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A 20-year-old male with Familial hypercholesterolemia and family history of premature CAD

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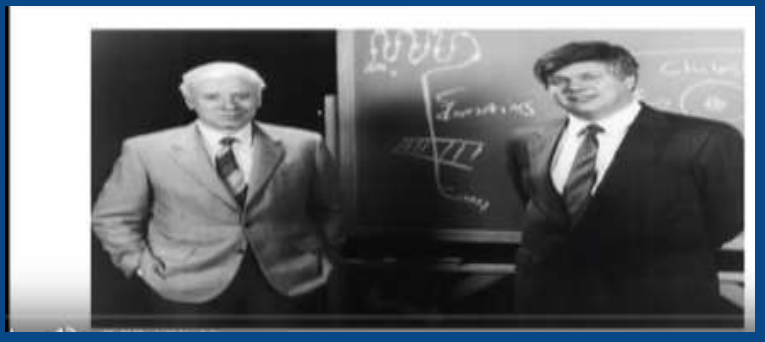
Molecular Basis of FH by Michael Brown and Joseph Goldstein , Nobel Prize 1974



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A 20-year-old male with Familial hypercholesterolemia and family history of premature CAD

- His mother died at the age of 44 with CAD
- TC 390 mg/dl
- LDL 330 mg/dl
- HDL 35 mg/dl
- TG 120 mg/dl
- Lp (a) 190 mg/dl
- Apart from this nothing is abnormal

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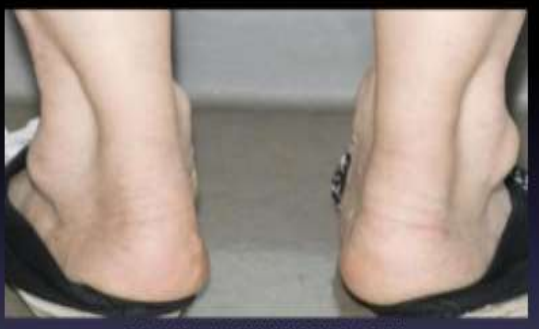
Achilles tendinopathy in patient with familial hypercholesterolaemia



Schofield J et al. BMJ 2013;346:bmj.f2171

In a study of patients with definite HeFH, 26.3% had consulted a doctor about symptoms of Achilles tendinopathy, but none of these consultations had led to a diagnosis of FH*

*Beeharry D *et al*. 2006;65:312–5

Familial Hypercholesterolemia: Prevalence and Risk

- **FH is caused by genetic mutations passed on by:**
  - One parent (heterozygous, HeFH)[1]
  - Both parents (homozygous, HoFH)[1]
- **HoFH prevalence ranges from 1 in 160,000 to 1 in 250,000[2,3]**
  - Individuals with HoFH have extremely high LDL-C levels (>500 mg/dL) and premature CV risk[4]
  - Many with HoFH experience their first coronary event in childhood or adolescence[4]
- **HeFH prevalence ranges from 1 in 200 to 1 in 250[3]**
  - Individuals with HeFH can present with LDL-C levels 90 to 500 mg/dL and have premature CV risk[4]
  - On average, individuals with HeFH experience their first coronary event at age 42 (about 20 years younger than the general population)[4]
- **Early treatment is recommended for all individuals with FH, with a goal of reducing LDL-C levels by 50% from baseline[3]**

Abbreviations: CV, cerebrovascular; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

1. Zimmerman MP. *Am Health Drug Benefits*. 2015;8:436-442; 2. Goldstein J, et al. *The Metabolic and Molecular Bases of Inherited Disease*. 7th ed. New York, NY: McGraw-Hill; 1995: 1981-2030; 3. Bouhairie VE, et al. *Cardiol Clin*. 2015;33:169-179; 4. Turgeon RD, et al. *Can Fam Physician*. 2016;62:32-37.

Familial Hypercholesterolemia: Diagnosis

- **FH diagnostic criteria include lipid levels and family history, physical symptoms (if any), and genetic analysis (if available)[1]**
- **Three clinical diagnostic tools:[2-3]**
  - Simon Broome Register Diagnostic Criteria
  - Dutch Lipid Clinic Network Diagnostic Criteria
  - U.S. MEDPED
- **Factors that lead to an FH diagnosis include:**
  - Premature ASCVD, fasting LDL-C >190 mg/dL, the presence of tendon xanthomas, full corneal arcus in individuals <40 years of age, or a family history of high cholesterol and/or premature ASCVD[1]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MEDPED, Make Early Diagnoses Prevent Early Deaths Program Diagnostic Criteria.

1. Bouhairie VE, et al. *Cardiol Clin*. 2015;33:169-179; 2. Haralambos K, et al. *Curr Opin Lipidol*. 2016;27:367-374; 3. Turgeon RD, et al. *Can Fam Physician*. 2016;62:32-37.

Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia (1)

Criteria	Points
1) Family history	
First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or	
First-degree relative with known LDL-C above the 95th percentile.	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or	
children <18 years of age with LDL-C above the 95th percentile.	2
2) Clinical history	
Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
3) Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4

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European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehw272
Atherosclerosis 253 (2016) 281-344-d oi:10.1016/j.atherosclerosis.2016.08.018

Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia (2)

Criteria	Points
4) LDL-C levels	
LDL-C ≥ 8.5 mmol/L (325 mg/dL)	8
LDL-C 6.5–8.4 mmol/L (251–325 mg/dL)	5
LDL-C 5.0–6.4 mmol/L (191–250 mg/dL)	3
LDL-C 4.0–4.9 mmol/L (155–190 mg/dL)	1
5) DNA analysis	
Functional mutation in the LDLR, apoB or PCSK9 gene	8

Choose only one score per group, the highest applicable Diagnosis
(diagnosis is based on the total number of points obtained)

A 'definite' FH diagnosis requires >8 points

A 'probable' FH diagnosis requires 6–8 points

A 'possible' FH diagnosis requires 3–5 points

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Genetic disorders of lipoprotein metabolism

Disorder	Prevalence	Gene(s)	Effect on lipoproteins
HeFH	1 in 200–250	*LDLR* *APO B* *PCSK9*	↑ LDL-C
HoFH	1 in 160 000–320 000	*LDLR* *APO B* *PCSK9*	↑↑ LDL-C
FCH	1 in 100/200	*USF1 + modifying genes*	↑ LDL-C ↑ VLDL-C ↑ apoB
Familial dysbetalipoproteinaemia	1 in 5000	*APO E*	↑↑ IDL and chylomicron remnants (βVLDL)
Familial lipoprotein lipase deficiency	1 in 10^6	*LPL* *APO C2*	↑↑ chylomicrons and VLDL-C
Tangier disease (analpha-lipoproteinaemia)	1 in 10^6	*ABCA1*	↓↓ HDL-C
Familial LCAT deficiency	1 in 10^6	*LCAT*	↓ HDL-C

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Detection and treatment of patients with heterozygous familial hypercholesterolaemia (1)

Recommendations	Class	Level
FH is recommended to be suspected in patients with CHD before the age of 55 years for men and 60 years for women, in subjects with relatives with premature fatal or non-fatal CVD, in subjects with relatives having tendon xanthomas, and in subjects with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL), in children >4 mmol/L (150 mg/dL)].	I	C
Diagnosis is recommended to be confirmed with clinical criteria and, when available, with DNA analysis.	I	C
Family cascade screening is recommended to be performed when an index case of FH is diagnosed.	I	C
FH patients are recommended to be treated with intense-dose statin, often in combination with ezetimibe.	I	C

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Detection and treatment of patients with heterozygous familial hypercholesterolaemia (2)

Recommendations	Class	Level
Treatment should be considered to aim at reaching an LDL-C <2.6 mmol/L (100 mg/dL) or in the presence of CVD <1.8 mmol/L (70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations.	IIa	C
Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very high-risk for CHD, such as other CV risk factors, family history, high Lp(a) or statin intolerance.	IIa	C
In children, testing is recommended from age 5 years, or earlier if homo-zygous FH is suspected.	I	C
Children with FH should be educated to adopt a proper diet and treated with statin from 8–10 years of age. Targets for treatment should be LDL-C <3.5 mmol/L (135 mg/dL) at >10 years of age.	IIa	C

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Familial hypercholesterolaemia patients without clinically diagnosed atherosclerotic cardiovascular disease :

- The elevated cardiovascular risk of undertreated heterozygous FH patients is well recognized, with up to **eight-fold higher risk** in patients with an FH-causative mutation compared with unaffected relatives. Furthermore, despite long-term, high-intensity statin treatment to lower LDL-C levels, asymptomatic FH patients often have evidence of an increased plaque burden in multiple vascular territories.

- Task Force recommends that an LDL-C threshold of >4.5 mmol/L (180 mg/dL) despite maximally tolerated statin plus ezetimibe identifies patients at high risk likely to derive maximum benefit from PCSK9 inhibition.
- A lower LDL-C threshold (>3.6 mmol/L or >140 mg/dL) is recommended when patients have additional indices of risk severity.

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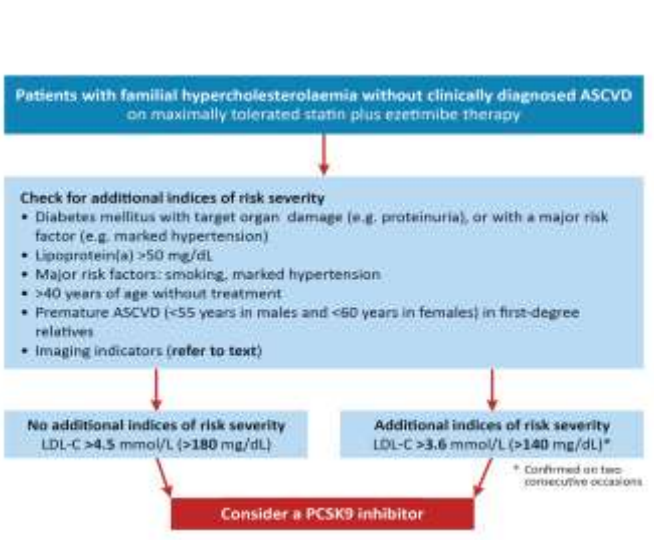

From: 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

Eur Heart J. Published online October 16, 2017. doi:10.1093/eurheartj/ehx549

- Given the mode of action of PCSK9 inhibition, some level of LDL receptor activity is required for efficacy. Consequently, treatment with a PCSK9 inhibitor is not recommended in patients with *LDLR* mutations which have LDL receptor activity below 2%

Take Home Message

- Still there is low awareness,detection and control of FH
- Clinical Diagnostic Criteria should be used for diagnosis of FH
- Intensive LDL reduction should be started as early as possible
- Novel therapies like PCSK9 inhibitors are likely to change dramatically the outcome of patients with FH

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THANK YOU