ΚΡΙΤΗΡΙΑ ΓΙΑ ΤΗ ΔΙΑΓΝΩΣΗ ΚΑΙ ΑΝΤΙΜΕΤΩΠΙΣΗ ΤΗΣ ΣΟΒΑΡΗΣ ΟΙΚΟΓΕΝΕΙΑΚΗΣ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑΣ

MOSES ELISAF, PROFESSOR OF MEDICINE, UNIVERSITY OF IOANNINA, MEDICAL SCHOOL, DEPARTMENT OF INTERNAL MEDICINE
FAMILIAL HYPERCHOLESTEROLEMIA (1)
CO-DOMINANT AUTOSOMAL DISEASE
DUE TO MUTATIONS IN:
• LDLR: LDLR NEGATIVE OR NULL MUTATIONS (<2% RECEPTORS ACTIVITY) AND LDLR DEFECTIVE MUTATIONS (2-25% RECEPTORS ACTIVITY)
• ApoB
• PCSK9
or RARELY
ApoE
STAP1
FAMILIAL HYPERCHOLESTEROLEMIA

AUTOSOMAL RECESSIVE HYPERCHOLESTEROLEMIA (2)

DUE TO MUTATIONS IN:

**LDLRAP1**: WHICH ENCODES LDLR ADAPTOR PROTEIN 1

**LIPA**: WHICH ENCODES LYSOSOMAL ACID LIPASE

**ABCG5 AND ABCG8**: WHICH ENCODE STEROLIN 1 AND 2
RANGE OF LDL CHOLESTEROL LEVELS IN SEVERE HYPERCHOLESTEROLEMIA, ACCORDING TO MONOGENIC DEFECTS

- Homozygotes for LDLR null mutations
- Compound heterozygotes for LDLR null and LDLR defective mutations
- Homozygotes for LDLR defective mutations or LDLRAP1
- Homozygotes for defective APOB or PCSK9 gain-of-function mutations
- Double heterozygotes (eg, LDLR and PCSK9 gain-of-function, or LDLR and defective APOB mutations)
- Heterozygotes for LDLR null mutations
- Heterozygotes for LDLR defective mutations

≥10–13 mmol/L (≥400–500 mg/dL)

≥5 mmol/L (≥190 mg/dL)
SMALL-EFFECT VARIANTS IN HYPERCHOLESTEROLEMIA IN FH

• IN 20-40% OF PATIENTS WITH PROBABLE OR DEFINITE FH NO CAUSATIVE VARIANTS ARE FOUND

POLYGENIC FAMILIAL HYPERCHOLESTEROLEMIA

A high polygenic risk score may worsen the phenotype in large-effect mutation carriers
FH: GENE-GENE AND GENE-ENVIRONMENTAL INTERACTIONS

COMBINED EFFECT OF LDLR AND ApoB MUTATIONS

MODULATION OF PHENOTYPIC EXPRESSION OF FH BY ApoE GENOTYPE

MODULATION OF PHENOTYPIC EXPRESSION OF FH BY ApoB MUTATIONS LEADING TO HYPOBETALIPOPROTEINEMIA

ENVIRONMENTAL FACTORS (DIET AND PHYSICAL ACTIVITY) BUT ALSO CHRONIC HEPATITIS C INFECTION CAN ALSO AFFECT THE PHENOTYPIC EXPRESSION OF FH

EPIGENETIC MODIFICATIONS (e.g., DNA METHYLATION) CAN ALSO AFFECT PHENOTYPIC EXPRESSION OF FH
THE RESPONSE OF LDL CHOL TO STATIN THERAPY DEPENDS ON THE GENOTYPE STATUS OF PATIENTS WITH FH

ATVB 1998;18:1007
ATHEROSCLEROSIS 2014;223:206
Genetic and environmental factors affecting the response to statin therapy in patients with molecularly defined familial hypercholesterolaemia

