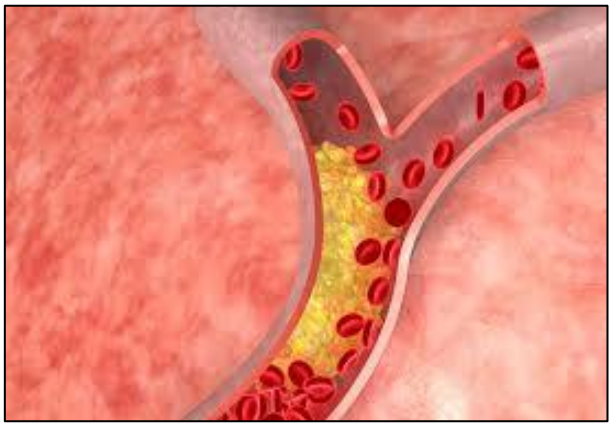
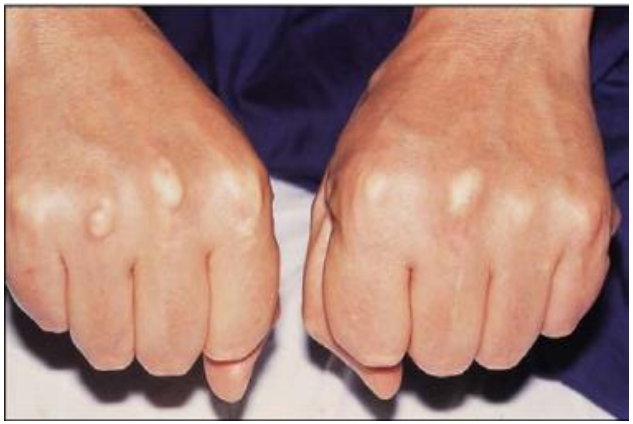




Familial hypercholesterolaemia

Jaimini Cegla MRCP FRCPath PhD
Consultant in Chemical Pathology
and Metabolic Medicine
Hammersmith Hospital Lipid Clinic

20 April 2017

An unrecognised, potentially fatal, treatable disease

- **Genetic disorder** – we know the genes involved
- **Common** –as Type 1 DM
- **50% men will have MI by age of 50 and 60% of women by age of 60**
- **Treatable**
- **Underdiagnosed**

Format

1. What is FH?
2. Genetics
3. Presentation
4. Diagnosis
5. Management
6. Homozygous FH
7. Cascade screening

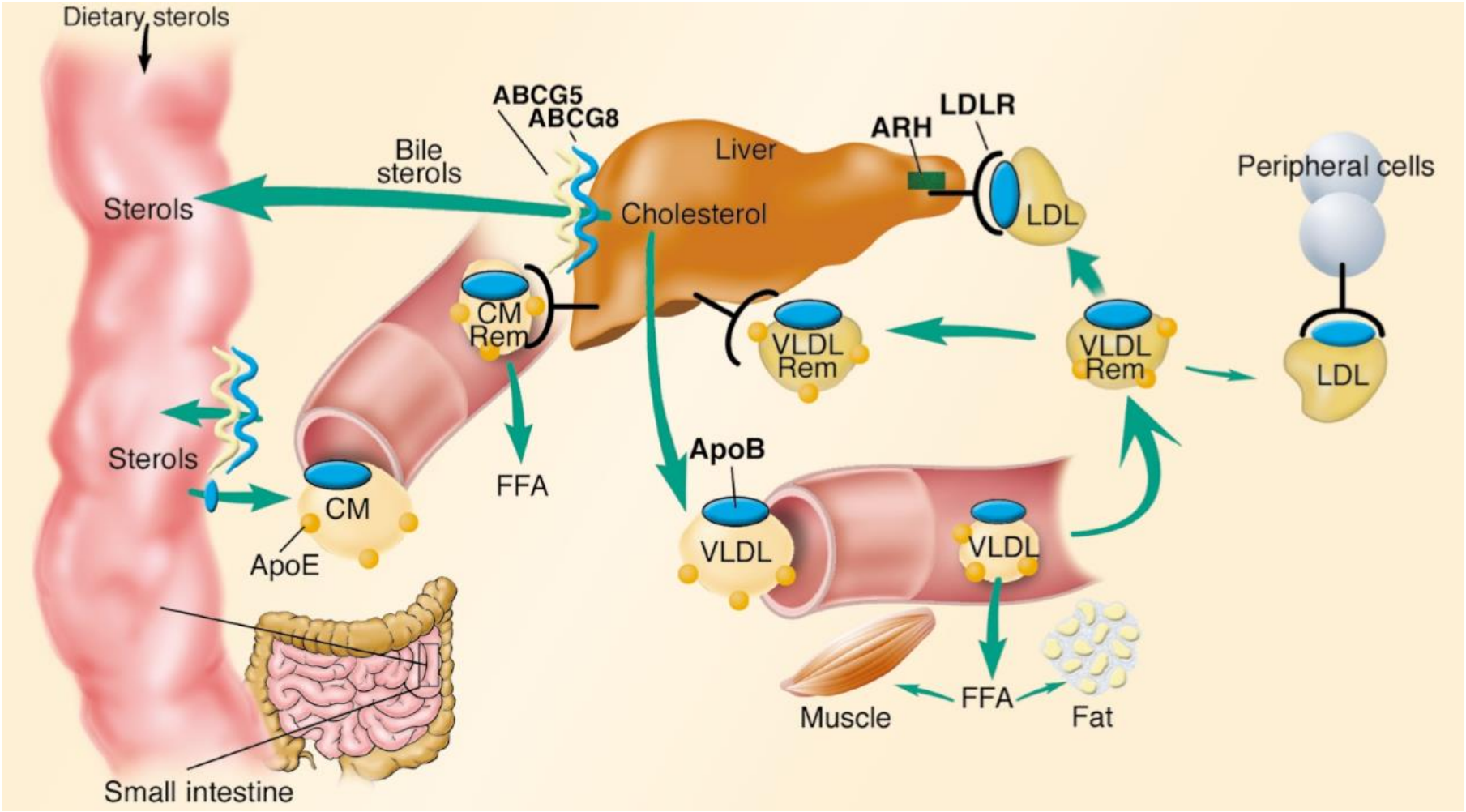
Familial hypercholesterolaemia

- The most common dominantly inherited disorder
- Autosomal dominant disorder
- High levels of low density lipoprotein cholesterol
- Early coronary artery disease
- Heterozygous ~1 in 500
- Homozygous ~1/1,000,000

What is LDL?


