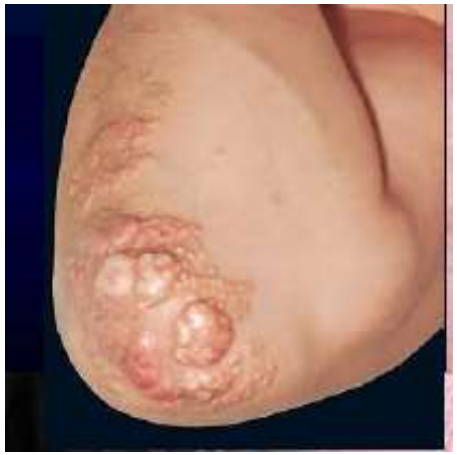
Familial Hypercholesterolemia

Presented By

Dr. Khaled Refaat, MD, FEgSC

Case study

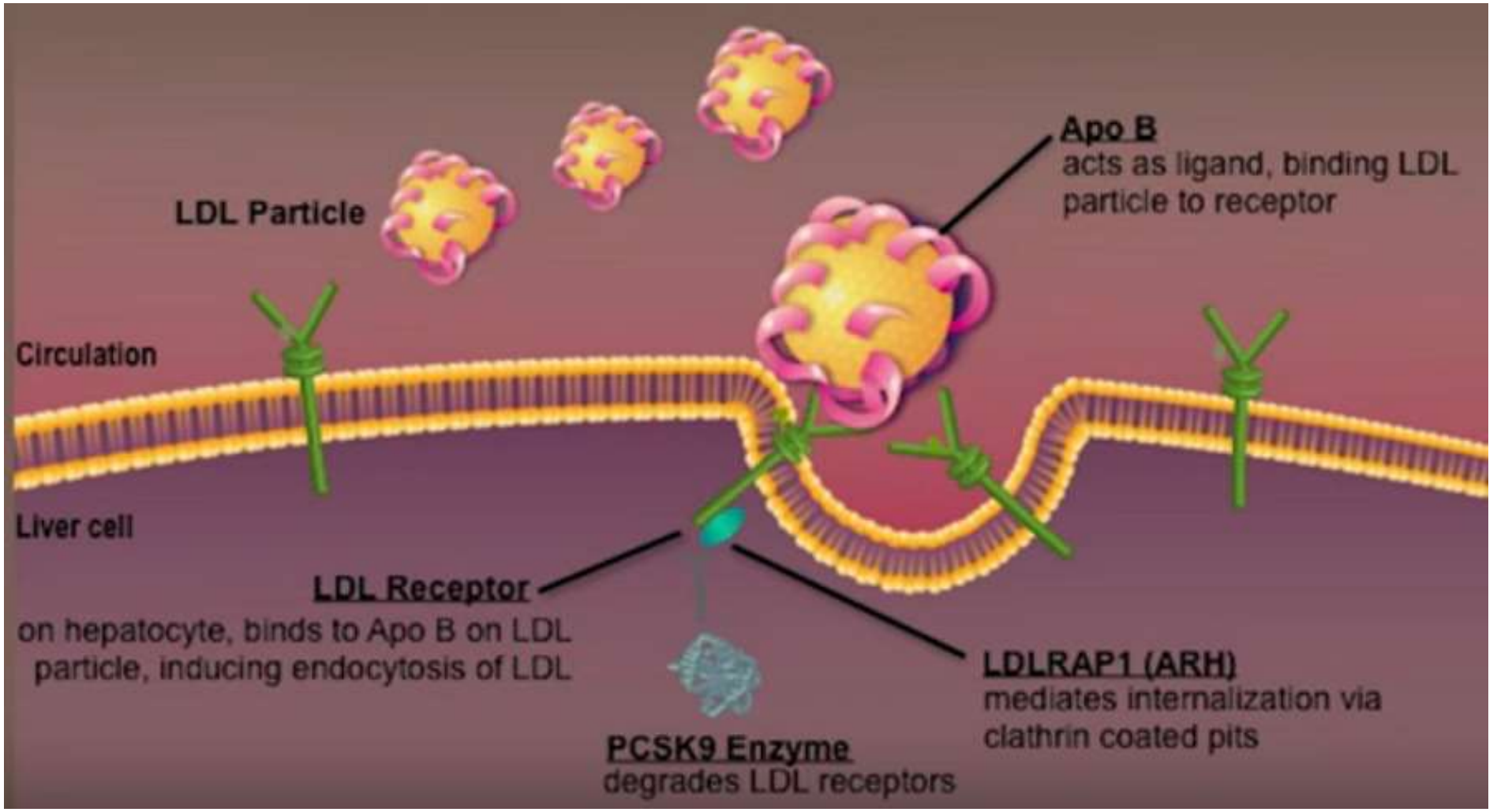
- 26-year old male
- Complains of chest tightness
- Brother died at age of 28 year due to MI and his sister died at the age of 29 soon after her second delivery
- Lipogram: LDL-C : 430 mg/dl; HDL: 40 mg/dl; TG = 287 mg/dl



Familial Hypercholesterolemia

- **Monogenic disorder (Briefing on genetics)**
- Changing prevalence
- Under diagnosis
- Increased lifetime CV risk
- Diagnostic criteria (clinical / genetic)
- Family screening
- Current management

Genetics


LDL Particle
Apo B
acts as ligand, binding LDL particle to receptor
Circulation
Liver cell
LDL Receptor
on hepatocyte, binds to Apo B on LDL particle, inducing endocytosis of LDL
LDLRAP1 (ARH)
mediates internalization via clathrin coated pits
PCSK9 Enzyme
degrades LDL receptors

Genetics

- **3 most common genes**:
  - LDLR (> 1700 mutations): 95%
  - apoB: 4-5%
  - PCSK9: 1%

- **Autosomal dominant**

An older Perspectives….

