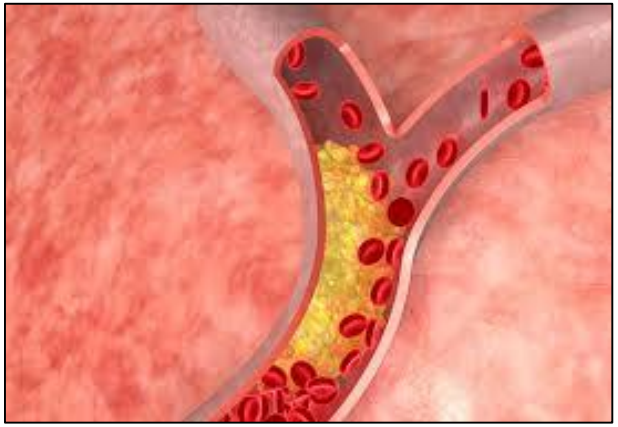
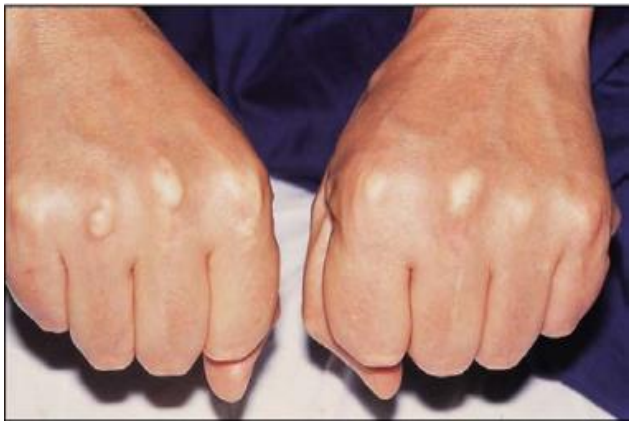




Lipids for Medics in Primary Care

Jaimini Cegla MRCP FRCPath PhD, Consultant in Metabolic Medicine
Hammersmith Hospital Lipid Clinic, Imperial College Healthcare NHS Trust

September 2018

Format

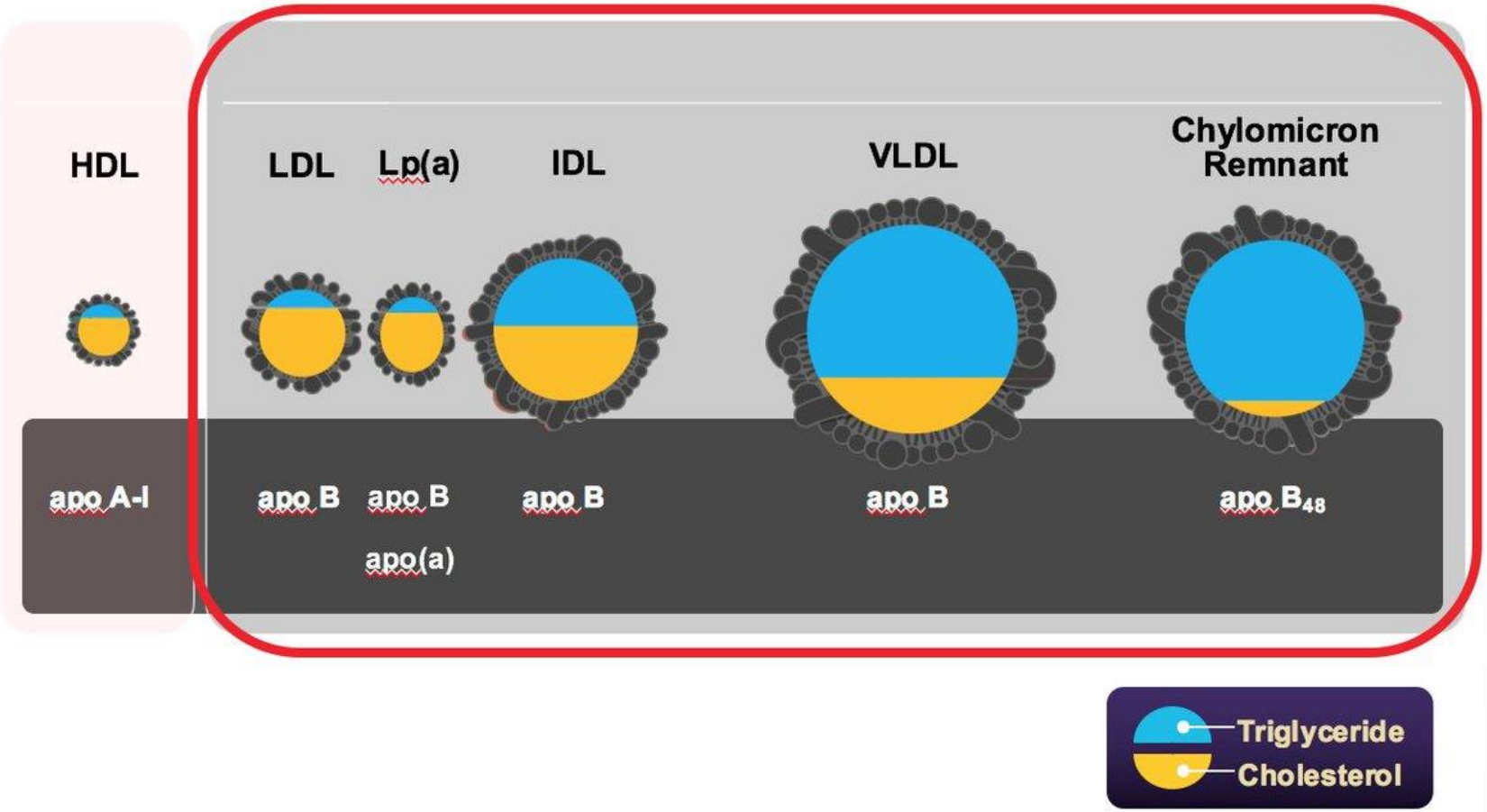
1. **CV Risk and lipid lowering**
2. **Familial Hypercholesterolaemia**
3. **Hypertriglyceridaemia**
4. **Lipoprotein(a)**

Case 1

- 59 year old male
- Barrister
- Asymptomatic
- No Family History of CVD

- Total cholesterol 7.2 mmol/L
- HDL-c 1.4 mmol/L
- LDL 4.1 mmol/l
- TG 1.4 mmol/l
- Non-HDL 5.8 mmol/l

Non-HDL-C captures cholesterol in all atherogenic (apoB-containing) lipoproteins



Non-HDL-C = Total cholesterol – HDL-C

Case 1

- 59 year old male
- Barrister
- Asymptomatic
- No Family History of CVD
- Total cholesterol 7.2 mmol/L
- HDL-c 1.4 mmol/L
- LDL 4.1 mmol/l
- TG 1.4 mmol/l
- Non-HDL 5.8 mmol/l

Does he need a statin?