Lipoprotein
Chylomicron
Apolipoprotein
Phospholipid
Triglycerides
Cholesterol ester
Unesterified cholesterol
VLDL
LDL
HDL
IDL

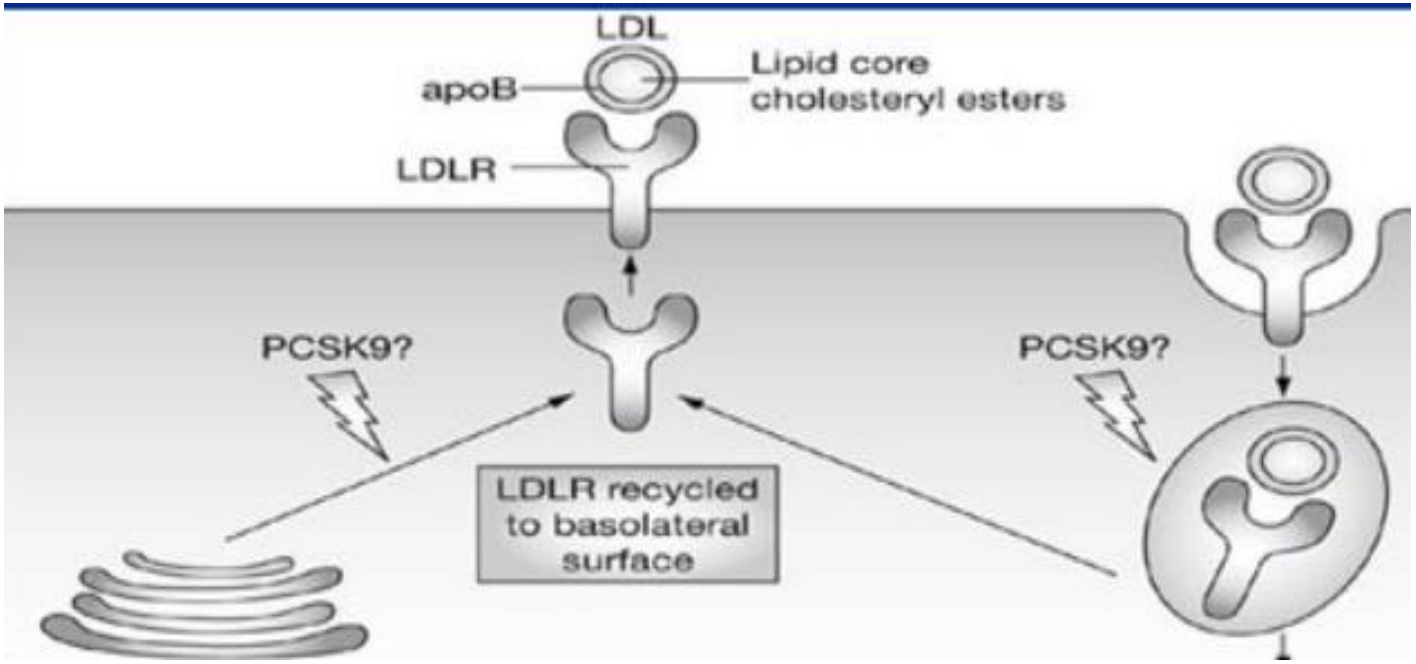
LDL metabolism



Hobbs et al; J Clin Inv, 2003

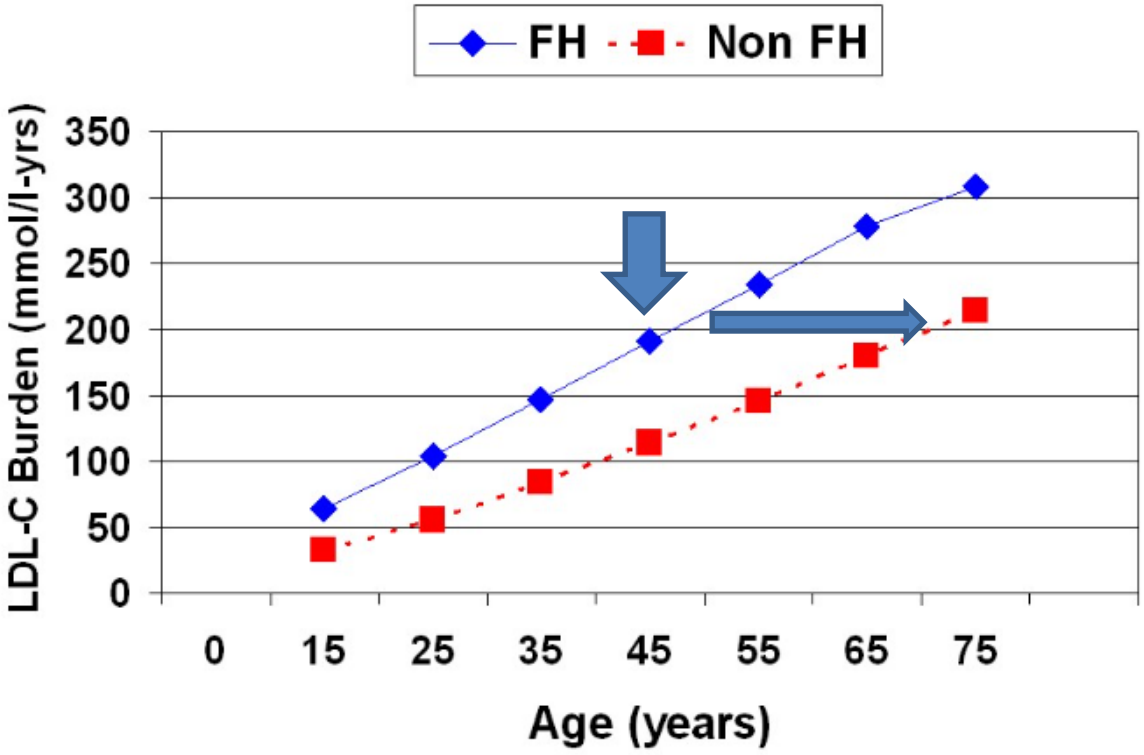
Genetics of FH

- Mutations in 3 genes:
  - Low-density lipoproteins receptors gene (LDLR)
  - Apoliprotein B-100 gene (APOB)- involved in LDLR binding
  - Proprotein convertase subtilisin/kexin type (PCSK9) – cholesterol homeostasis



Why do FH patients have such premature CHD?