Clinical characteristic	HoFH	HeFH
Untreated LDL-C (mg/dL)	Generally >465 mg/dL[2]	Average >220 mg/dL
Treated LDL-C	>300 mg/dL after max tolerated drug therapy[3]	Mean 135 +/- 38 mg/dL after treatment with high dose statins
Cutaneous features	Tendon xanthomas Xanthelasma Tuberous xanthomas Planar xanthomas	Tendon xanthomas Xanthelasma
Corneal arcus	Possible before age 20	Common after age 40
Symptomatic Atherosclerosis	Within 2nd decade	Within 4th-5th decade

Metabolic abnormalities

- **LDL-C: ↑↑↑**
- **Lp(a): ↑**
- **TG: ↑↔**
- **HDL-C: ↓**

Familial Hypercholesterolemia

- Monogenic disorder (Briefing on genetics)
- **Changing prevalence**
- Under diagnosis
- Increased lifetime CV risk
- Diagnostic criteria (clinical / genetic)
- Family screening
- Current management

Prevalence

	Hetero FH	Homo FH
Old data	1/500	1/ million

Br Med J 1980;281:633e6
Arteriosclerosis 1989;9:211e6
Mol Genet Metab 2011;102:181e8

Prevalence

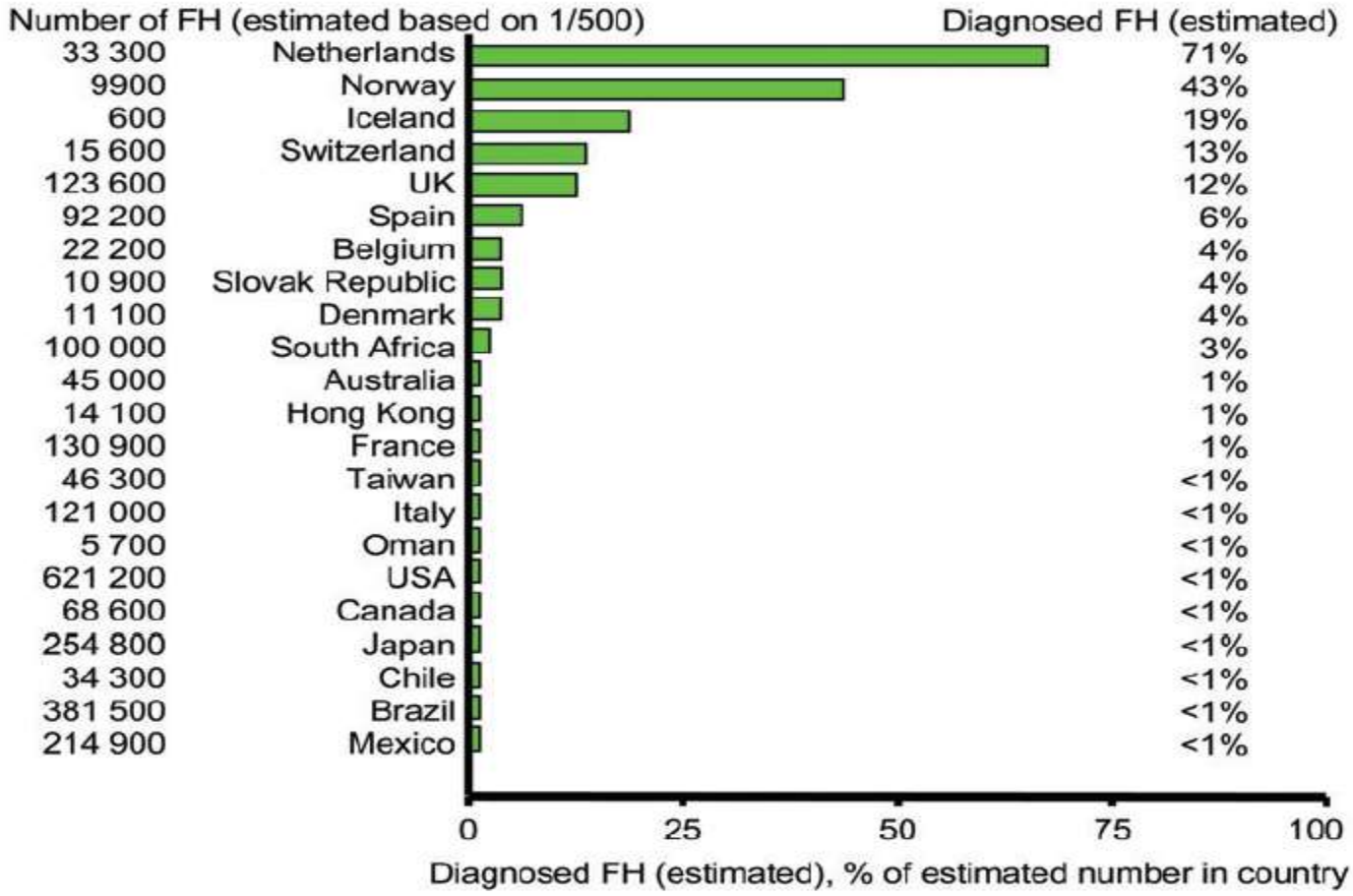
	Hetero FH	Homo FH
Old data	1/500	1/ million
New data	1/200-250	1 / 160-300 x 10^3

Br Med J 1980;281:633e6
Arteriosclerosis 1989;9:211e6
Mol Genet Metab 2011;102:181e8

Familial Hypercholesterolemia

- Monogenic disorder (Briefing on genetics)
- Changing prevalence
- **Under diagnosis**
- Increased lifetime CV risk
- Diagnostic criteria (clinical / genetic)
- Family screening
- Current management

