ACC Latin America Conference 2017

MEXICO CITY

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GLOBAL EXPERTS, LOCAL LEARNING

Familial Hipercholesterolemia

From Molecular to Clinical Management

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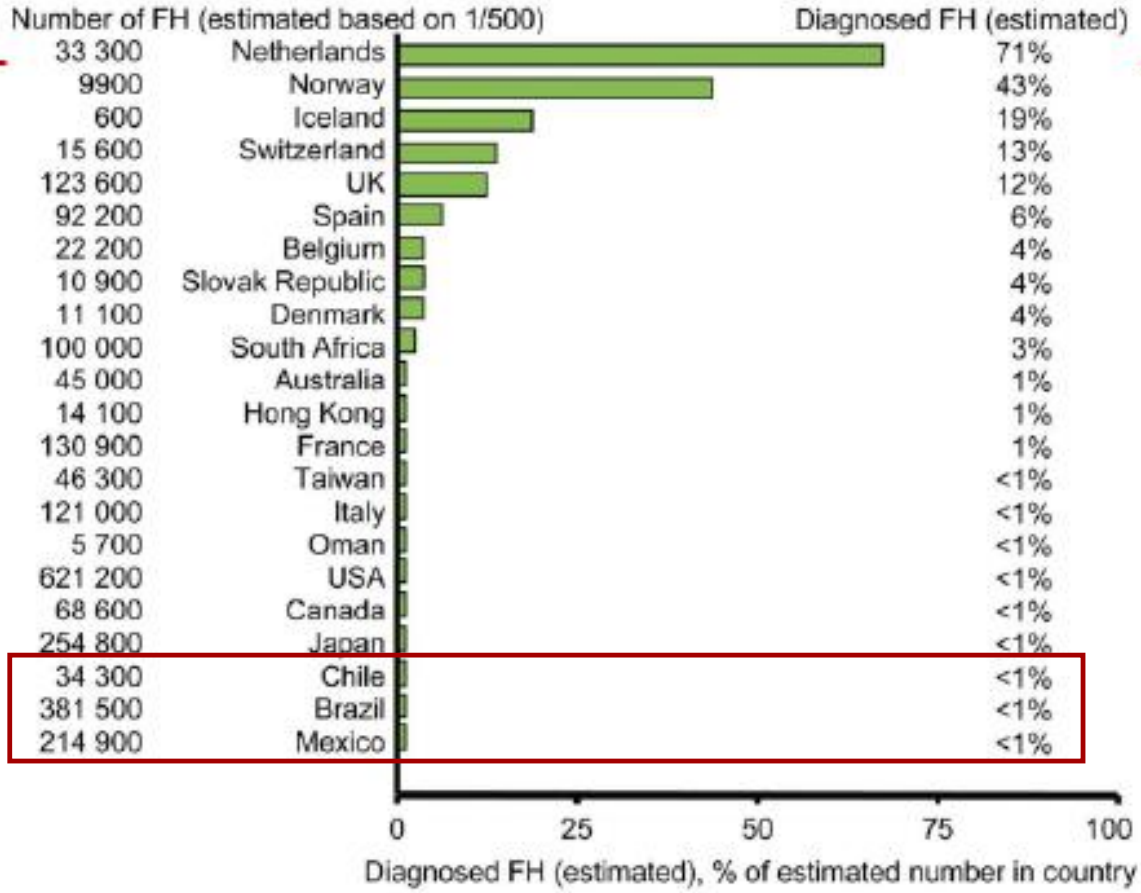
Familial Hypercholesterolaemia is an autosomal, dominant genetic disorder that leads to elevated blood cholesterol and a dramatically increased risk of atherosclerosis.

It is perceived as a rare condition. However it affects 1 in 250 of the population globally, making it an important public health.

Henderson et al. Journal of Biomedical Science (2016) 23:39

Estimated % Diagnosed FH in Different Countries, as a Fraction of Those Predicted Based on a Frequency of 1/500 in the General Population



Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273

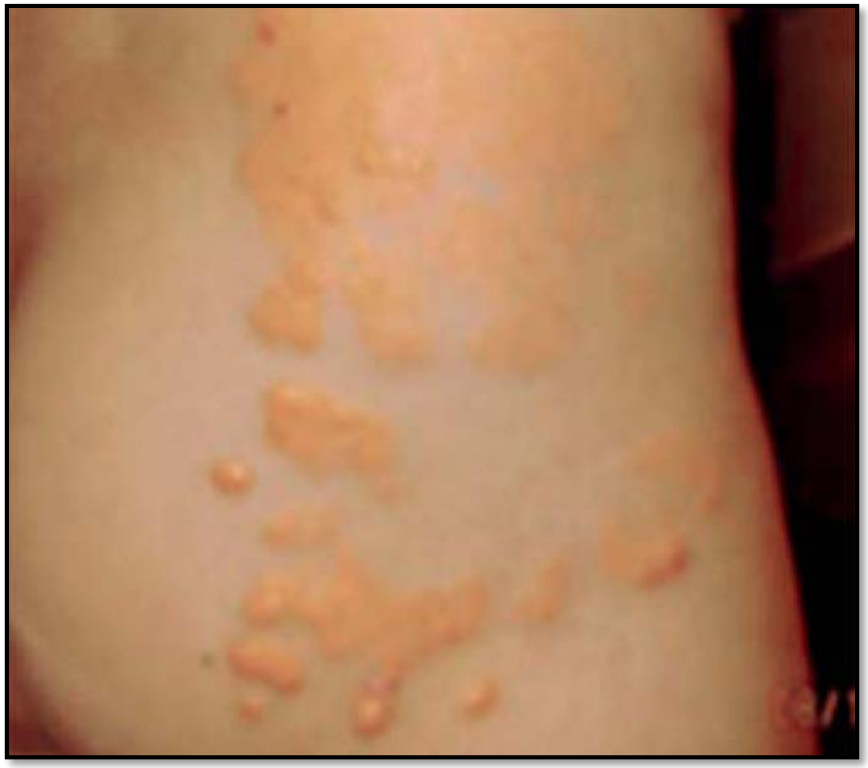
European Heart Journal

FH - Features

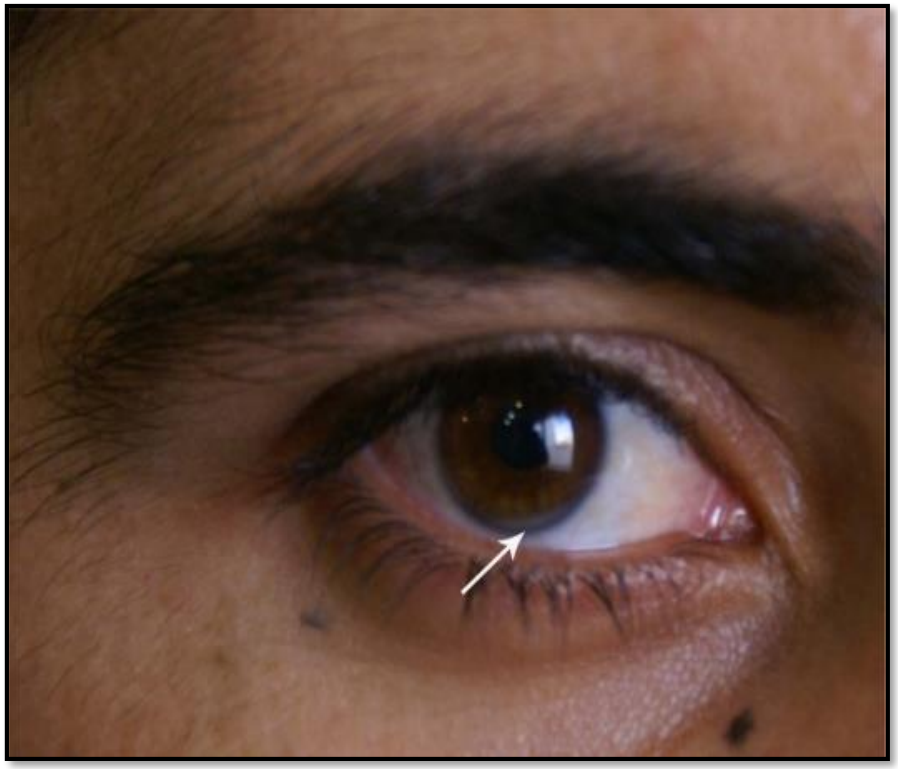
- Markely elevated blood cholesterol – LDLc
- Family and clinical history
- Clinical signs
- Genetic findings