FH patients have high LDL-C from Birth → high LDL-C BURDEN

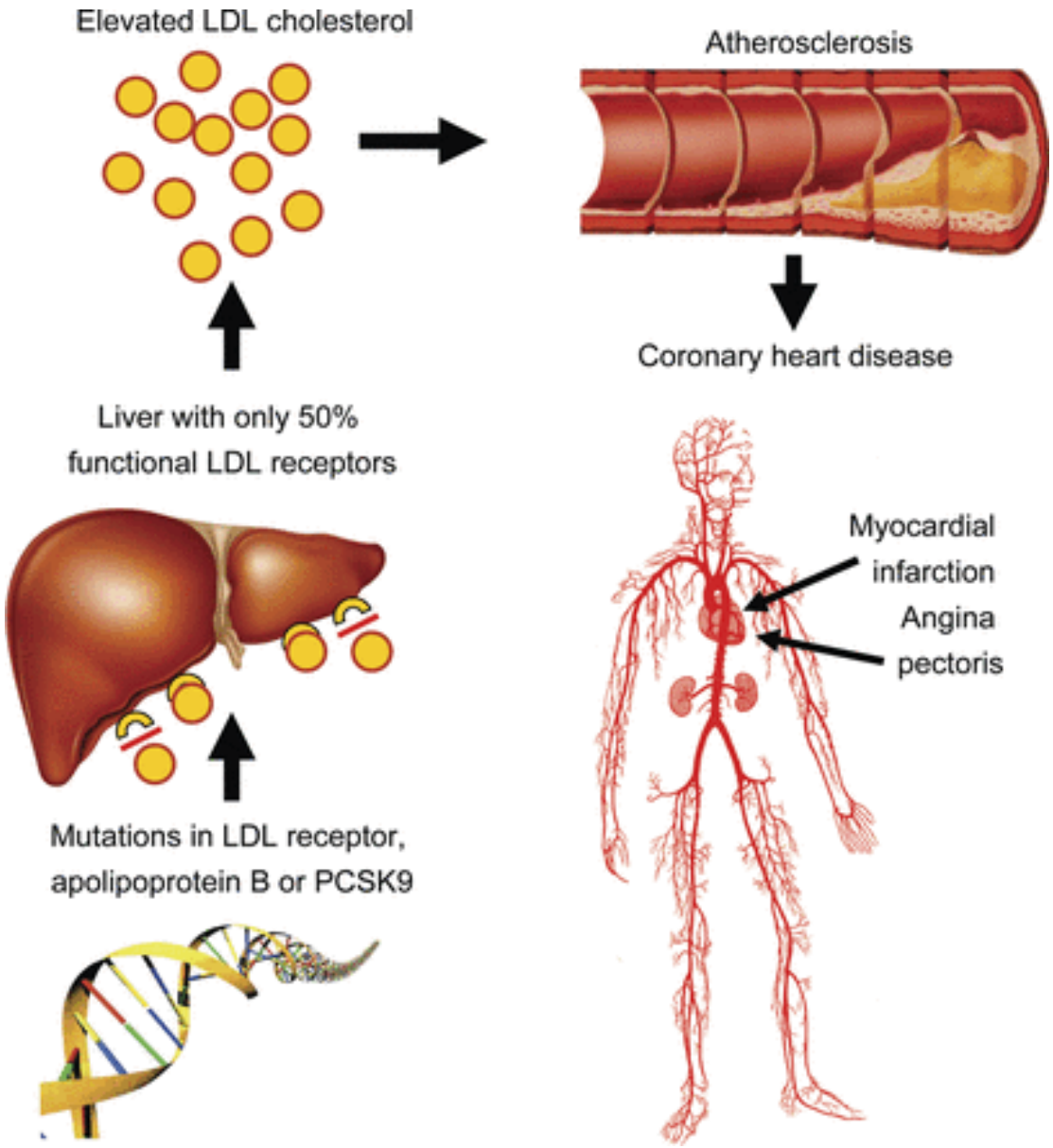


LDL-Burden = LDL-C level x years exposure

Like smoking pack-years

By 45y FH patient has accumulated LDL-C exposure of non-FH 70y old, explaining high CHD risk and need for aggressive lipid-lowering

Starr et al; 2008



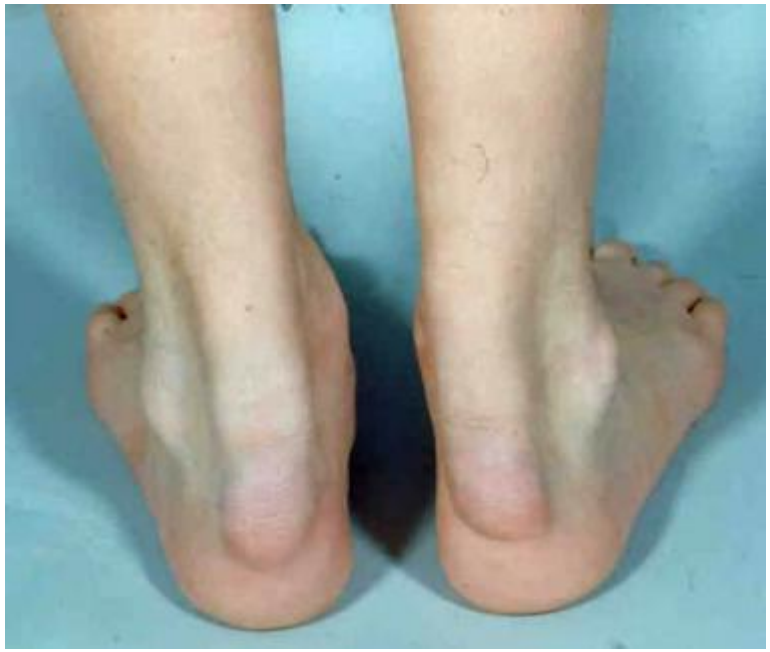
Nordestgaard et al; Eur Heart J, 2013

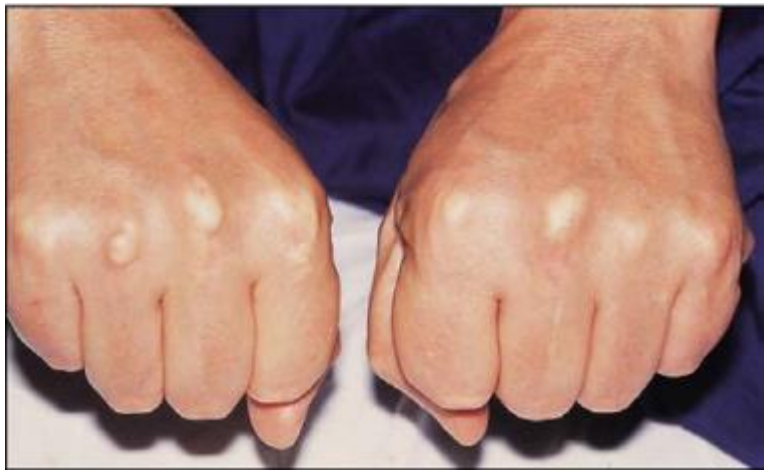
Presentation

- After a CV event
- Routine cholesterol testing
- Cascade screening
- Via dermatology clinic