Underdiagnosed

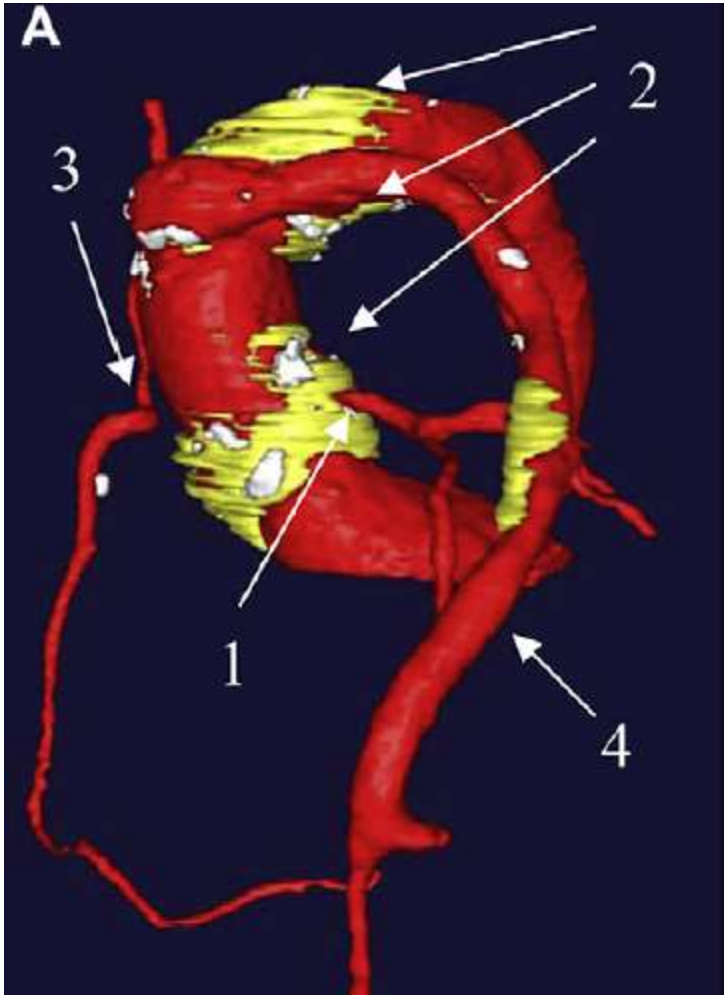


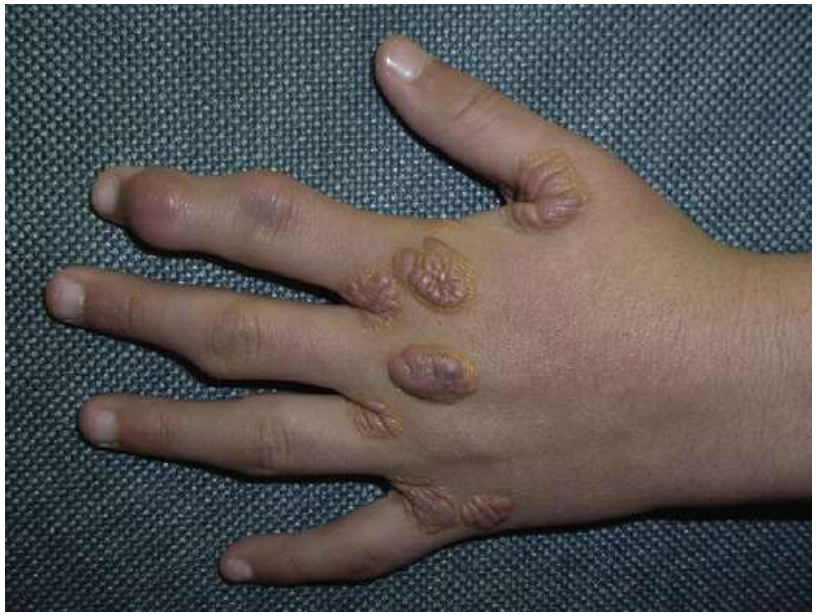
European Heart Journal (2013) 34, 3478–3490

Familial Hypercholesterolemia

- Monogenic disorder (Briefing on genetics)
- Changing prevalence
- Underdiagnosis
- **Increased lifetime CV risk**
- Diagnostic criteria (clinical / genetic)
- Family screening
- Current management

