

ANCHOR inflammatory markers: Response to the addition of VASCEPA to ongoing statin therapy in patients with high triglyceride levels (≥200 mg/dL and <500 mg/dL)

The clinical significance of these data has not been determined for EPA

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**Median percent change for VASCEPA 4 g/d compared to placebo**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Median Change %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp-PLA₂</td>
<td>-19%</td>
<td>0.0801</td>
</tr>
<tr>
<td>hsCRP</td>
<td>-22%</td>
<td>0.0005</td>
</tr>
<tr>
<td>Ox-LDL</td>
<td>-13%</td>
<td>0.0001</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>-2%</td>
<td>0.1888 NS</td>
</tr>
<tr>
<td>IL-6</td>
<td>-1%</td>
<td>0.0631 NS</td>
</tr>
</tbody>
</table>

VASCEPA + statin (median change vs baseline) Placebo + statin (median change vs baseline)

---

Unpublished Data

https://www.vascepahcp.com/vascepa-efficacy/anchor-study/
Genetics and Atrial Fibrillation
Clinical Utility of the 4q25 AF Test

Help to Detect Occult AF in Those at Risk of Embolic Stroke

For patients at high risk of CE stroke if having AF (>1 for the CHADS2 or CHA2DS2-VASc score), a positive test results could prioritize patients for detection of occult AF and aid decisions in optimal antithrombotic treatment

- A score of 2 or higher in either scoring system may benefit more from anticoagulant than from antiplatelet
- CHADS2
  - One point for CHF, Hypertension, Age>75, Diabetes,
  - two points for prior Stroke/TIA
- CHA2DS2-VASc
  - One point for CHF, Hypertension, Age>65, diabetes, female sex, vascular disease
  - Two points for Age>75, prior Stroke/TIA

http://www.daviddarling.info/encyclopedia/A/atrial_fibrillation.html
Biological Relevance of 4q25 Variants near \textit{PITX2} gene

- Adjacent upstream LD block to 4q25
- Critical function in left-right cardiac asymmetry
- Mouse Knockout: \(\downarrow\) SA Node Formation
- Essential for left atrial – pulmonary myocardial cell development

**Figure 2**
Functional genomics of PITX2 susceptibility variants in AF. SA, sinoatrial.

The 4q25 variants are near the \textit{PITX2} gene which encodes the transcription factor paired-like homeodomain 2. PITX2 protein functions in left-right cardiac asymmetry and SA node formation.
4q25 Variant Population Frequencies

- Population frequencies observed in patients tested at BHL:
  - rs2200733: among 916 patients, 30% are carriers and 70% are noncarriers
  - rs10033464: among 915 patients, 22% are carriers and 78% are noncarriers

- For the rs2200733 risk allele, approximately 20% of Caucasians, 70% of Asians, 40% of African Americans, and 50% of Hispanics are carriers

- For the rs10033464 risk allele, approximately 18% of Caucasians, 38% of Asians, 42% of African Americans, and 25% of Hispanics are carriers

- The increased risk estimates apply to Caucasians and Han Chinese. More research is needed to determine the risk estimates for African-Americans or other ethnic populations

4q25 rs2200733 is Associated with AF and CE Stroke

The associations of 4q25 with AF and with CE stroke are replicated in multiple populations:

- ~1.7 fold increased risk for AF
- ~1.5 fold for CE stroke per risk allele

The genotypes of rs2200733 and rs10033464 are not correlated ($r^2=0.01$)

- rs2200733: among 916 patients, 30% are carriers and 70% are noncarriers
- rs10033464: among 915 patients, 22% are carriers and 78% are noncarriers

- At least one copy of the rs2200733 risk allele is carried by ~21% of Caucasians, 70% of Asians, 40% of African Americans, and 50% of Hispanics

- The closest gene, PITX2, encodes a protein that is critical for determining left-right asymmetry, sinoatrial (SA) node formation, and the differentiation of the left atrium

---

**Atrial Fibrillation**

- **AF deCODE**: Discovery, Replication, Sweden, US, Hong Kong, FHS, VAIR, GAFNet, Polish, Italian, MGH, White
- **AF CHARGE**: Af.American, Af.American, Chinese, Discovery, Replication, TexGen
- **CARE**: Af.American, Af.American
- **Post Op AF**: ER AF, LR AF
- **Recurrent AF**: Combined

**Cardioembolic Stroke**

- **CE Stroke deCODE**: Iceland, Sweden, Germany-S, Germany-W, UK, Polish, VSR

---

14. Celera and Collaborators, to submit 2Q2012

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a. Per copy of the risk allele in additive models
b. Recurrent AF was not included
**Target Populations and Possible Clinical Utility (MORTALITY) CABG**