Presentation

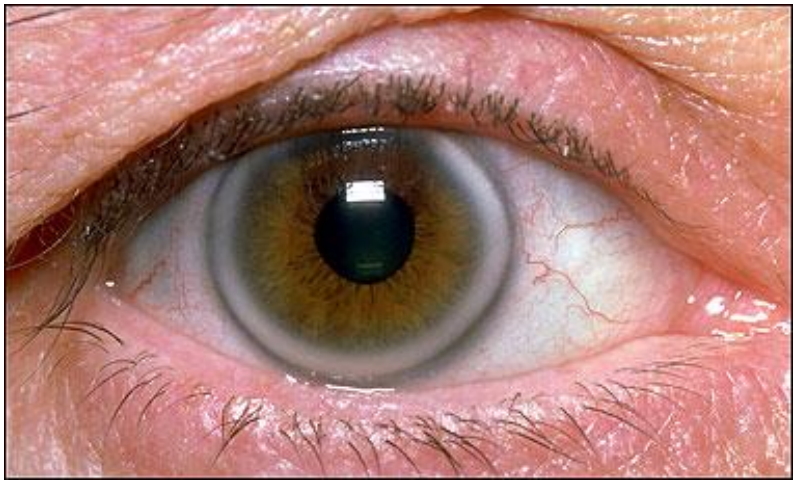
- Cholesterol 7.0-14 mmol/L
- tendon xanthomata are virtually diagnostic of heterozygous familial hypercholesterolaemia, and occur in about 70% of affected individuals after the age of 20 years

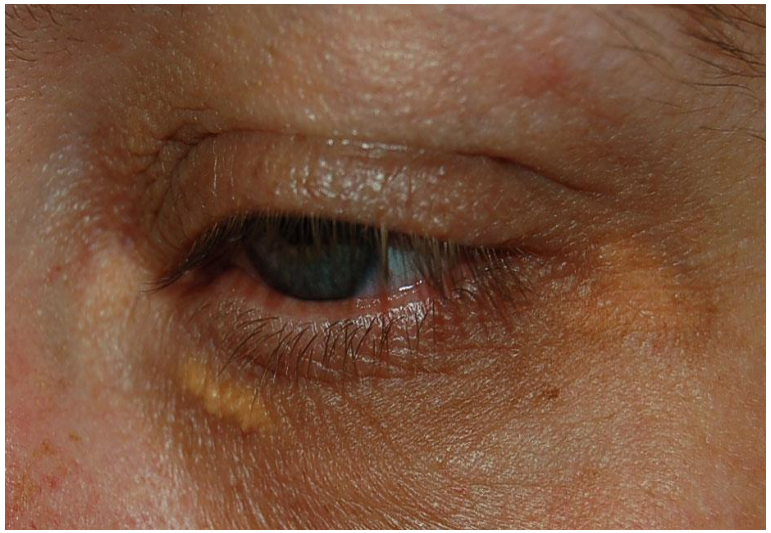


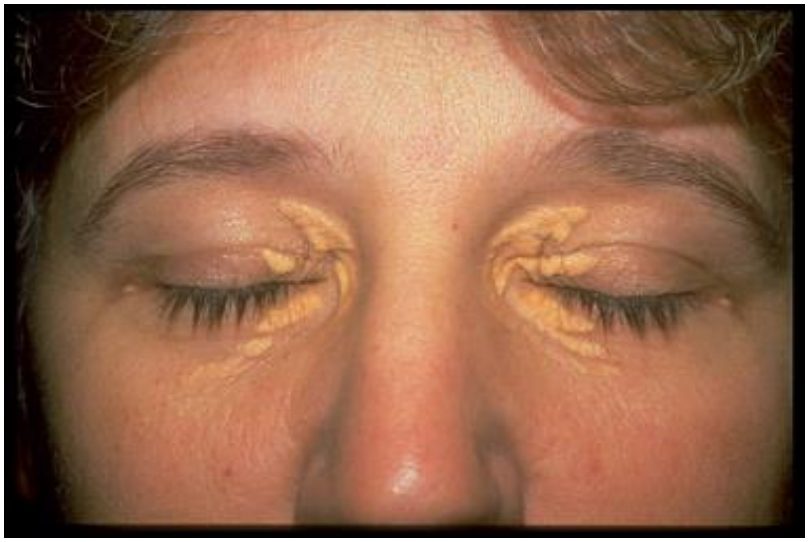


Presentation

xanthelasma and premature corneal arcus are commonly found but are less specific signs.







Diagnosis

- Exclude secondary causes of hypercholesterolaemia
- Phenotypic and/or genetic testing
- Genetic testing increases diagnostic accuracy

Simon-Broome criteria

Definite FH:

- TC > 6.7 mmol/l or LDL-C >4.0 mmol/l (child <16y)
  or TC > 7.5 mmol/l or LDL-C >4.9 mmol/l (adult)
  (levels either pre-treatment or highest on treatment)

plus

- tendon xanthomas in patient, or in 1° relative (parent, sibling, child), or in 2° relative (grandparent, uncle, aunt)

or

- DNA-based evidence of an LDL receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Possible FH is defined as above lipids plus one of:

- family history of myocardial infarction: below age of 50 years in 2° relative or below age 60 years in 1° relative

or

- family history of raised TC >7.5 mmol/l in adult 1° or 2° relative or > 6.7 mmol/l in child or sibling <16y

Genetic testing

- Offer ideally to all index cases who have a phenotypic diagnosis of FH
- Genetic testing must be carried out in an accredited laboratory
- If genetic testing detects a variant, its pathogenic significance needs to be assessed
- If genetic testing does not detect a variant, FH **cannot** be excluded, particularly if clinical phenotype is strongly suggestive of FH