NICE National Institute for Health and Care Excellence

Cardiovascular disease: risk assessment and reduction, including lipid modification

Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. **[new 2014]**

http://www.jbs3risk.com/pages/risk_calculator.htm

Obviously:

- Exclude secondary causes of hypercholesterolaemia
  (drugs, hypothyroidism, nephrotic syndrome, anorexia etc)

Do not use a risk assessment tool in people with:

- Secondary prevention
- type 1 diabetes
- eGFR less than 60 and/or albuminuria
- familial hypercholesterolaemia

Underestimates risk in people:

- treated for HIV
- with serious mental health problems
- taking medicines that can cause dyslipidaemia
  (eg antipsychotics, steroids or immunosuppressant)
- with autoimmune disorders such as SLE

JBS3 Cardiovascular Risk Assessment

Credits | Full Screen

Profile | Heart Age | Healthy Years | Outlook | more

Profile

Date of Birth: Day 8 | Month 12 | Year 1957

Gender: male / female

Ethnic group: White or not stated

Height (m): 1.80 (5' 11" (71.0"))

Weight (kg): 84.2 (13st 3.5 (185.5 lb))

BMI: 26.0

Townsend quintile (3 if unknown): 3: Average

I have never suffered from Cardiovascular Disease ☑

I have read the terms and conditions ☑

Do you smoke? I quit

Total Cholesterol: 7.2 mmol/L

HDL Cholesterol: 1.4

NonHDL Cholesterol: 5.8

Systolic Blood Pressure: 130 mm Hg

Have you received blood pressure treatment? ☐

Do you suffer from diabetes? ☐

Does a close relative under 60 suffer from CVD? ☐

Do you have a chronic kidney disease? ☐

Have you suffered atrial fibrillation? ☐

Do you have rheumatoid arthritis? ☐

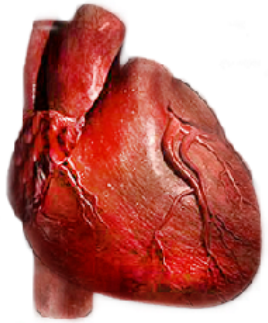
Save | Load | Next

JBS3 Cardiovascular Risk Assessment

Credits | Full Screen

Profile | Heart Age | Healthy Years | Outlook

more



Your heart age is about

66

compared to a person of the same age, gender and ethnicity with optimal risk factors

Interventions

Future smoking category

I quit

Systolic Blood Pressure

130 → 130

Total Cholesterol

7.2 → 7.2

HDL Cholesterol

1.4 → 1.4

NonHDL Cholesterol: 5.8

BMI: 26.0

Reset

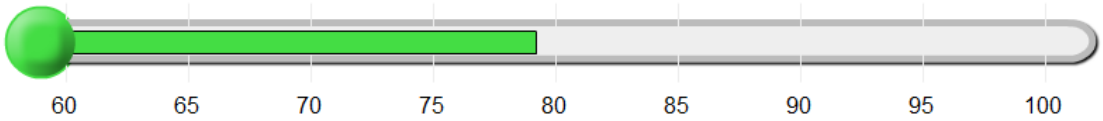
JBS3 Cardiovascular Risk Assessment

Credits | Full Screen

Profile | Heart Age | Healthy Years | Outlook

more

On average, expect to survive to age 79 without a heart attack or stroke



expected life without a heart attack or stroke

Your risk of a heart attack or stroke in the next 10 years is

11%

assuming you don't die of anything else

Interventions

Future smoking category

I quit

Systolic Blood Pressure

130 → 130

Total Cholesterol

7.2 → 7.2

HDL Cholesterol

1.4 → 1.4

NonHDL Cholesterol: 5.8

BMI: 26.0

Reset

JBS3 Cardiovascular Risk Assessment

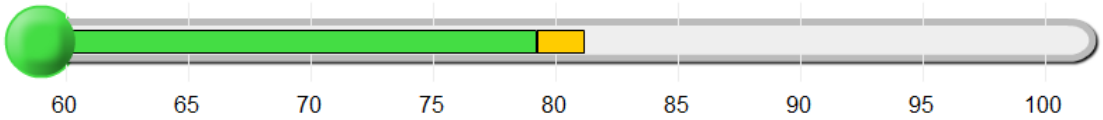
Credits | Full Screen

Profile | Heart Age | Healthy Years | Outlook

more

On average, expect
to survive to age 81
without a heart attack or stroke

gaining 2.0 years through interventions



expected life without a heart attack or stroke

Your risk of a heart attack or stroke
in the next 10 years is

6.4%

assuming you don't die of anything else

Interventions

Future smoking category

I quit

Systolic Blood Pressure

130 → 130

Total Cholesterol

7.2 → 4.1

HDL Cholesterol

1.4 → 1.4

NonHDL Cholesterol: 2.7

BMI: 26.0

Reset

- **What target lipids are we aiming for?**

Targets??