George Miltiadous\textsuperscript{a}, Stavroulla Xenophontos\textsuperscript{b}, Eleni Bairaktari\textsuperscript{c}, Manolis Ganotakis\textsuperscript{d}, Marios Cariolou\textsuperscript{b} and Moses Elisaf\textsuperscript{a}

Pharmacogenetics and Genomics 2005, 15:219–225
Genetic and environmental factors affecting the response to statin therapy (atorvastatin 20mg/day) in patients with molecularly defined familial hypercholesterolaemia

<table>
<thead>
<tr>
<th>Type of the LDLR mutation</th>
<th>n</th>
<th>-LDL-C% mean±SD</th>
<th>Covariate baseline LDL-C</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>28</td>
<td>34±9</td>
<td>297</td>
<td>0.001</td>
</tr>
<tr>
<td>V</td>
<td>21</td>
<td>49±9</td>
<td>254</td>
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</table>

Factors affecting the statin LDL-C lowering effect in patients with heterozygous FH

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>beta</th>
<th>P-value*</th>
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<tbody>
<tr>
<td>TYPE OF THE LDLR MUTATION</td>
<td>0.60</td>
<td>0.00</td>
</tr>
<tr>
<td>APOE POLYMORPHISM</td>
<td>0.07</td>
<td>0.60</td>
</tr>
<tr>
<td>CETP POLYMORPHISM</td>
<td>-0.15</td>
<td>0.41</td>
</tr>
<tr>
<td>SEX</td>
<td>0.00</td>
<td>0.98</td>
</tr>
<tr>
<td>AGE</td>
<td>0.06</td>
<td>0.66</td>
</tr>
<tr>
<td>TOBACCO</td>
<td>0.16</td>
<td>0.30</td>
</tr>
<tr>
<td>BMI</td>
<td>0.27</td>
<td>0.09</td>
</tr>
<tr>
<td>BASELINE LDL-C LEVELS</td>
<td>0.69</td>
<td>0.001</td>
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</tbody>
</table>

*multiple regression analysis (n=49)
The levels of LDL CHOL and not the causative mutations are the main drivers of risk for atherosclerotic cardiovascular events.

The identification of the causative gene variant is not essential for both diagnosis and treatment.
The risk of CV events is heterogeneous (even in patients carrying the same mutation).

Need to identify patients at highest risk based on LDL CHOL levels, initiation and response to treatment, coexisting cardiovascular risk factors as well as advanced coronary atherosclerosis.
THE CONCEPT OF SEVERE FAMILIAL HYPERCHOLESTEROLEMIA PHENOTYPE
Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel

PROPOSED CRITERIA FOR DEFINITION OF SEVERE FH

AT PRESENTATION (UNTREATED LDL CHOL)

LDL CHOL > 400mg/dl

OR LDL CHOL > 310mg/dl

PLUS ONE HIGH-RISK FEATURE

OR

LDL CHOL > 190mg/dl

PLUS TWO HIGH-RISK FEATURES
<table>
<thead>
<tr>
<th>HIGH RISK FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE &gt; 40 YEARS WITHOUT TREATMENT</strong></td>
</tr>
<tr>
<td>SMOKING</td>
</tr>
<tr>
<td>MALE SEX</td>
</tr>
<tr>
<td>Lp(a) &gt; 50mg/dl</td>
</tr>
<tr>
<td>HDL CHOL &lt; 40mg/dl</td>
</tr>
<tr>
<td><strong>HYPERTENSION</strong></td>
</tr>
<tr>
<td><strong>DIABETES MELLITUS</strong></td>
</tr>
<tr>
<td>FAMILY HISTORY OF EARLY CV DISEASE IN FIRST DEGREE RELATIVES (AGE &lt; 55 YEARS/MEN, &lt; 60 YEARS/WOMEN)</td>
</tr>
<tr>
<td>eGFR &lt; 60ml/min</td>
</tr>
<tr>
<td>BMI &gt; 30Kg/m²</td>
</tr>
</tbody>
</table>
SEVERITY OF THE FH PHENOTYPE:
THE IMPORTANCE OF AGE AT INITIATION OF TREATMENT