Assess additional CVD risk factors

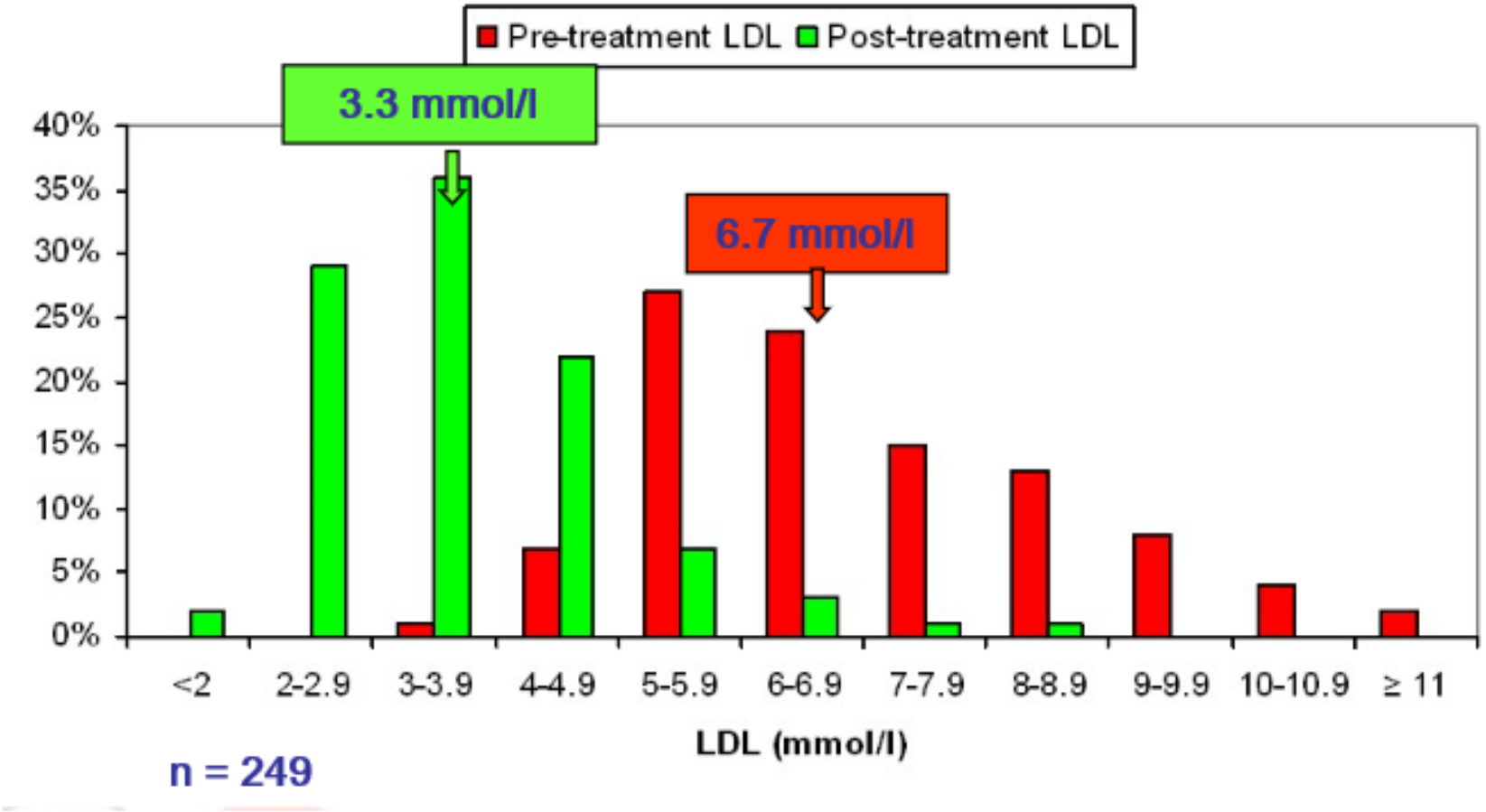
- Presence of additional CVD risk factors should guide the intensity of management
  - Hypertension, diabetes, obesity, smoking
  - Lipoprotein(a)
  - Level and duration of untreated LDL cholesterol
  - Prematurity of the family & personal history of CVD
  - **Framingham and other CVD risk equations should <u>not</u> be used**

- Cardiovascular imaging may be useful for assessing asymptomatic patients
  - Cardiac computed tomography
  - Carotid ultrasonography
  - Clinical value of imaging not fully established

Management

- Lifestyle modification
- LDL lowering drugs
- LDL-Apheresis

Can LDL be lowered in FH patients?

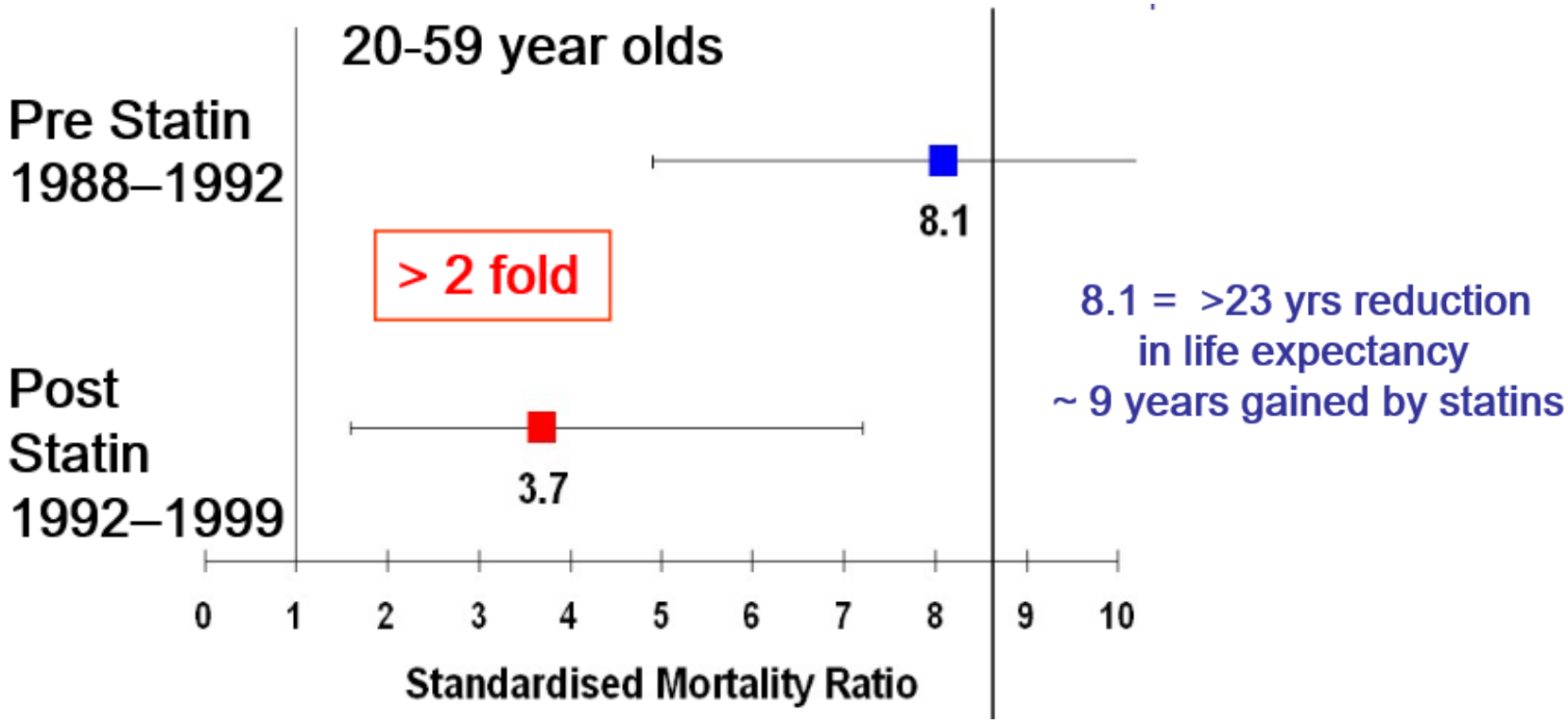


Hadfield et al; 2007

LDL-lowering

- Therapy should ideally aim for at least 50% reduction in plasma LDL cholesterol, followed by
  - LDL cholesterol < **2.5** mmol/L (no CVD or other risk factors)
  - LDL cholesterol < **1.8** mmol/L (with CVD or other risk factors)
- Statin therapy - monitor hepatic aminotransferases, glucose and creatinine
- Drug combinations
  - ezetemibe
  - bile acid sequestrants
  - PCSK9 inhibitors