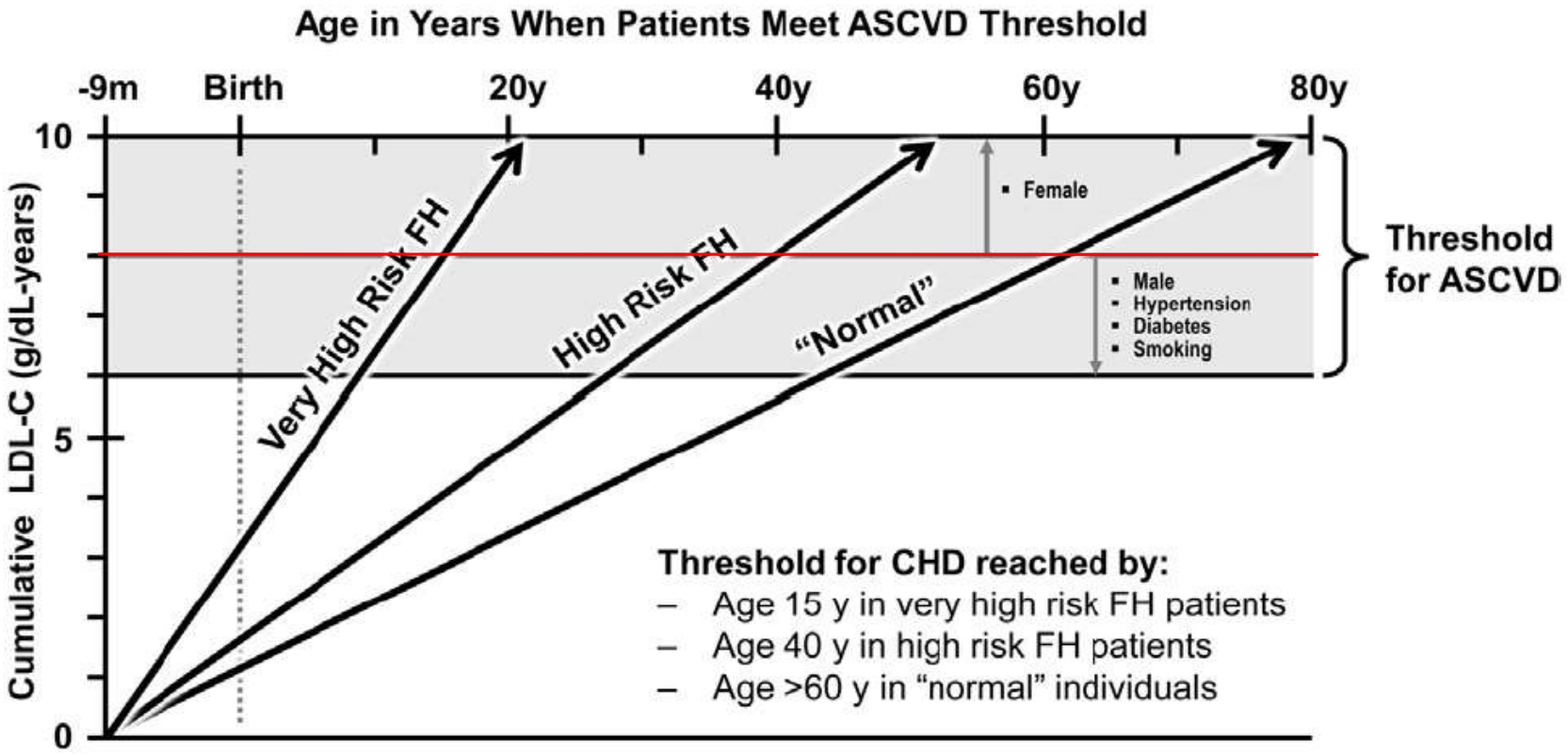
Pathology





Life time risk

Time is plaque



cholesterol-year score

Hetero : ASCVD

- 20 fold increased risk of ASCVD
- 50% of men have ASCVD by age of 50
- 30% of women have ASCVD by age of 60
- Among all MIs:
  - Before age of 45 : 20% have FH
  - Before age of 60 : 2-5% have FH

Familial Hypercholesterolemia

- Monogenic disorder (Briefing on genetics)
- Changing prevalence
- Underdiagnosis
- Increased lifetime CV risk
- **Diagnostic criteria (clinical / genetic**)
- Family screening
- Current management

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

Familial Hypercholesterolemia

- Briefing on etiology / genetics
- Changing prevalence
- Underdiagnosis
- Increased CV risk
- **Diagnostic Criteria**
- Family screening
- Management

European Heart Journal (2016) 37, 2999–3058

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

Index cases should be identified when:

- plasma cholesterol ≥8 mmol/L (310 mg/dL) in an adult or adult family member (or >95th percentile by age and gender for country),
- premature CHD in the subject or a family member,
- tendon xanthomas in the subject or a family member or
- sudden premature cardiac death in a family member

European Heart Journal (2016) 37, 2999–3058

Dutch Lipid Clinic Network Diagnostic Criteria

1). FH	2). Clinical History	3). Exam	4). LDL-C	5). DNA

A 'definite' FH diagnosis requires >8 points

A 'probable' FH diagnosis requires 6–8 points

A 'possible' FH diagnosis requires 3–5 points

Exclude 2^{ry} causes of hypercholesterolemia

Semin Vasc Med 2004;4:59–65

Dutch Lipid Clinic Network diagnostic criteria

1). FH | 2). Clinical History | 3). Exam | 4). LDL-C | 5). DNA

Criteria	Points
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 (see 9.1.2.3)	2

Semin Vasc Med 2004;4:59–65

Dutch Lipid Clinic Network diagnostic criteria

1). FH | **2). Clinical History** | 3). Exam | 4). LDL-C | 5). DNA

Criteria	Points
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

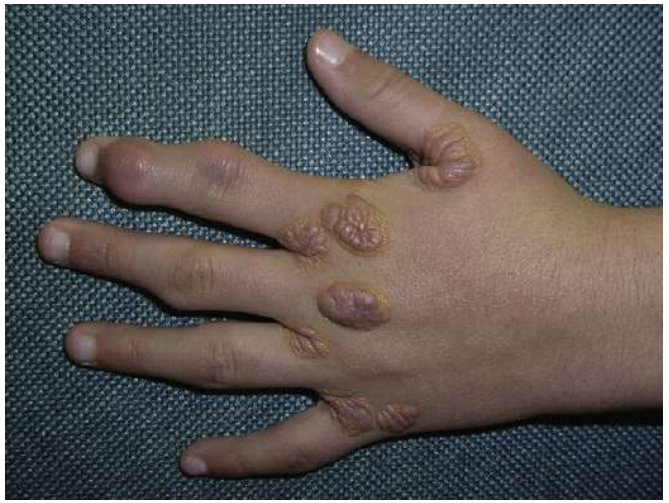
Semin Vasc Med 2004;4:59–65

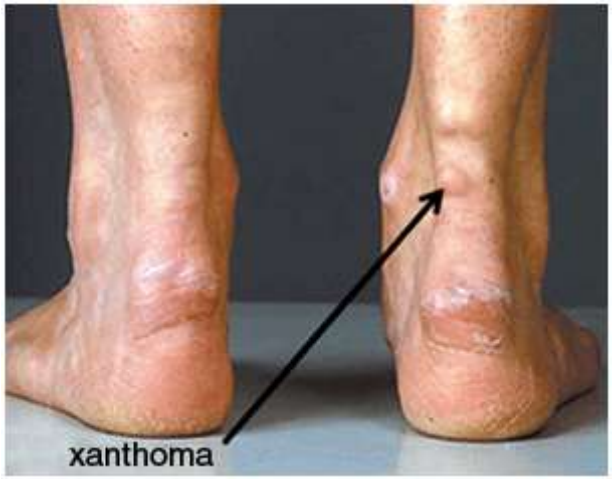
Dutch Lipid Clinic Network diagnostic criteria