Diagnostic Criteria

FH - Signs



Cutaneous xanthomas



Corneal arcus eye

FH - Signs

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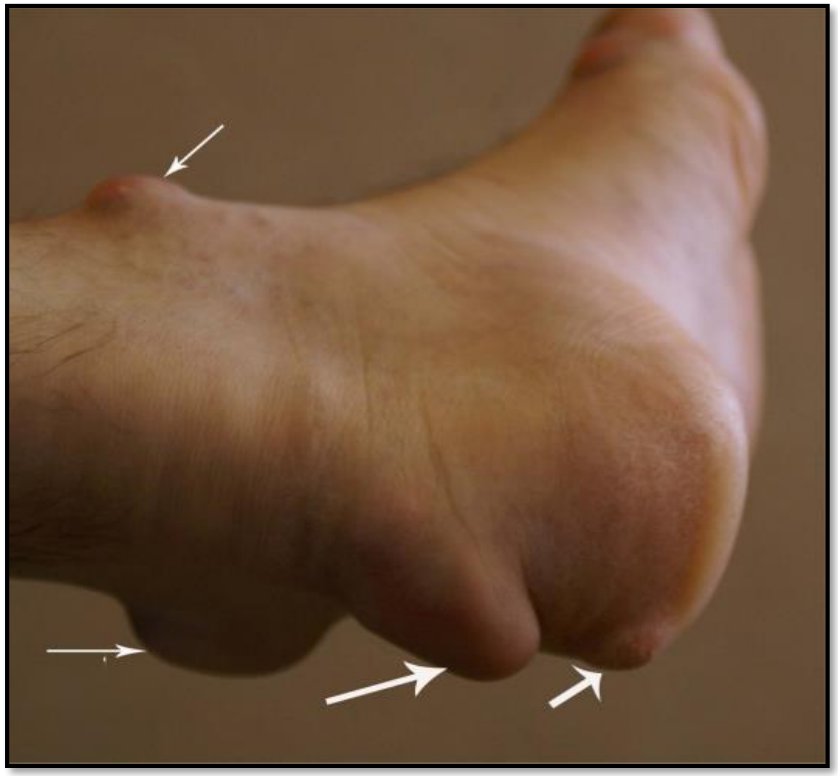
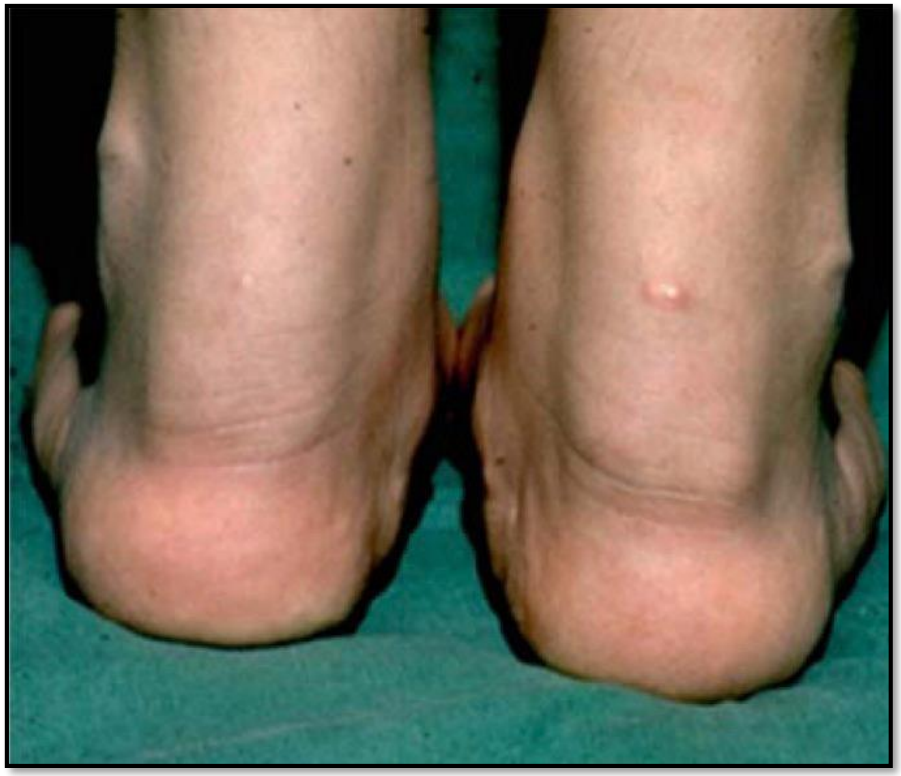