LATE TREATMENT (>40 YEARS) ➔ PROLONGED EXPOSURE OF THE ARTERIAL WALL TO HIGH LDL CONCENTRATIONS

HIGHER RISK OF Atherosclerotic CV DISEASE
SEVERITY OF THE FH PHENOTYPE (2)

- The importance of elevated LDL chol
- The importance of the age at initiation of treatment

Cholesterol-year score
SEVERITY OF THE FH PHENOTYPE (3)

THE IMPORTANCE OF COEXISTING TRADITIONAL CARDIOVASCULAR RISK FACTORS
Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: A study of a cohort of 14,000 mutation carriers

Joost Besseling a,*, Iris Kindt b, Michel Hof c, John J.P. Kastelein a, Barbara A. Hutten c, G. Kees Hovingh a

a Department of Vascular Medicine, Academic Medical Centre, The Netherlands
b StOEH, Foundation for Identification of Persons with Inherited Hypercholesterolemia, Amsterdam, The Netherlands
c Department of Clinical Epidemiology, Biostatistics and Biostatistics, Academic Medical Centre, Amsterdam, The Netherlands
n=14,283 WITH MOLECULARLY DEFINED HeFH/UNTREATED LDL CHOL LEVELS > 309mg/dl (8mmol/L)*

11% OF THE HeFH POPULATION ➔ SEVERE FH
PREVALENCE OF SEVERE FH: 1:3000
CVD RISK: HR 1.25 (SEVERE vs NON SEVERE HeFH)

*THE PERCENTILE CORRESPONDING TO AN LDL CHOL LEVEL OF 309mg/dl IN MEN 36-40 YEARS WAS SELECTED AS THE CUT-OFF VALUE FOR SEVERE FH

ATHEROSCLEROSIS 2014;233:219
KAPLAN-MEIER INCIDENCE ESTIMATES FOR SEVERE AND NON-SEVERE HeFH PATIENTS

HR 1.25

logrank test: p=0.01

No. at risk
Severe HeFH 1,580 1,175 703 236
Non-severe HeFH 12,703 9,452 5,788 1,898

ATHEROSCLEROSIS 2014;233:219-223
### INDEPENDENT CVD RISK FACTORS (2)

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Increased age</td>
</tr>
<tr>
<td>Increased BMI</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>High LDL CHOL</td>
</tr>
<tr>
<td>Low HDL CHOL</td>
</tr>
</tbody>
</table>
Importance of HDL cholesterol levels and the total/HDL cholesterol ratio as a risk factor for coronary heart disease in molecularly defined heterozygous familial hypercholesterolaemia

J. T. Real¹, F. J. Chaves², I. Martínez-Usó¹, A. B. García-García², J. F. Ascaso¹ and R. Carmena¹

¹Service of Endocrinology and Nutrition, Department of Medicine, Hospital Clínico Universitario, University of Valencia, Valencia, Spain; ²Instituto de Investigaciones Citológicas, Valencia, Spain
Association Between Cholesterol Efflux Capacity and Atherosclerotic Cardiovascular Disease in Patients With Familial Hypercholesterolemia

Masatsune Ogura, Mika Hori, Mariko Harada-Shiba

Conclusions—Cholesterol efflux capacity was independently and inversely associated with the presence of ASCVD in heterozygous FH. In view of residual risks after treatment with statins, cholesterol efflux capacity might be a novel biomarker and a therapeutic target for preventing atherosclerosis in patients with FH. (Arterioscler Thromb Vasc Biol. 2016;36:181-188. DOI: 10.1161/ATVBAHA.115.306665.)
Cardiovascular disease in familial hypercholesterolaemia: Influence of low-density lipoprotein receptor mutation type and classic risk factors

R. Alonso a,*, N. Mata b, S. Castillo c, F. Fuentes d, P. Saenz e, O. Muñiz f, J. Galiana g, R. Figueras h, J.L. Diaz i, P. Gomez-Enterría j, M. Mauri k, M. Piedecausa l, L. Irigoyen m, R. Aguado n, P. Mata a,

on behalf of the Spanish Familial Hypercholesterolaemia Group l
Table 2
Predictors of cardiovascular disease in familial hypercholesterolemia