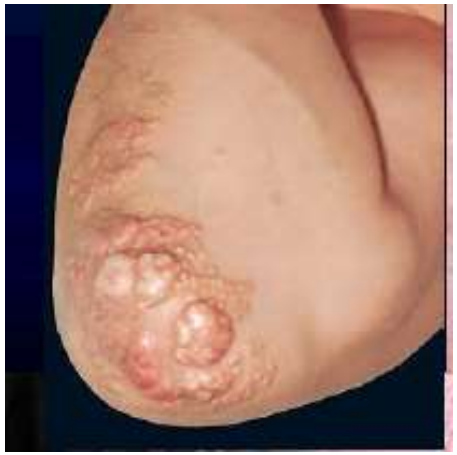
1). FH | 2). Clinical History | **3). Exam** | 4). LDL-C | 5). DNA

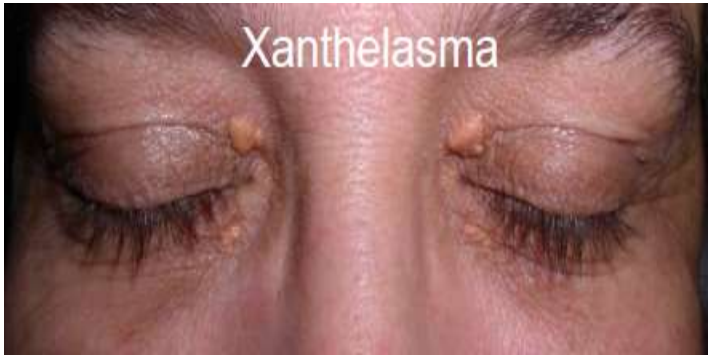
Criteria	Points
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4

Semin Vasc Med 2004;4:59–65

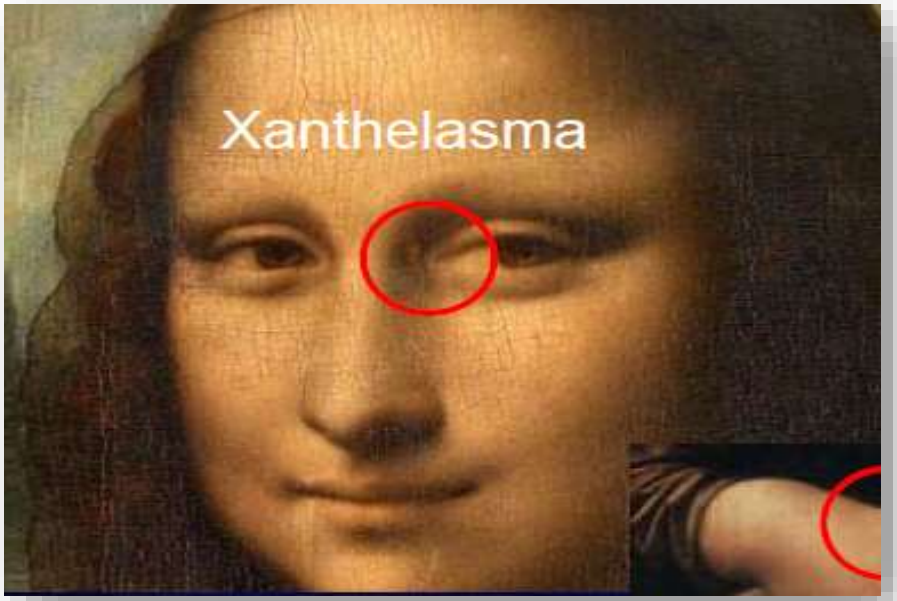



xanthoma




Xanthelasma

Did Mona Lisa have FH?



Curr Cardiol Rev. 2008 Feb; 4(1): 60–62.

Dutch Lipid Clinic Network diagnostic criteria

1). FH | 2). Clinical History | 3). Exam | **4). LDL-C** | 5). DNA

Criteria	Points
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

Semin Vasc Med 2004;4:59–65

Dutch Lipid Clinic Network diagnostic criteria

1). FH | 2). Clinical History | 3). Exam | 4). LDL-C | **5). DNA**

Criteria	Points
Functional mutation in the LDLR, apoB or PCSK9 gene	8

Genetic testing: when and why?

Table 22 Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia

Recommendations	Class [a]	Level [b]
Diagnosis is recommended to be confirmed with clinical criteria and, when available, with DNA analysis.	I	C

European Heart Journal (2016) 37, 2999–3058

Genetic testing: when and why?