NICE National Institute for Health and Care Excellence

Cardiovascular disease: risk assessment and reduction, including lipid modification

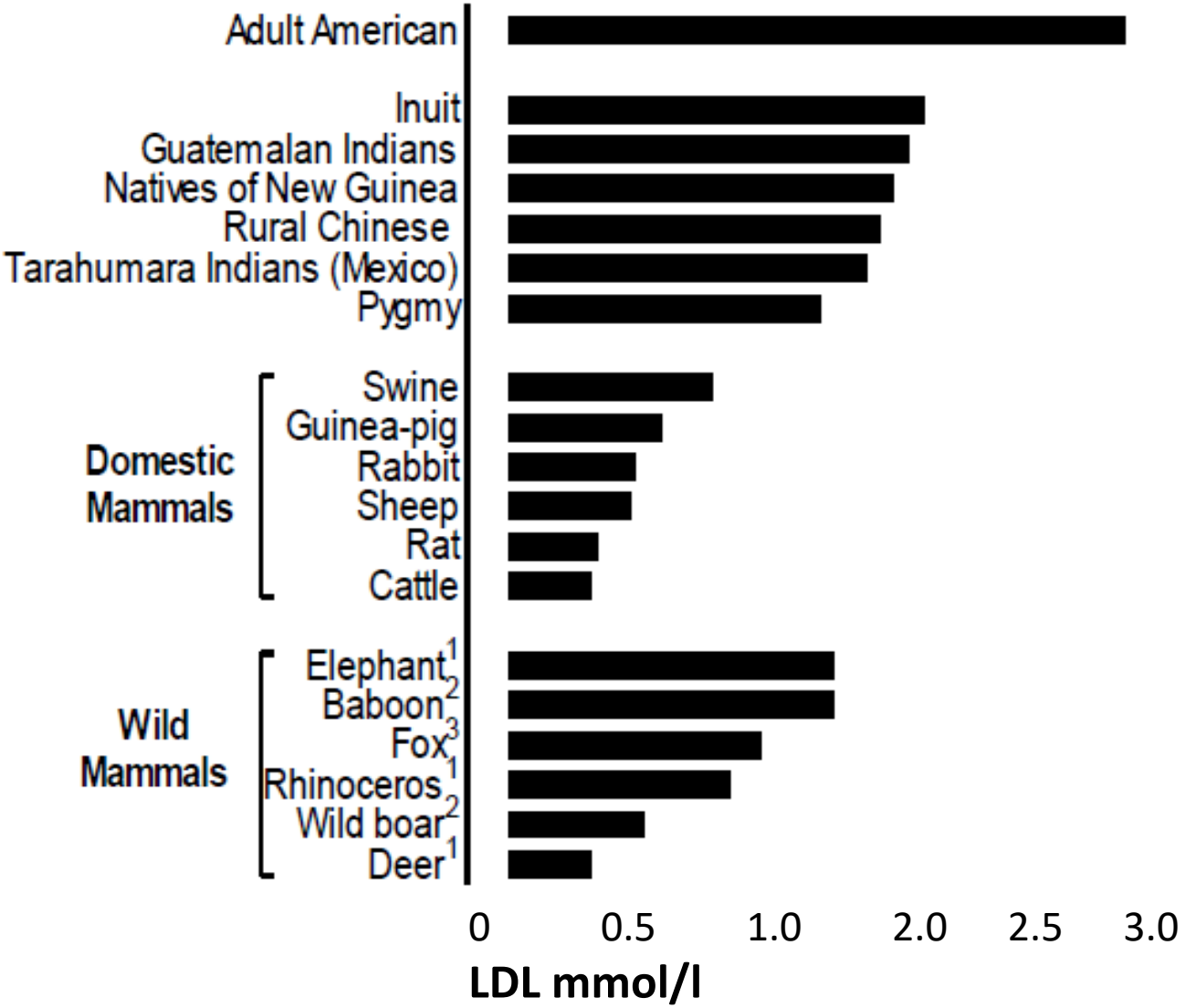
Aim for a greater than 40% reduction in non-HDL cholesterol.

JBS3

Joint British Societies for the prevention of cardiovascular disease

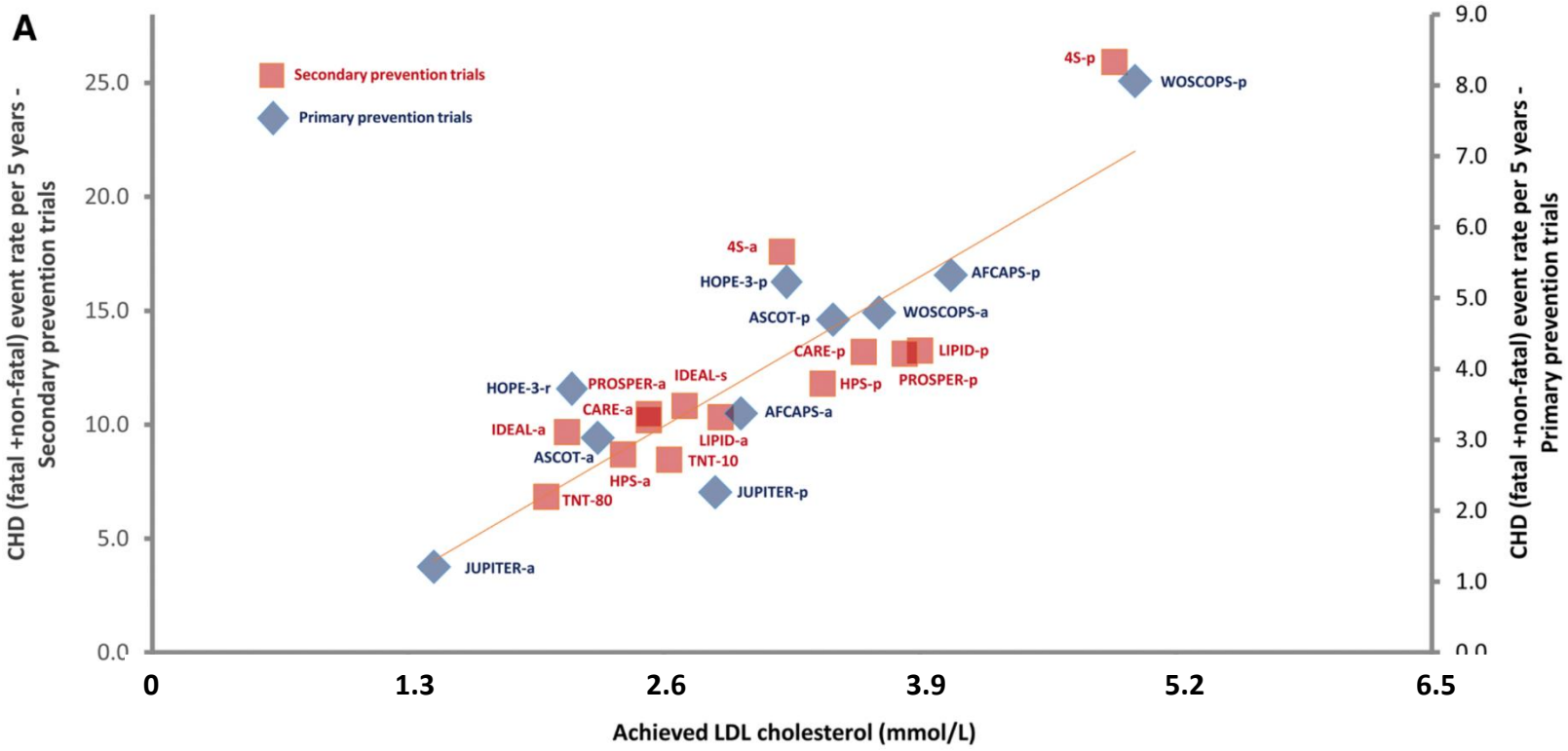
Aim for non-HDL-c of <2.5 mmol/L (broadly equivalent to an LDL-c of <1.8 mmol/l)