*Help to Predict Short or Long-Term AF and Long-Term Survival After CABG*

<table>
<thead>
<tr>
<th>Target Population:</th>
<th>coronary artery bypass graft (CABG) candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>4q25 Carriers:</td>
<td>have an increased risk of postoperative AF (POAF), long-term AF, and long-term <strong>mortality</strong> (rs2200733 only); results may affect the choice of therapy used to decrease postoperative AF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Risk of Postoperative AF (95% CI)</th>
<th>Risk of Long-Term AF (95% CI)</th>
<th>Risk of Long-Term Mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2200733</td>
<td>1.41 (1.04-1.91)</td>
<td>1.32 (1.05-1.67)</td>
<td><strong>1.57</strong> (1.10-2.24)</td>
</tr>
<tr>
<td>rs10033464</td>
<td>1.47 (1.05-2.06)</td>
<td>1.28 (1.00-1.66)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

AF Ablation and Recurrent AF
Assess the Risk and Treatment Options for Recurrent AF Post Ablation

Target Population: AF patients considered for catheter ablation treatment

4q25 Carriers: have a two-fold increase in early (7 day) recurrence or a 3-fold increase in late (up to 6 months) recurrence; results may inform risk assessment prior to ablation, and management and treatment decisions post-ablation

Table 6 Independent Pre-Procedural Predictors of AF Recurrence in Multivariable Analysis

<table>
<thead>
<tr>
<th>Prediction Model</th>
<th>p Value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n10033464 dominant</td>
<td>0.027</td>
<td>2.061</td>
<td>1.087-3.986</td>
</tr>
<tr>
<td>n2200733 dominant</td>
<td>0.018</td>
<td>2.108</td>
<td>1.135-3.917</td>
</tr>
<tr>
<td>Multivariable prediction model 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n10033464 additive</td>
<td>0.025</td>
<td>2.027</td>
<td>1.091-3.766</td>
</tr>
<tr>
<td>n2200733 additive</td>
<td>0.023</td>
<td>1.693</td>
<td>1.074-2.668</td>
</tr>
<tr>
<td>LRAF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable prediction model 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n10033464 additive</td>
<td>0.009</td>
<td>2.821</td>
<td>1.294-6.146</td>
</tr>
<tr>
<td>n2200733 dominant</td>
<td>0.036</td>
<td>2.458</td>
<td>1.061-5.693</td>
</tr>
<tr>
<td>Multivariable prediction model 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n10033464 dominant</td>
<td>0.013</td>
<td>2.881</td>
<td>1.252-6.634</td>
</tr>
<tr>
<td>n2200733 dominant</td>
<td>0.041</td>
<td>2.379</td>
<td>1.035-5.468</td>
</tr>
</tbody>
</table>

“Ultimately, there is an urgent need to develop a robust clinical risk algorithm for AF which may include genetic variants. Such an algorithm would be invaluable not only in guiding catheter ablation therapy but also improving clinical outcomes in patients with AF.” – Darbar. J Atr Fib. June 2010; 1(12):699

This guideline contains hyperlinks to recommendations and supporting text that have been updated by the "2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline)" (J Am Coll Cardiol 2011;57:223–42; doi:10.1016/j.jacc.2010.10.001) and the "2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran)" (J Am Coll Cardiol 2011;57:1330–7; doi:10.1016/j.jacc.2011.01.010). Updated sections are indicated in the Table of Contents and text.

2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines

2006 WRITING COMMITTEE MEMBERS

Developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society

Valentin Fuster, MD, PhD, FACC, FAHA, FESC, Co-Chair;
Familial (Genetic) Atrial Fibrillation

Familial AF, defined as lone AF running in a family, is more common than previously recognized but should be distinguished from AF secondary to other genetic diseases like familial cardiomyopathies. The likelihood of developing AF is increased among those whose parents had AF, suggesting a familial susceptibility to the arrhythmia, …
Are genetic markers for AF ready for prime time?
D Darbar, MD November 2013 Genetic Expert Consensus Conference

- Identification of individuals at high risk of developing AF is a major clinical priority
- AF risk algorithms (non genetic) are developed but are sub-optimal
- 4q25 genotype predicts response to antiarrhythmics, ablation therapy and electrical cardioversion identifying an AF sub-type (Parvez, JACC 2012;60:539; Husser, et al. J Am Coll Cardiol. 2010;55:747)
- Current clinical application of some genetic markers is limited but may change in the near-future especially for selecting therapy for AF
Family Heart Disease Clinic
“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.”

“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)
Conclusions:

- **LDL-C reduction** alone leaves many patients **still at risk** for a CVD event
- Genetic tests can **identify high/low risk** status (9p21)
- Genetic tests can identify who benefits from **daily ASA** and CHD event reduction vs. GI bleed risk
- Genetic tests can help identify who benefits from **OM3** in regard to blood levels->events
- Genetic tests can identify patients at high risk for **AF**, ablation failure, and mortality
- Genetic tests can be useful in a **Family Heart Disease Clinic**