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR</th>
<th>P</th>
<th>CI 95%</th>
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<tbody>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.98</td>
<td>0.023</td>
<td>1.09</td>
</tr>
<tr>
<td>Tobacco (ever smokers)</td>
<td>1.80</td>
<td>0.039</td>
<td>1.03</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>1.26</td>
<td>0.041</td>
<td>1.01</td>
</tr>
<tr>
<td>Age</td>
<td>1.05</td>
<td>0.000</td>
<td>1.02</td>
</tr>
</tbody>
</table>
INCREASED Lp(a) LEVELS IN PATIENTS WITH FH (1)

HOMOZYGOUS PATIENTS > HETEROZYGOUS PATIENTS > CONTROL POPULATION

Which is the role of LDLR in Lp(a) clearance?
INCREASED Lp(a) LEVELS

- META-ANALYSES OF PROSPECTIVE STUDIES
- GENOME-WIDE ASSOCIATION STUDIES
- MENDELIAN RANDOMISATION STUDIES

CHD

ISCHEMIC STROKE

AORTIC STENOSIS
<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAFEHEART STUDY JACC, 2014</td>
<td>INCREASED Lp(a) LEVELS ARE AN INDEPENDENT PREDICTOR OF CV DISEASE INDEPENDENT OF THE TYPE OF LDL MUTATION</td>
</tr>
<tr>
<td>COPENHAGEN GENERAL POPULATION STUDY LANCET DIABETES ENDOCRINOL, 2016</td>
<td>Lp(a) LEVELS &gt;50mg/dl ARE ASSOCIATED WITH THE ONSET OF ATHEROSCLEROTIC CV DISEASE</td>
</tr>
<tr>
<td>ASYMPTOMATIC FH PATIENTS TREATED WITH STATINS J INTERN MED, 2015</td>
<td>Lp(a) LEVELS ARE ASSOCIATED WITH AORTIC VALVE CALCIFICATION IS ASYMPTOMATIC PATIENTS WITH FH</td>
</tr>
</tbody>
</table>
PROPOSED CRITERIA FOR DEFINITION OF SEVERE FH

AT PRESENTATION (UNTREATED LDL CHOL)

- LDL CHOL > 400mg/dl
- OR LDL CHOL > 310mg/dl
- PLUS ONE HIGH-RISK FEATURE
- OR
- LDL CHOL > 190mg/dl
- PLUS TWO HIGH-RISK FEATURES

REALISTIC GOAL: A REDUCTION OF LDL CHOL > 50%
IDEAL GOAL: LDL CHOL < 100mg/dl
SEVERE FH: PRESENCE OF ADVANCED SUBCLINICAL ATHEROSCLEROSIS

ADVANCED SUBCLINICAL ATHEROSCLEROSIS DIAGNOSED WITH A CAC SCORE > 100 AGASTRON UNITS OR >75th PERCENTILE FOR AGE AND SEX OR CT ANGIOGRAPHY WITH OBSTRUCTIONS >50% OR PRESENCE OF NON-OBSTUCTIVE PLAQUES IN MORE THAN ONE VESSEL.

REALISTIC GOAL: A REDUCTION OF LDL CHOL >50%

IDEAL GOAL: LDL CHOL <70mg/dl
FH: INCREASED CORONARY Atherosclerosis

PLAQUE SCORE

n=101 PATIENTS WITH FH (65-70% ON STATINS FOR 7-9 YEARS), FOLLOW UP: ~ 3 YEARS

INCREASED (BY CCTA) CORONARY Atherosclerotic Plaque Score (>3.35): CORONARY EVENTS HR 3.65

AM J CARDIOL 2015;115:724
Assessment of Coronary Atherosclerosis in Patients With Familial Hypercholesterolemia by Coronary Computed Tomography Angiography