LDL in nature



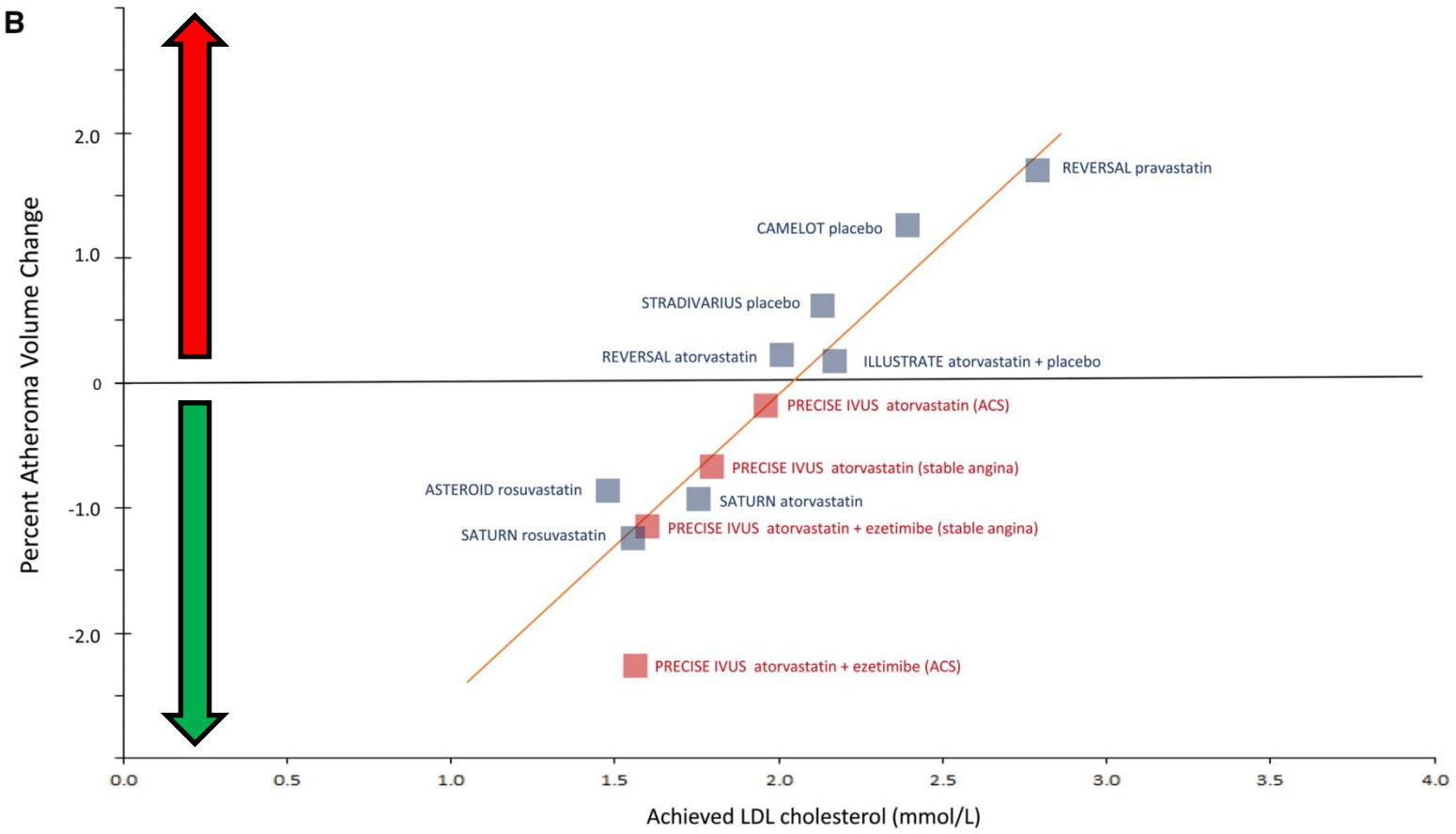
Hochholzer W & Giugliano RP. *Ther Adv Cardiovasc Dis* 2010;