- Borderline cases (eg, score >5)
- Cascade screening in family members

DD

- Polygenic hypercholesterolemia
- Familial combined hyperlipidemia
- Severe forms of secondary hypercholesterolemia (hypothyroidism, cholestasis)
- Type 3 hyperlipoproteinemia

Risk Stratification

- FH are high / very high risk patients

- No need to use cardiovascular risk calculators (eg, the European SCORE or the US Framingham Risk Score)

NICE, 2008
National Lipid Association Expert Panel, 2011

HoFH: screening for subclinical atherosclerosis

Aim: to monitor progression

- TTE (annually)
- CCTA (≤ 5 years)
- Stress test (±)
- Coronary catheter

Familial Hypercholesterolemia

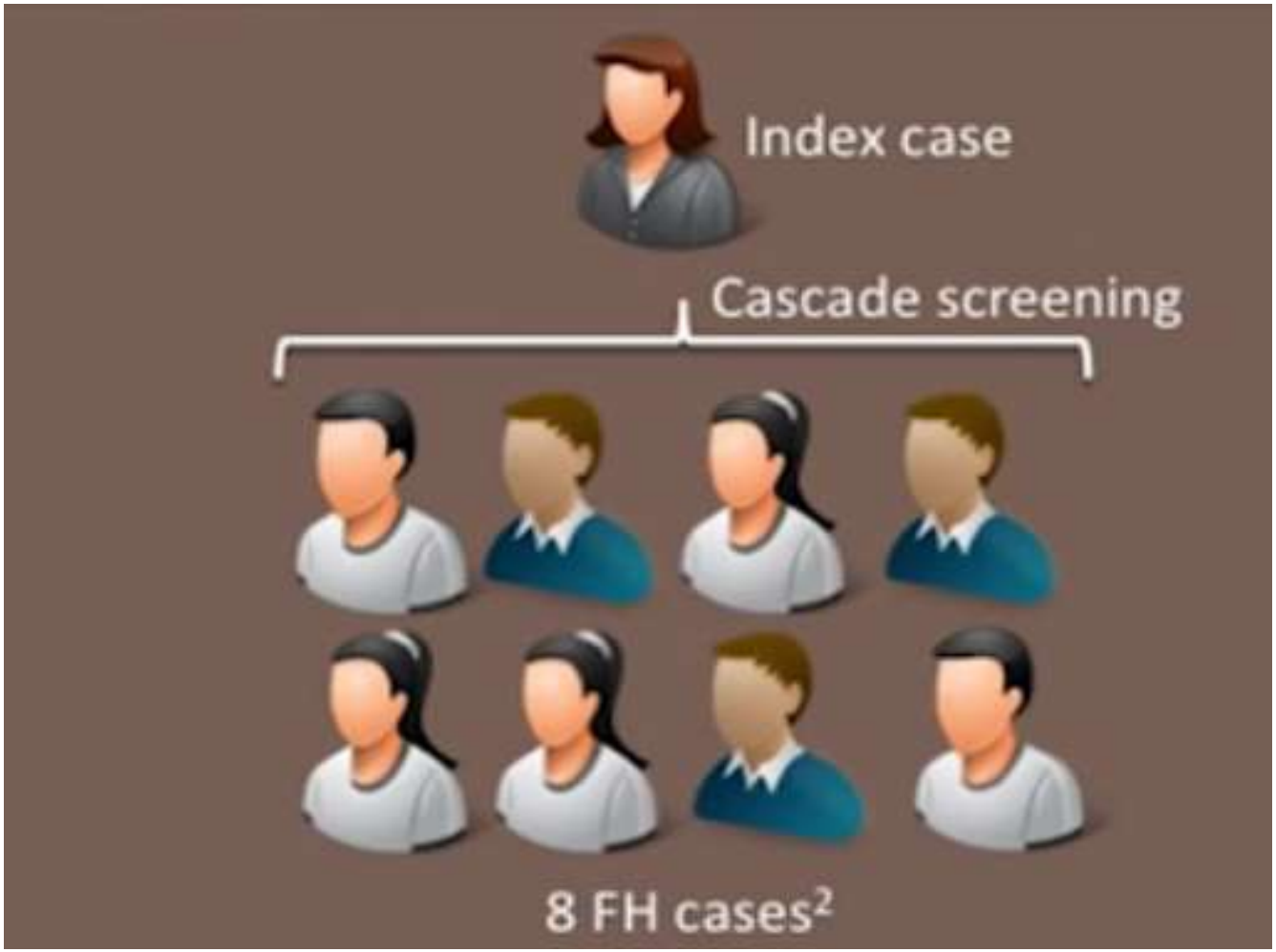
- Monogenic disorder (Briefing on genetics).
- Changing prevalence.
- Underdiagnosis.
- Increased lifetime CV risk.
- Diagnostic criteria (clinical / genetic).
- **Family screening.**
- Current management.

Cascade Screening

Family cascade screening is recommended to be performed when an index case of FH is diagnosed.	I	C

European Heart Journal (2016) 37, 2999–3058

Cascade Screening



Familial Hypercholesterolemia

- Monogenic disorder (Briefing on genetics)
- Changing prevalence
- Underdiagnosis
- Increased lifetime CV risk
- Diagnostic criteria (clinical / genetic)
- Family screening
- **Current management**

Life Style Modification

- Heart-healthy diet
- Exercise
- Risk factor modification: smoking ,obesity HTN, DM
- Aspirin

Pharmacotherapy

- No RCT
- As early as possible $^{8\text{-}10\ y}$ (time is plaque)
- Lipid specialist