Hayato Tada, MD\textsuperscript{a,*}, Masa-aki Kawashiri, MD\textsuperscript{a}, Hirofumi Okada, MD\textsuperscript{a}, Ryota Teramoto, MD\textsuperscript{a}, Tetsuo Konno, MD\textsuperscript{a}, Tsuyoshi Yoshimuta, MD\textsuperscript{a}, Kenji Sakata, MD\textsuperscript{a}, Atsushi Nohara, MD\textsuperscript{b}, Akihiro Inazu, MD\textsuperscript{c}, Junji Kobayashi, MD\textsuperscript{d}, Hiroshi Mabuchi, MD\textsuperscript{b}, Masakazu Yamagishi, MD\textsuperscript{a}, and Kenshi Hayashi, MD\textsuperscript{a}
CUMULATIVE EVENT RATES ACCORDING TO THE PLAQUE BURDEN SCORE OF 3.35 AS THE OPTIMAL CUT OFF

H.R.: 3.65
DETECTION OF ADVANCED SUBCLINICAL ATHEROSCLEROSIS

No strict recommendations are available however, in homozygous FH (LDL chol > 400mg/dl):
Frequent monitoring for subclinical atherosclerosis is suggested.

Severe FH:
In specific subgroups, such as in untreated patients diagnosed with FH in adulthood and those with multiple risk factors for ASCVD.
SEVERE FH: PRESENCE OF CLINICAL ATHERTOSCLEROTIC CARDIOVASCULAR DISEASE

CLINICAL ATHERTOSCLEROTIC CVR DEFINED AS

- PREVIOUS MI
- ANGINA
- CORONARY REVASCULARIZATION
- NON-EMBOLIC ISCHEMIC STROKE OR TRANSITORY ISCHEMIC ATTACK
- INTERMITENT CLAUDICATION

REALISTIC GOAL: A REDUCTION OF LDL CHOL > 50%
IDEAL GOAL: LDL CHOL < 70mg/dl
FAMILIAL HYPERCHOLESTEROLEMIA: PRIMARY vs SECONDARY PREVENTION

n=3,382 PATIENTS WITH HETEROZYGOUS FH, FOLLOW-UP: 26 YEARS

- STATINS DECREASE CVD MORTALITY BY 37%
- THE EXCESS MORTALITY RATIO IN THOSE RECEIVING SECONDARY PREVENTION WITH STATINS x4 (vs GENERAL POPULATION)
- BENEFIT: PRIMARY vs SECONDARY PREVENTION x 2

Eur Heart J 2008;29:2625
INCIDENCE OF RECURRENT CORONARY EVENTS AFTER ACUTE CORONARY SYNDROME (n=4534)

HR: 3.53
TREATMENT ALGORITHM FOR SEVERE FAMILIAL HYPERCHOLESTEROLEMIA

Step 1
Patient with severe familial hypercholesterolaemia
High-intensity statin therapy (atorvastatin or rosuvastatin) at maximum tolerated dose plus ezetimibe

LDL cholesterol not at ideal goal or <50% reduction

Step 2
Triple-drug therapy
Add PCSK9 inhibitor (bile acid sequestrants, or niacin optional depending on availability, toxic effects, and costs)

Step 3
LDL cholesterol still not at ideal goal

Consider four-drug therapy
Add lomitapide or mipomersen (approved for homozygous familial hypercholesterolaemia in some countries), or lipoprotein apheresis, or liver transplantation (in homozygous familial hypercholesterolaemia)

Maintain treatment
Minimum LDL cholesterol reduction ≥50% or at ideal LDL cholesterol goal
Treatment Algorithm for FH

FH patients

Not at goal/intolerant

Statin

Cholesterol absorption inhibitors

Not at goal/intolerant

Bile acid sequestrants

PCSK9 inhibitors

Initiation of high-dose statin monotherapy is standard of care

Ezetimibe is added when patient is not at goal

Bile acid sequestrants, nicotinic acid, and fibrates are added alone or in combination for those not at goal

Potential future therapy