LDL and CV risk



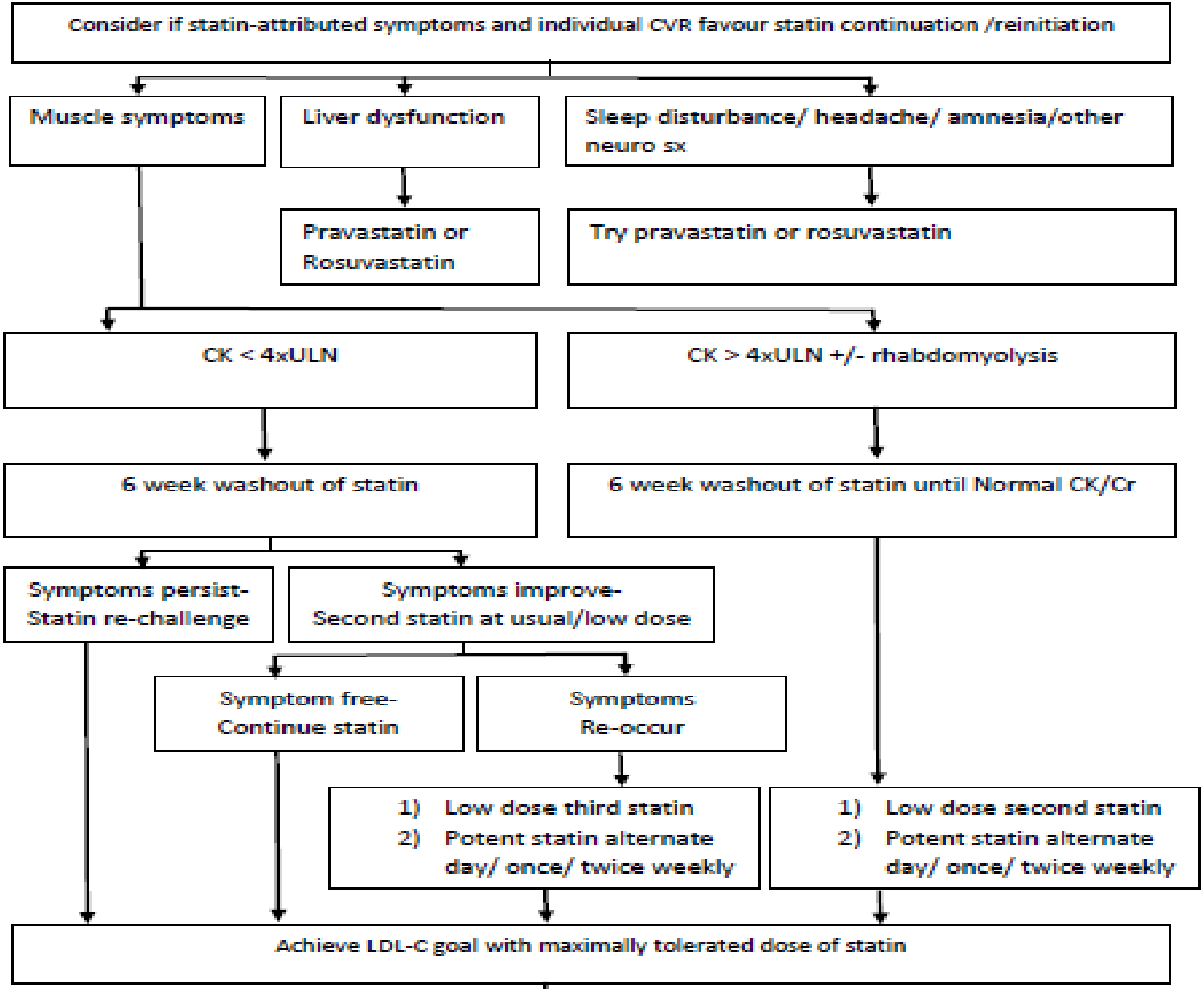
Eur Heart J. 2017

LDL-C and atheroma formation



Eur Heart J. 2017

Statin intolerance



SAMSON

Self-assessment toolkit trial

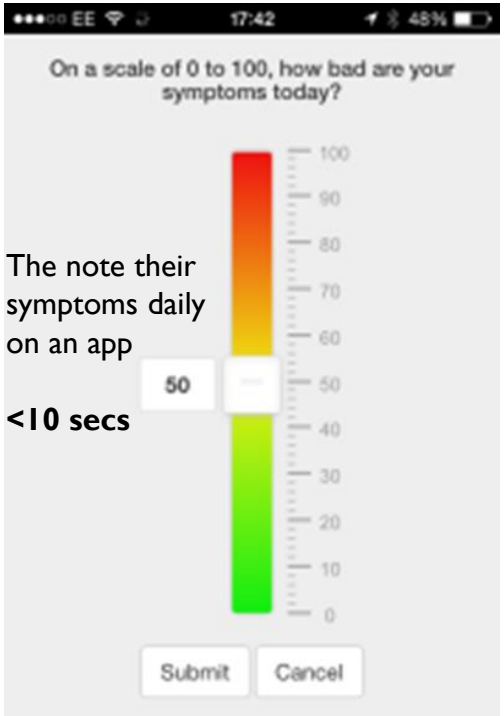
for people who have **stopped statins** due to adverse symptoms

4 months
nothing

4 months
placebo

4 months
statin

?



The note their symptoms daily on an app

<10 secs

www.samson-trial.org

Statins and LDL reduction

	Reduction in low-density lipoprotein cholesterol				
Dose (mg/day)	5	10	20	40	80
Fluvastatin	–	–	21%[1]	27%[1]	33%[2]
Pravastatin	–	20%[1]	24%[1]	29%[1]	–
Simvastatin	–	27%[1]	32%[2]	37%[2]	42%[3,4]
Atorvastatin	–	37%[2]	43%[3]	49%[3]	55%[3]
Rosuvastatin	38%[2]	43%[3]	48%[3]	53%[3]	–

Statins!