Statins decrease mortality in FH



Simon Broome UK FH Registry papers; Athero, 1999

LDL-lowering in women

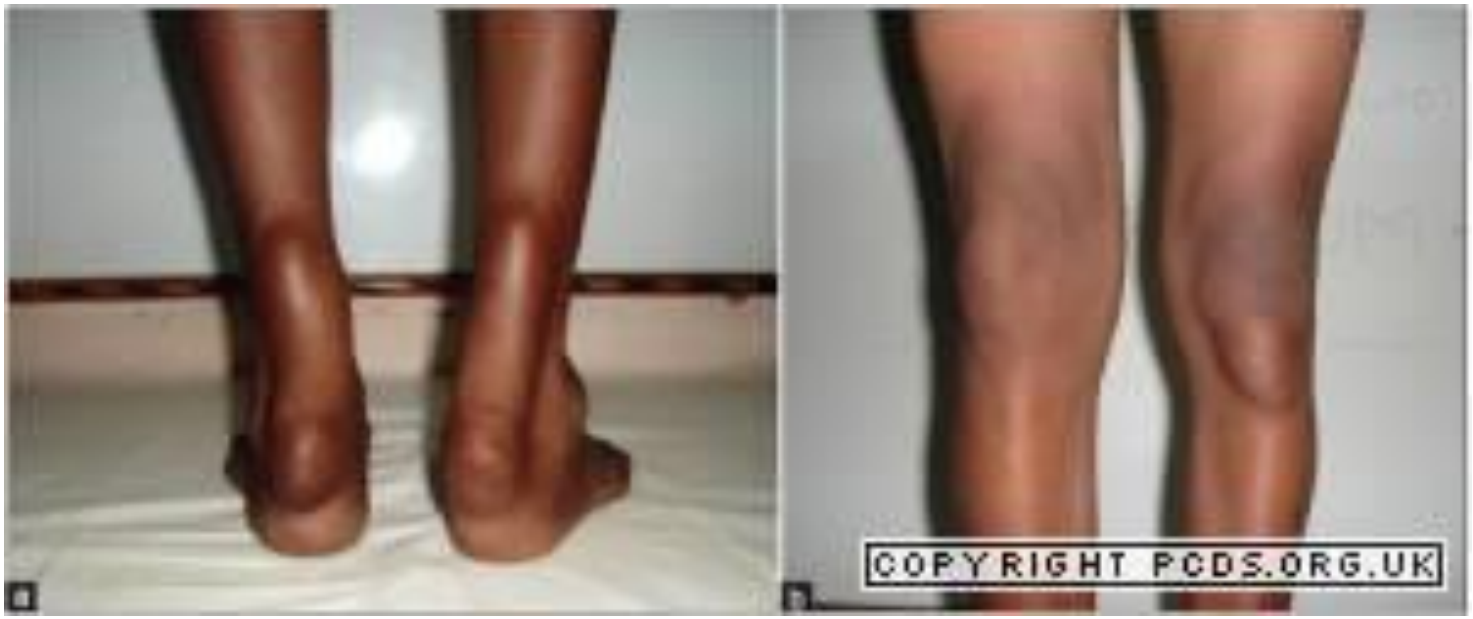
- All women of child-bearing age should receive pre-pregnancy counselling
  - Appropriate advice on contraception before starting a statin
- Statins and other systemically absorbed lipid regulating drugs should be discontinued 3 months before conception, as well as during **pregnancy** and **lactation**
- Menopausal hormone therapy should be avoided in women

Lipoprotein apheresis

- LA should be considered in patients with heterozygous FH with CHD who cannot achieve LDL cholesterol targets or have progressive disease despite maximal drug therapy