Pharmacotherapy

- **LDL-C target:**

  Adults: < 100 mg/dl Children: < 135 mg/dl

  ASCVD: < 70 mg/dl

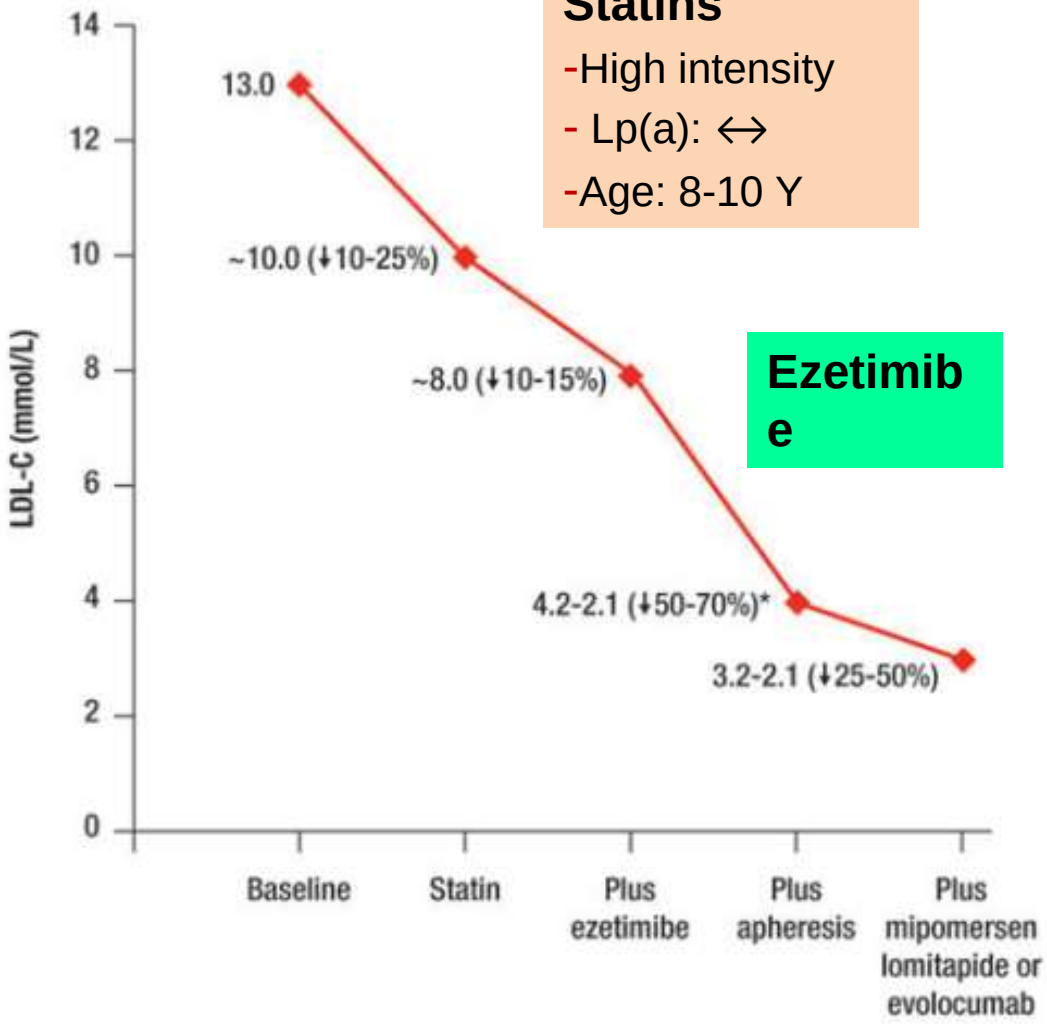
  If difficult: > 50% reduction

- **ASCVD risk factor:** < 70 mg/dl (ACC,2016)