- For every 10000 patients treated with statins, 500 CVD events will be avoided but 1 case rhabdomyolysis, 5 cases myopathy and 75 cases diabetes mellitus.
- Annual glucose / HbA1c recommended
- Benefit of statin outweighs risk of DM
- Mechanism unclear but higher risk in patients with prediabetes
- Starting statin doesn’t affect DM management

Summary Case 1

- Use QRISK to estimate risk of CV event
- If risk >10%, recommend atorvastatin 20mg od
- Aim for non-HDL-C <2.5 mmol/l

Case 2 19 yo man

- Referred by plastic surgeon
- Fit and well
- Professional footballer
- FHx: Father MI aged 40, died aged 46

- Total cholesterol 10.2 mmol/L
- HDL-c 1.4 mmol/L
- TG 1.1

Case 2 Questions

- What is his LDL-c?
- **Friedewald equation**

LDL-C = Total cholesterol – HDL-C – TG/2.2

10.2 – 1.4 – 1.1/2.2

= 8.3 mmol/l

Case 2 Questions

- **What is the genetic basis of his hypercholesterolaemia?**

Format

1. **CV Risk and lipid lowering**
2. **Familial Hypercholesterolaemia**
3. **Hypertriglyceridaemia**
4. **Lipoprotein(a)**

Familial hypercholesterolaemia

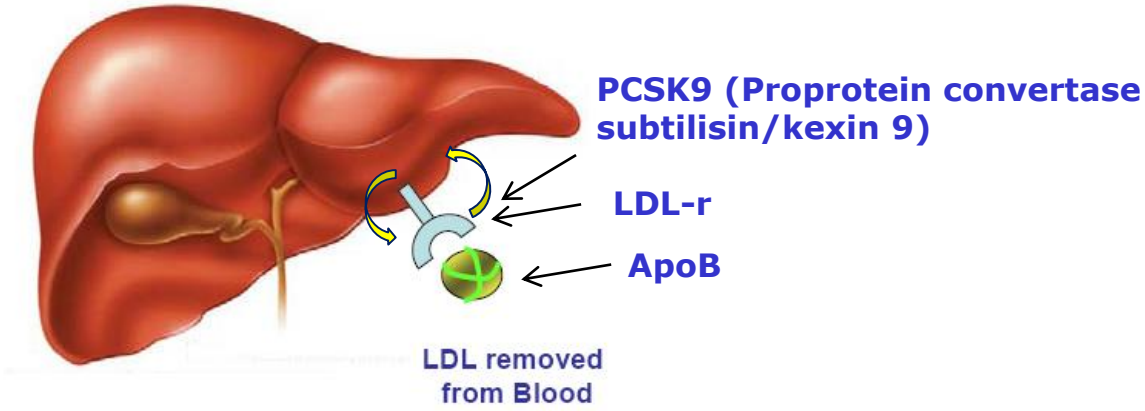
- The most common dominantly inherited disorder
- Autosomal dominant disorder
- High levels of low density lipoprotein cholesterol
- Early coronary artery disease
- Heterozygous ~1 in 250
- Homozygous ~1/1,000,000

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**

Genetics of FH

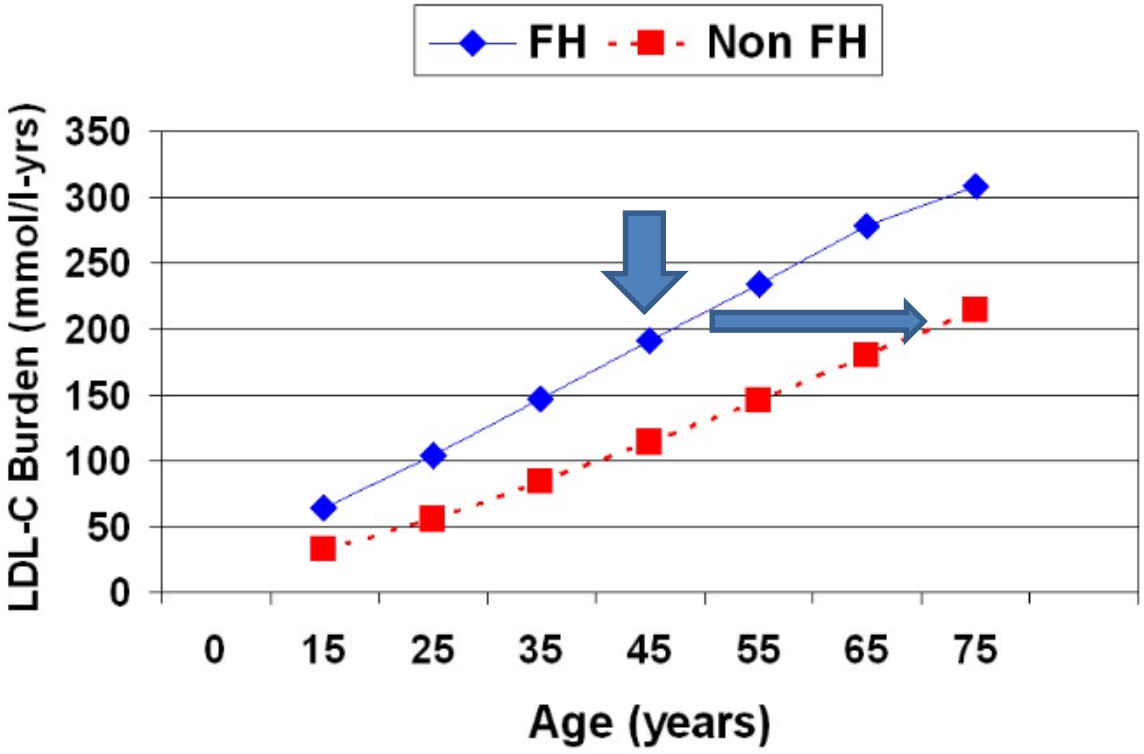
- What genes are affected in FH?



LDL-R mutations	93%	chromosome 19
ApoB	5%	chromosome 2
PCSK9	2%	chromosome 1

Why do FH patients have such premature CHD?