Homozygous FH

- Cholesterol 10-28 mmol/L
- Two major genetic defects in LDL metabolism
- Tendon and cutaneous xanthomas often before age 10 years
- CHD onset in childhood
- Poorly responsive to drugs; apheresis often indicated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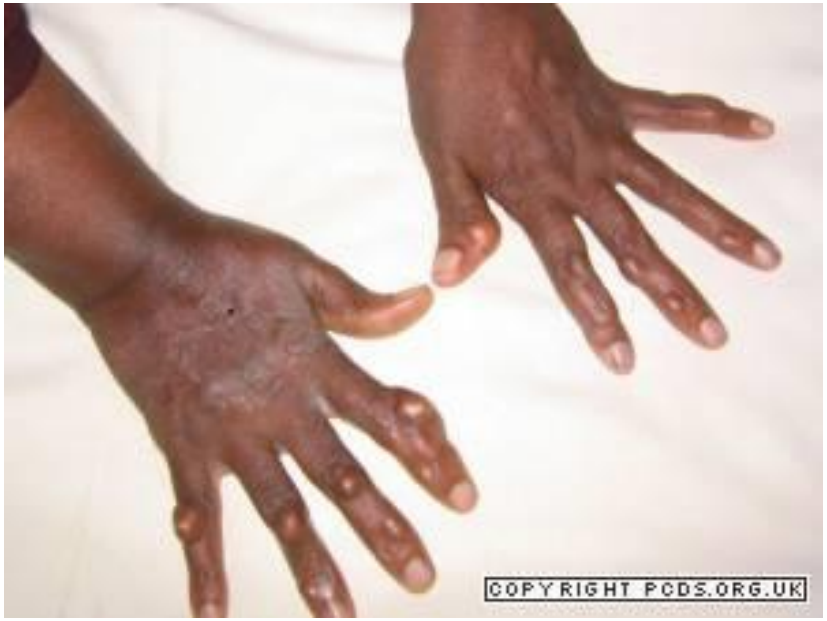
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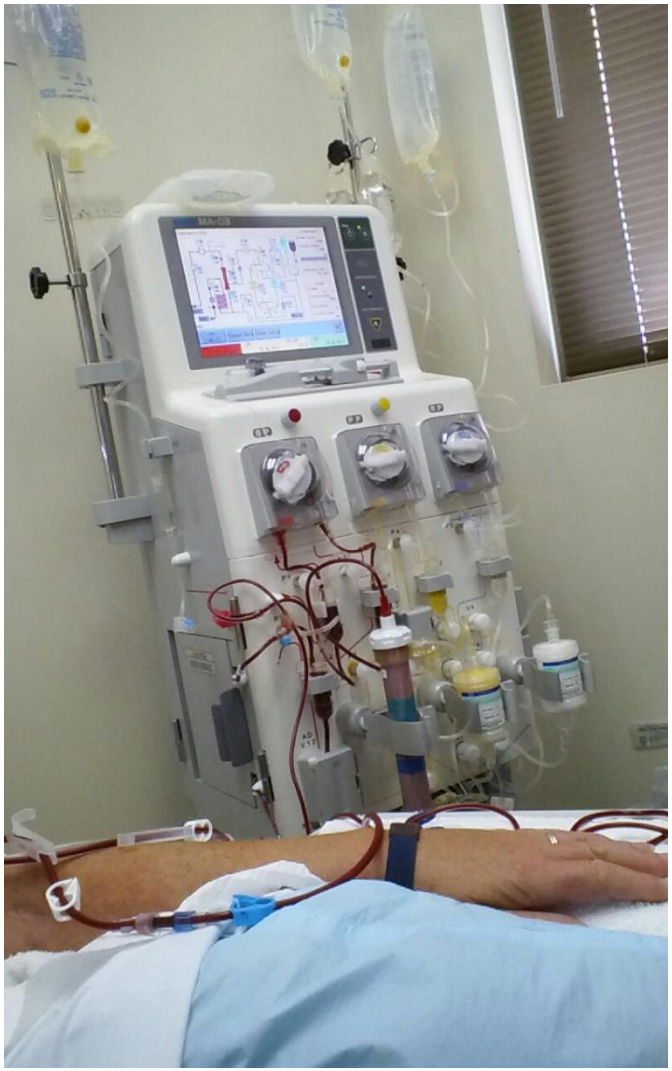
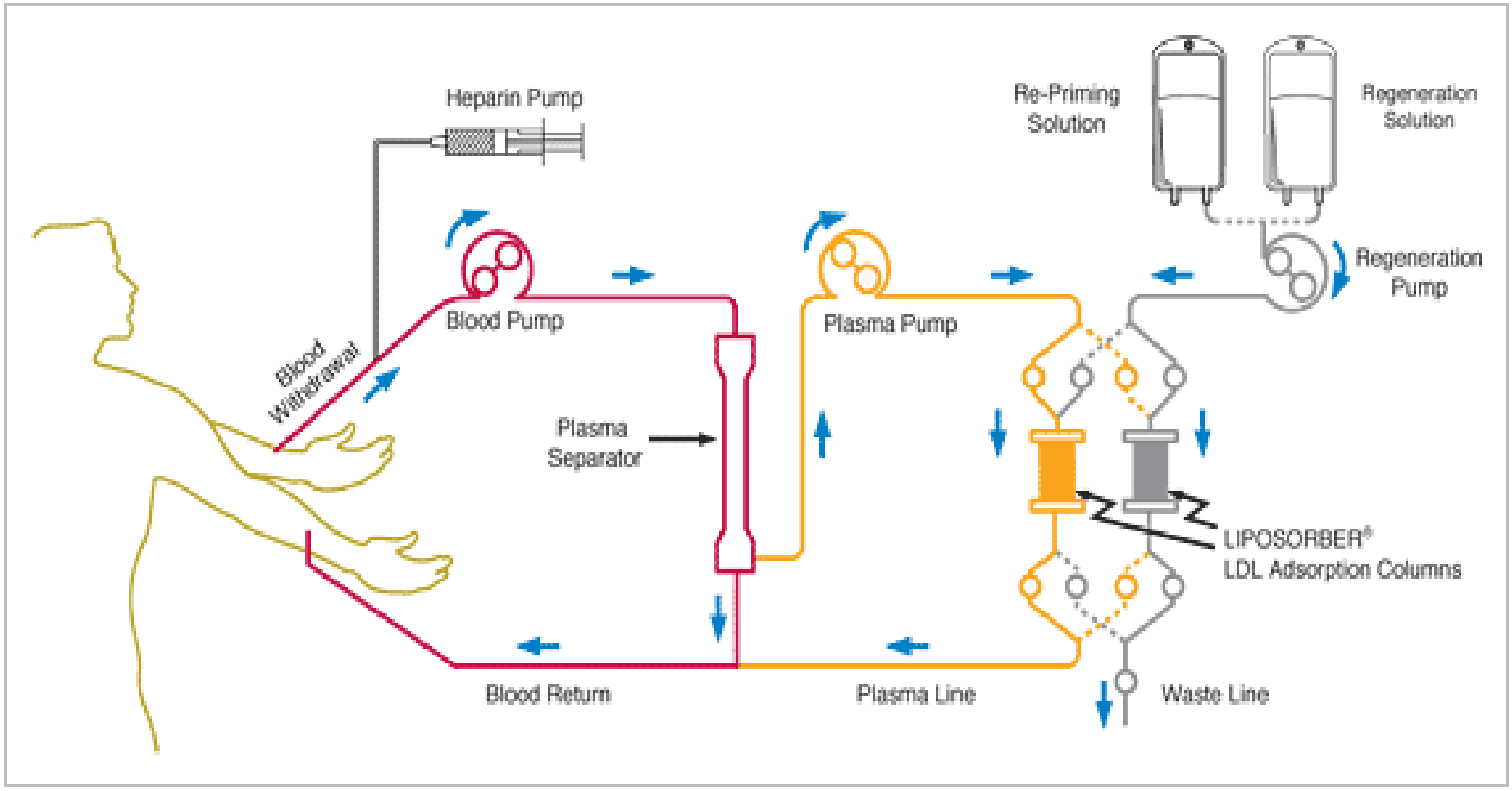
Lipoprotein apheresis

- Lipoprotein apheresis should be considered in all patients with homozygous or compound heterozygous FH
- Apheresis should be considered in children with homozygous FH by the age of 5 and no later than 8 years



Lipoprotein apheresis how it works



New therapies on the horizon

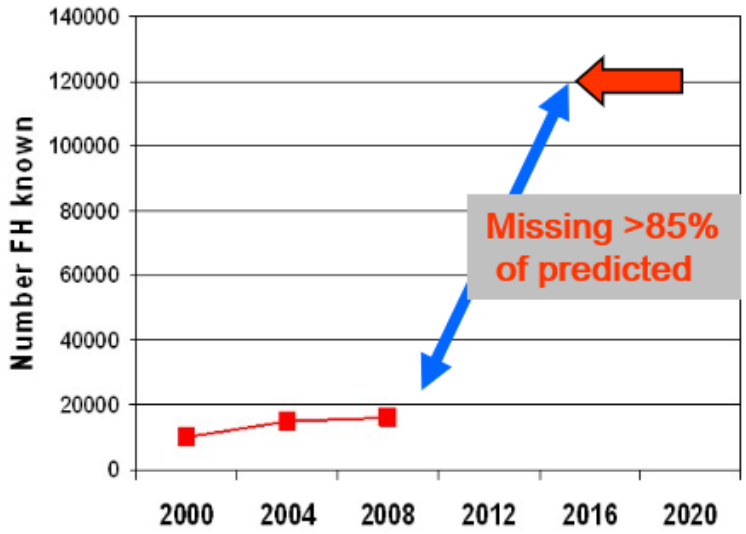
- Lomitapide should be considered as adjunctive treatments to diet and cholesterol lowering drugs in adults with homozygous FH
- Experience with these agents in patients on lipoprotein apheresis is limited