- HTN
- DM
- Smoking
- CKD

- ↑ Lp(a)
- ↑CRP
- Subclinical atherosclerosis

Pharmacotherapy



Statins

-High intensity

- Lp(a): ↔

-Age: 8-10 Y

Ezetimibe

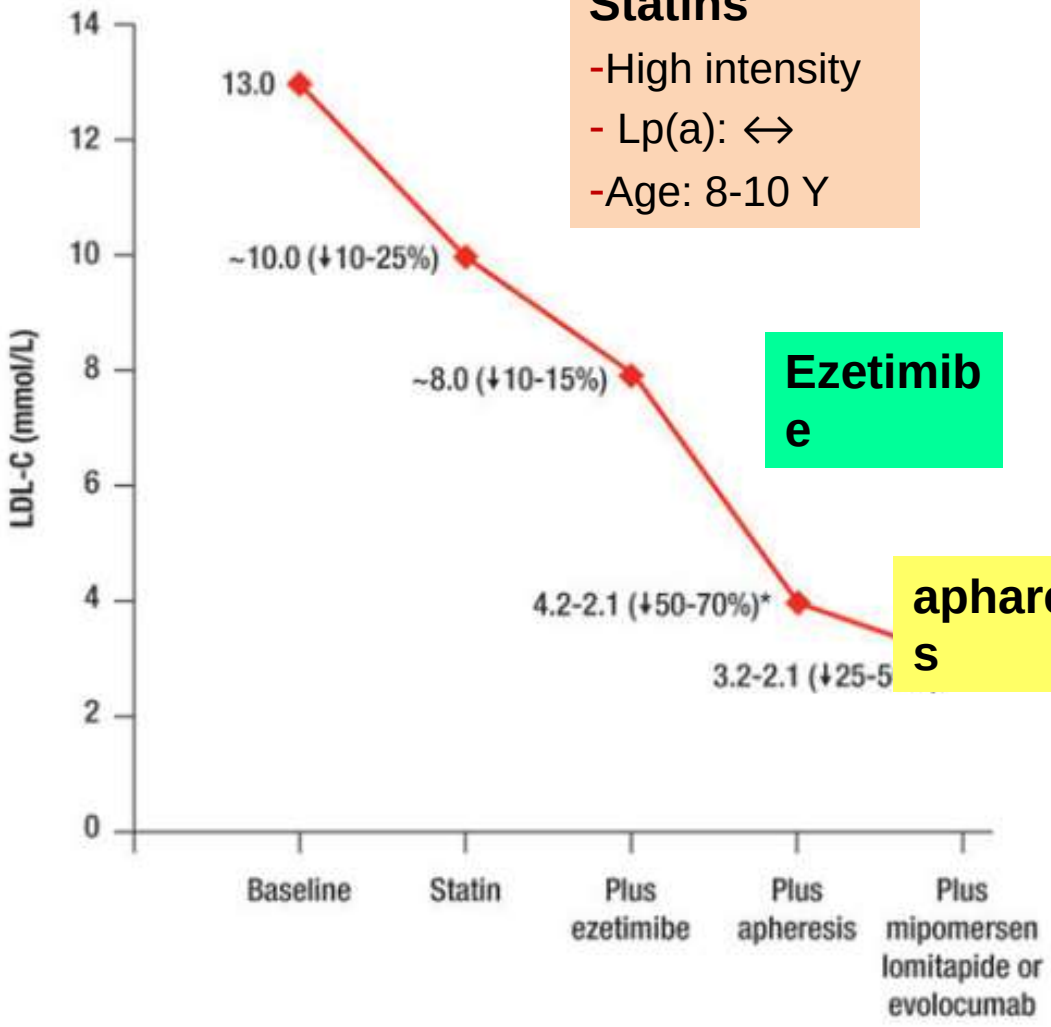
- BAS
- Niciacin
- Fibrates

Apharesis

- Plaque regression
- Lp(a): ↓
- Age: 5-8 years
- Cost: 8000$

Clin Res Cardiol Suppl 2012;7:7– 14

Pharmacotherapy



Statins

-High intensity

- Lp(a): ↔

-Age: 8-10 Y

Ezetimibe

- BAS
- Niciacin
- Fibrates

apharesis

- PCSK9 inhibitors
- Mipomersen
- Lomitapide

Clin Res Cardiol Suppl 2012;7:7– 14

Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: A large cross-sectional study in The Netherlands

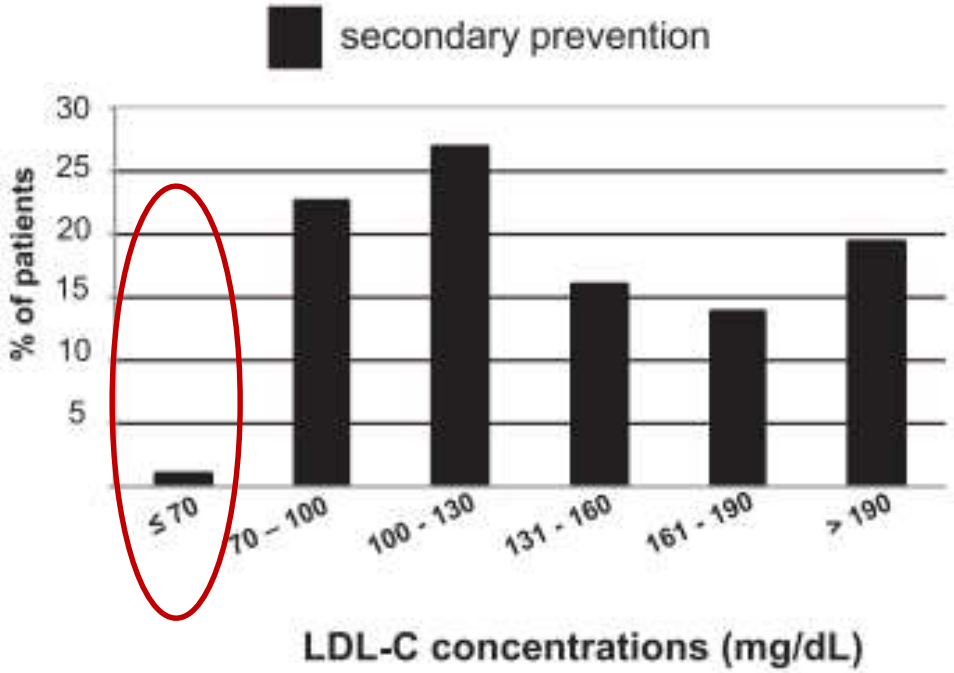
1,249 patients with heFH (96% on statins)

- Goal of LDL –C < 97.5 mg/dl: 21%
- Goal of >50% of LDL reduction: 47%

Atherosclerosis 209 (2010) 189–194

Improvement in LDL-cholesterol levels of patients with familial hypercholesterolemia: Can we do better? Analysis of results obtained during the past two decades in 1669 French subjects

616 HeFH patients treated after 2005



Atherosclerosis 234 (2014) 136e141

PCSK9 i: Effect on lipogram

	% Δ
LDL-C	↓ 40's-70's
Lp(a)	↓20-30%
HDL	↑ 5-10%
VLDL	↓5-20

PCSK9i: Indications

High risk patients:

- FH
- High CV risk

✓ Failed to achieve LDL-C target
✓ Adjunct to diet + maxim tolerated **statins**

- **Statin intolerance**

PCSK9 inhibitors

Table 22 Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia

Recommendations	Class [a]	Level [b]
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

European Heart Journal (2016) 37, 2999–3058

LDL apheresis

- FDA:

  Group A : homozygotes FH + LDL-C > 500 mg/dl
  Group B : heterozygotes FH + LDL-C ≥ 300 mg/dl
  Group C : heterozygotes FH + LDL-C ≥ 200 mg/dl + CAD

- Early initiation
- LDL-C reduction: 55-70%
- Plaque regression
- Frequency: every 1-2 week
- Limited by: cost; availability; SE

Remaining options

- Liver transplantation
- Partial ileal bypass
- Portocaval shunting
- Gene Therapy

Pregnancy

- **FH Mother**
  - Preconception cardiological evaluation
  - Discontinue all therapy; except BAS
  - LDL pharesis is safe
  - Monitor for LDL elevation

- **Child**

- 50% risk of FH
- LDL-C level at age of 2-5 years

Conclusions

Changing Face:

- FH is more frequent than we thought
- Marked genetic heterogeneity and phenotypic variability
- Overlapping spectra between: homoFH; heteroFH; severe polygenic HC

Conclusions

In Practice:

- Pharmacotherapy: early , aggressive
- High intensity statins + Ezetimibe
- Novel drugs (eg, PCSK9 inhibitors) are considered in difficult to treat / high risk patients
- Cascade screening: very effective (1:8)

Thank You…