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

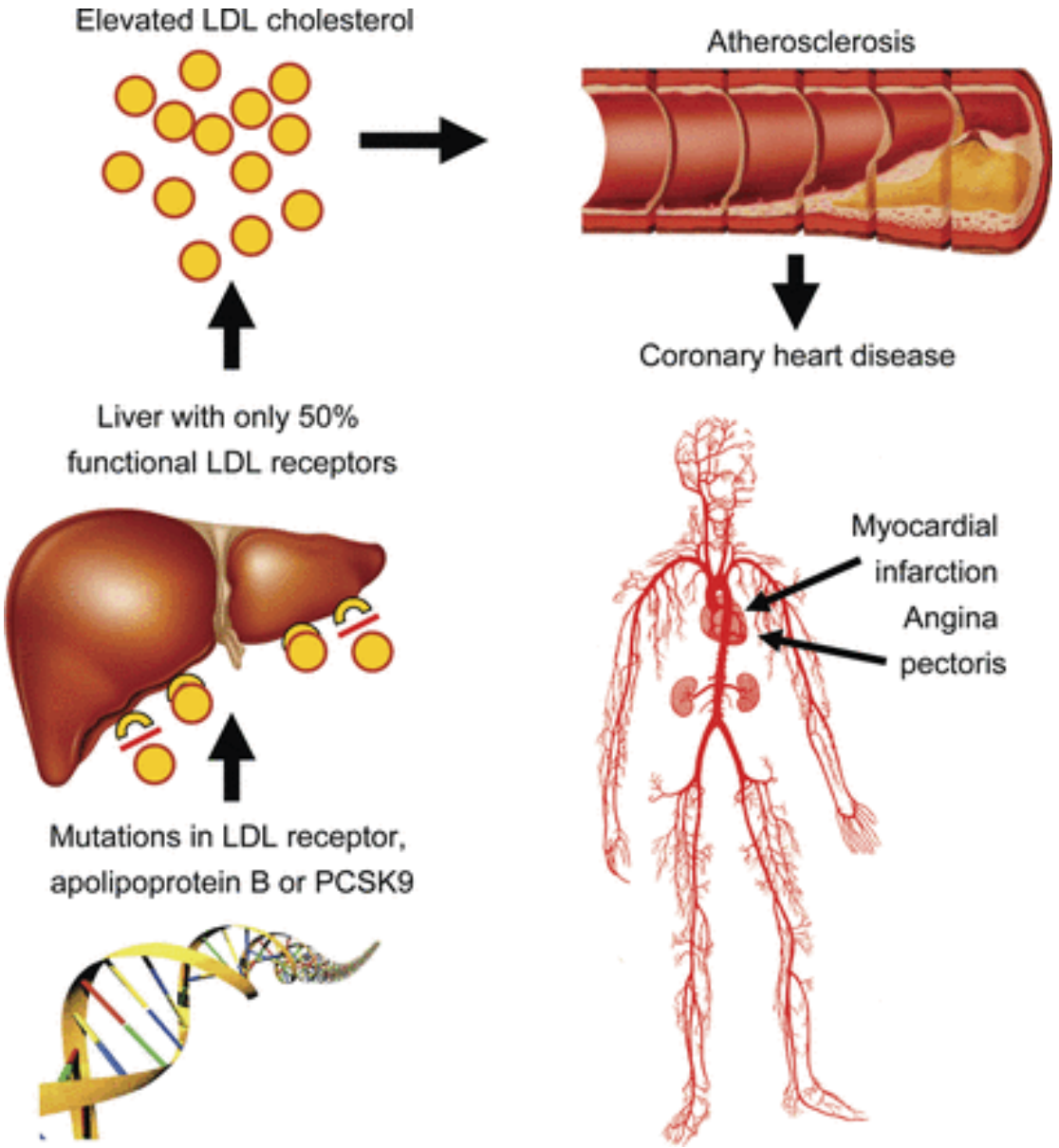


LDL-Burden = LDL-C level x years exposure

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

- ***TC > 7.5mmol/l or LDL > 4.9mmol/l in adults**
- *TC > 6.7mmol/l or LDL > 4.0mmol/l in children
- PLUS tendon xanthoma (absence does not exclude)
- OR PLUS DNA confirmation

POSSIBLE

- Biochemical criteria as above
- PLUS family history of CVD (<50 2nd degree relative, <60 1st degree relative) OR of high cholesterol

- NOTE – mutation identified in ~80% of „clinically definite“ FH, only 30% of „possible“ FH!