Xanthoma of Achilles tendon



Broadening of the Achilles tendon

Diagnostic Criterias

	Simon Broome	Dutch
Process of diagnosis	Mutation or cholesterol plus xanthoma or family history	Sum of score for each item
Items	Total cholesterol >290 or LDL-C >190 mg/dL; xanthoma; mutation; family history of MI or hypercholesterolemia	Family history of CAD or hypercholesterolemia; history of CAD, cerebral or peripheral vascular disease; xanthoma or corneal arcus; LDL-C ≥150–330 mg/dL

	MEDPED	Japanese
Process of diagnosis	Cholesterol level alone	Any two of cholesterol, xanthoma, or family history
Items	Total cholesterol ≥290–360 or LDL-C ≥220–260 mg/dL	LDL-C ≥180 mg/dL; xanthoma; family history of hypercholesterolemia or CAD

Endocrinol Metab 2017;32:36-40

Table 1 DLCN Diagnostic Criteria for FH

Group 1: Family History	Points
i. First-degree relative with premature CHD[a]	1
ii. First-degree relative with LDL-C > 95th percentile by age, gender for country	1
iii. First-degree relative with tendinous xanthomata and/or arcus cornealis	2
iv. Children under 18 years with LDL-C > 95th percentile by age, gender for country	2
Group 2: Clinical History	**Points**
i. Premature CHD	2
ii. Premature cerebrovascular or peripheral vascular disease	1
Group 3: Physical Examination Points	
i. Tendinous xanthomata	6
ii. Arcus cornealis prior to 45 years	4
Group 4: LDL-C Levels	**Points**
i. LDL-C > 8.5 mmol/l (~330 mg/dl)	8
ii. LDL-C 6.5-8.4 mmol/l (~250-329 mg/dl)	5
iii. LDL-C 5.0-6.4 mmol/l (~190-249 mg/dl)	3
iv. LDL-C 4.0-4.9 mmol/l (~155-189 mg/dl)	1
Group 5: DNA Analysis Points	
i. Causative mutation in the LDLR, ApoB or PCSK9 gene	8

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Total score

Definitive FH > 8 points
Probable FH 6 - 8 points
Possible FH 3 - 5 points
Unlikely FH 0 - 2 points

Genetic Testting for:

- Score > 5 points
- Xanthoma + ↑LDLc + CHD familial history

Causative mutation found:

- Genetic test for all first degree relatives

Pathophysiology of FH

Decreased LDL receptor function due to a genetic defect:

- LDL receptor is not synthesized
- LDL receptor is not properly transported from the endoplasmic reticulum to the Golgi apparatus for expression on the cell surface
- LDL receptor does not properly bind LDL on the cell surface
- LDL receptor does not properly cluster in clathrin-coated pits for receptor endocytosis
- LDL receptor is not recycled back to the cell surface

Therefore, LDL receptor-mediated endocytosis is decreased → **LDL levels ⇑**

Premature development of atherosclerotic plaque

Cardiol Clin. 2015 May ; 33(2): 169–179

FH - Genetics

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- Mutations of **LDLcR**, **APOB** or **PCSK9 genes**.
- In 85% to 90% of cases it is caused by a mutation in the LDLR gene.
- There are currently more than **1700 LDLR mutations.**
- Most FH patients without a monogenic cause are suspected to have polygenic FH that is caused by a multiple lipid-related common variants.
- Pathogenic mutations are not identified in about 60% of clinically diagnosed FH patients.

FH – Treatment

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Overall Comments

- Early treatment is beneficial and long term drug therapy can substantially reduce the added lifetime risk of CHD.
- Most recent guidelines indicate that it is desirable to reduce LDL-C to 50% of baseline levels or <100 mg/dL in adults with FH.
- Statins – first-line therapeutics option

FH – Treatment

Strategies

- Life style modifications - *diet and physical exercise*
- Statins
- Ezetimibe
- Lomitapide - inhibits microsomal triglyceride transfer protein
- Mipomersen - blocks the translation of apoB
- PCSK9 inhibitors – *Alirocumab / Evolucumab*