Cascade screening

It is Common - Frequency FH ~1/500 → 120,000 in UK

Same as childhood diabetes

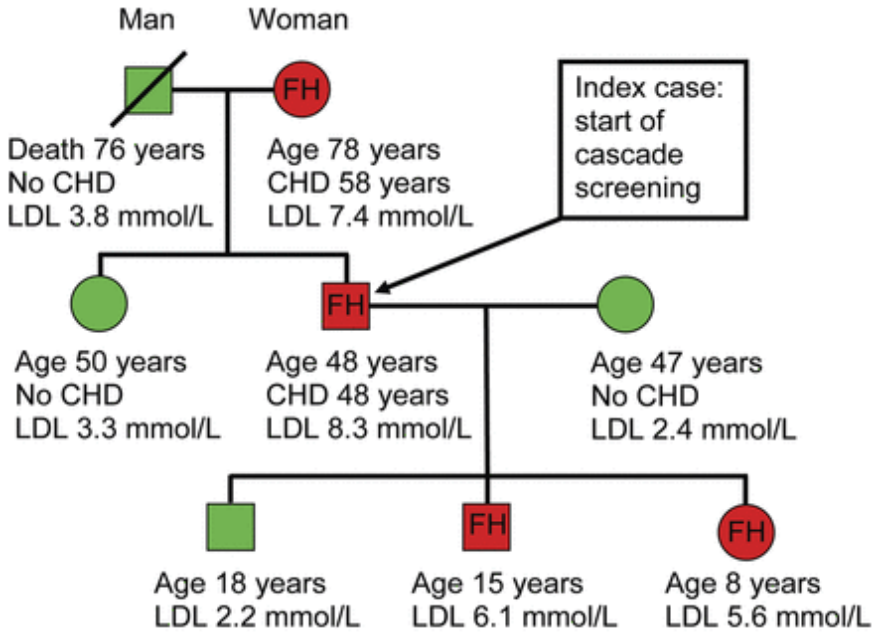
It is underdiagnosed < 15,000 known, particularly in the < 35 years group (600/14,000 children)



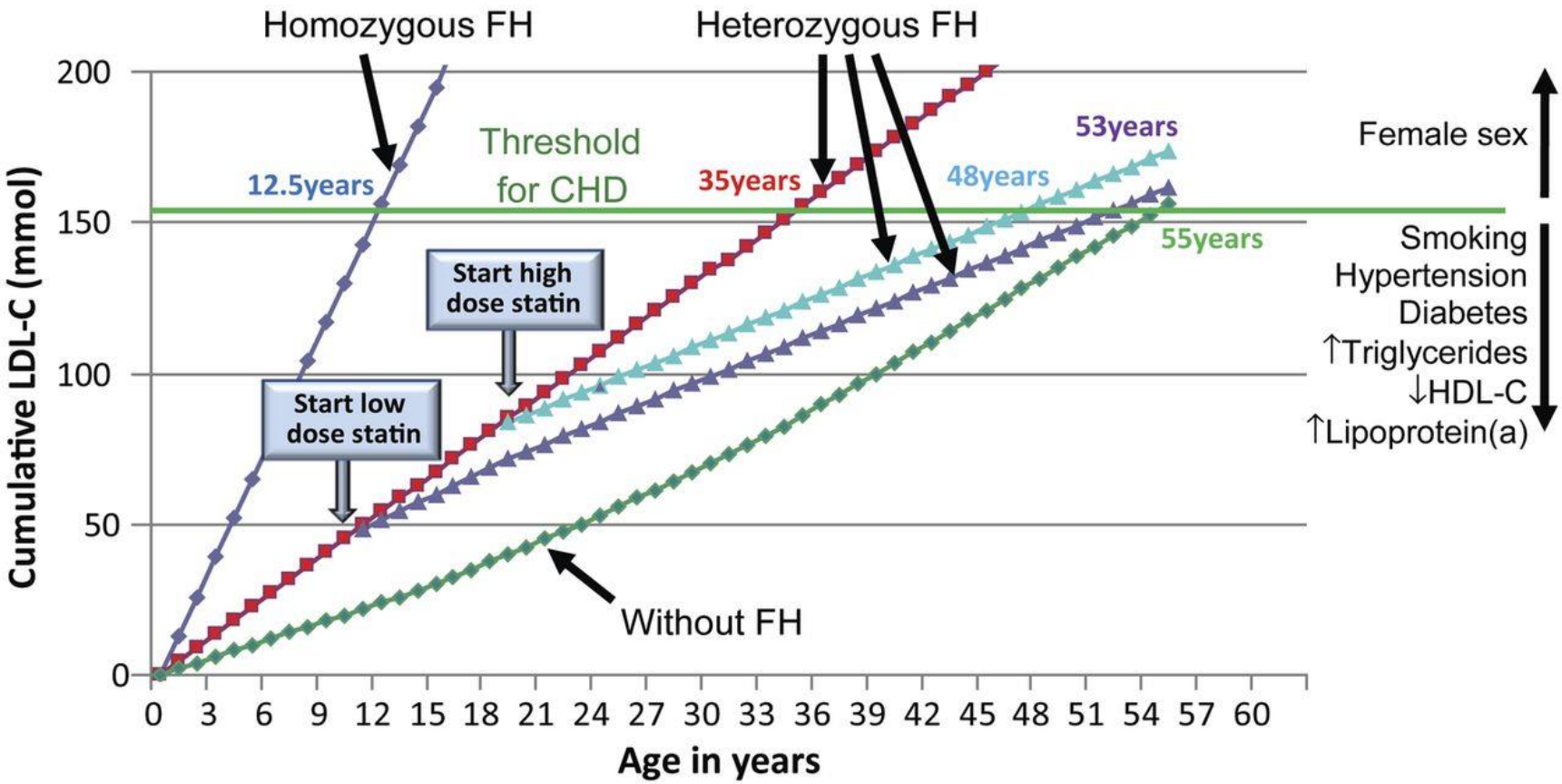
Marks, et al 2004
HEARTUK 2008
Neil, et al BMJ 2000

Cascade screening

- 85% of affected individuals remain undiagnosed



Nordestgaard et al; Eur Heart J, 2013



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