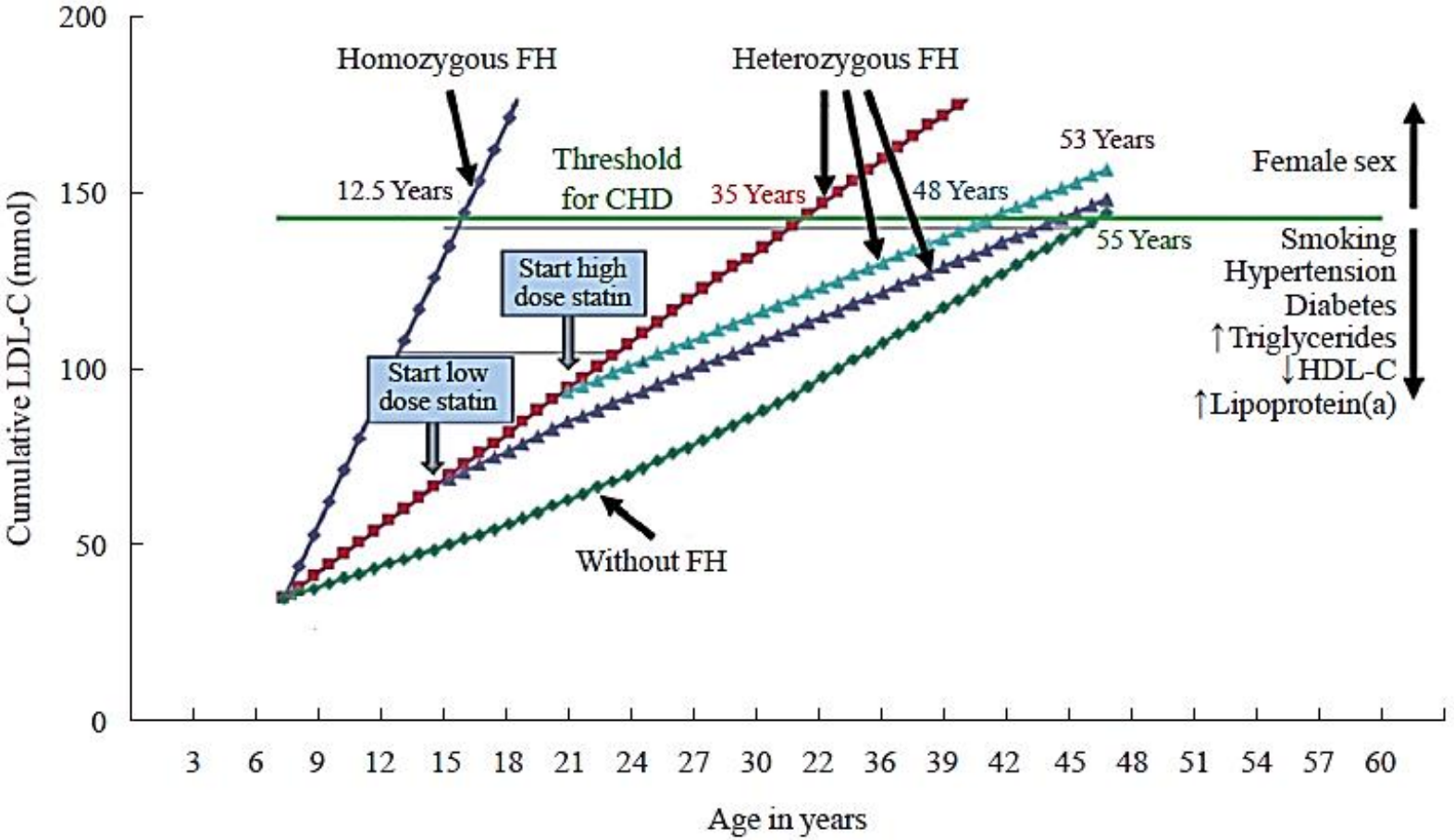
THE WALL STREET JOURNAL.

LIFE

When Cholesterol Drugs Cost $14,000, an Insurance Tug-of-War

Patients struggle to obtain PCSK9 inhibitors, a powerful class of drugs that lower bad cholesterol in difficult cases and when statins don't work

Carlyn Cirrincione, 22, and her mother Tracey, 45, at home in Gibsonia, Pa. Carlyn has familial hypercholesterolemia, a genetic disorder that causes high cholesterol. She is hoping to be approved for PCSK9 inhibitors. *ROSS MANTLE FOR THE WALL STREET JOURNAL*



LDL-C burden in individuals with or without familial hypercholesterolemia (FH) as function of the onset of statin therapy

European Heart Journal (2013) **34**, 3478–3490

Familial Hipercholesterolemia

From Molecular to Clinical Management

- FH is a relatively frequent genetic disorder.
- Diagnosis of FH by clinical rather than genetic criteria is more common in real world practice.
- Reduction of premature complications is most critical in patients with FH.

Thank you