Assess additional CVD risk factors

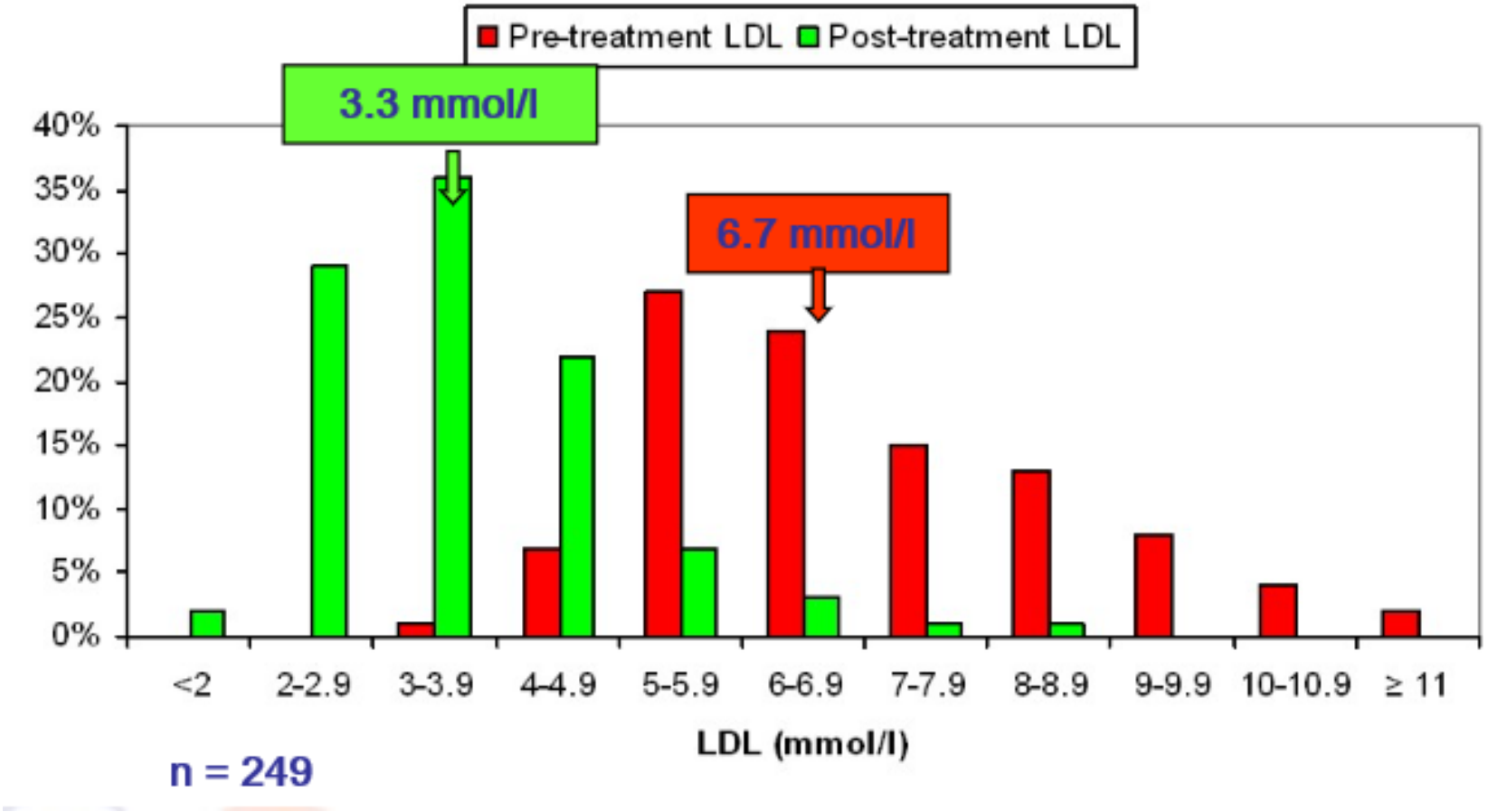
- Presence of additional CVD risk factors should guide the intensity of management
  - Hypertension, diabetes, obesity, smoking
  - Lipoprotein(a)
  - Level and duration of untreated LDL cholesterol
  - Prematurity of the family & personal history of CVD
  - **Framingham and other CVD risk equations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

- Cardiovascular imaging may be useful for assessing asymptomatic patients
  - Cardiac computed tomography
  - Carotid ultrasonography

Management

- Lifestyle modification
- LDL lowering drugs
- LDL-Apheresis

Can LDL be lowered in FH patients?

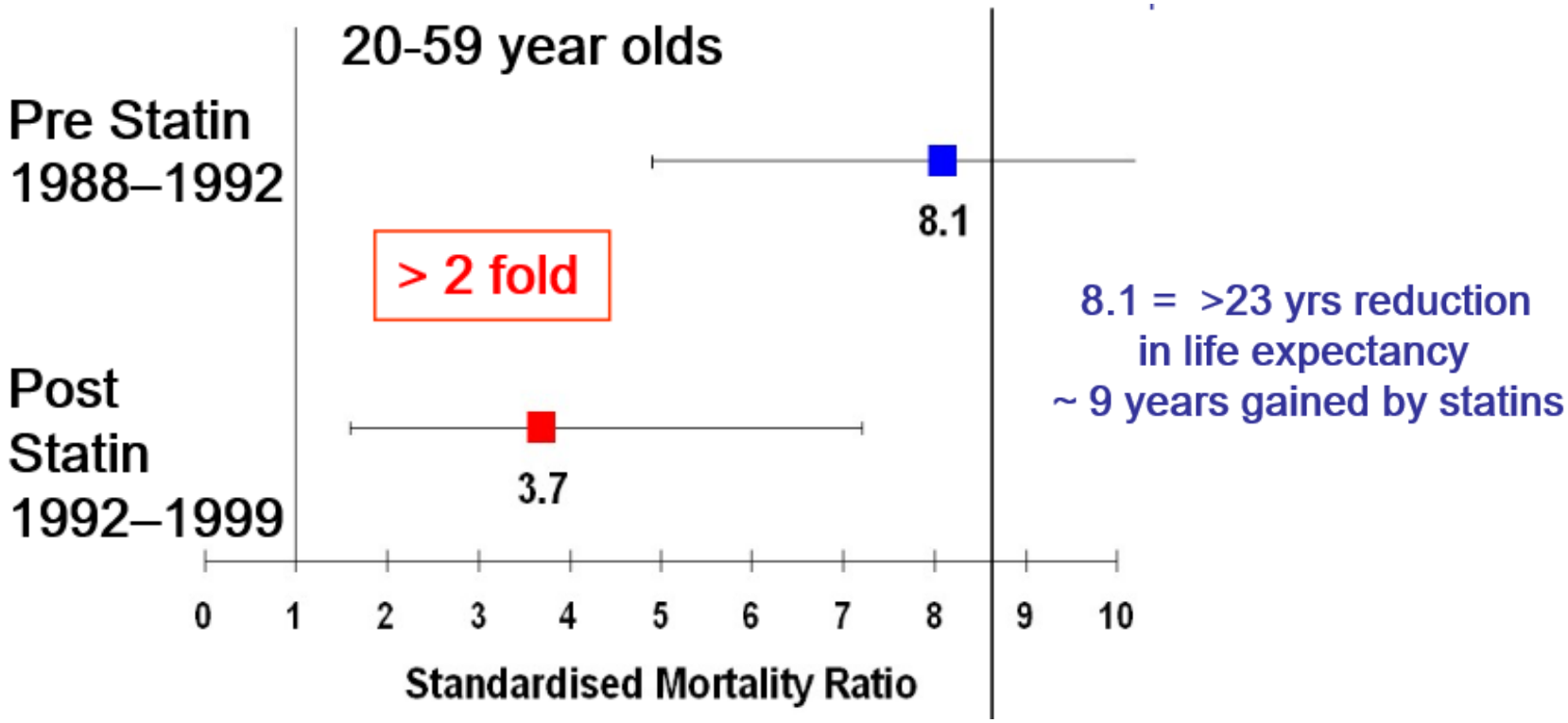


Hadfield et al; 2007

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

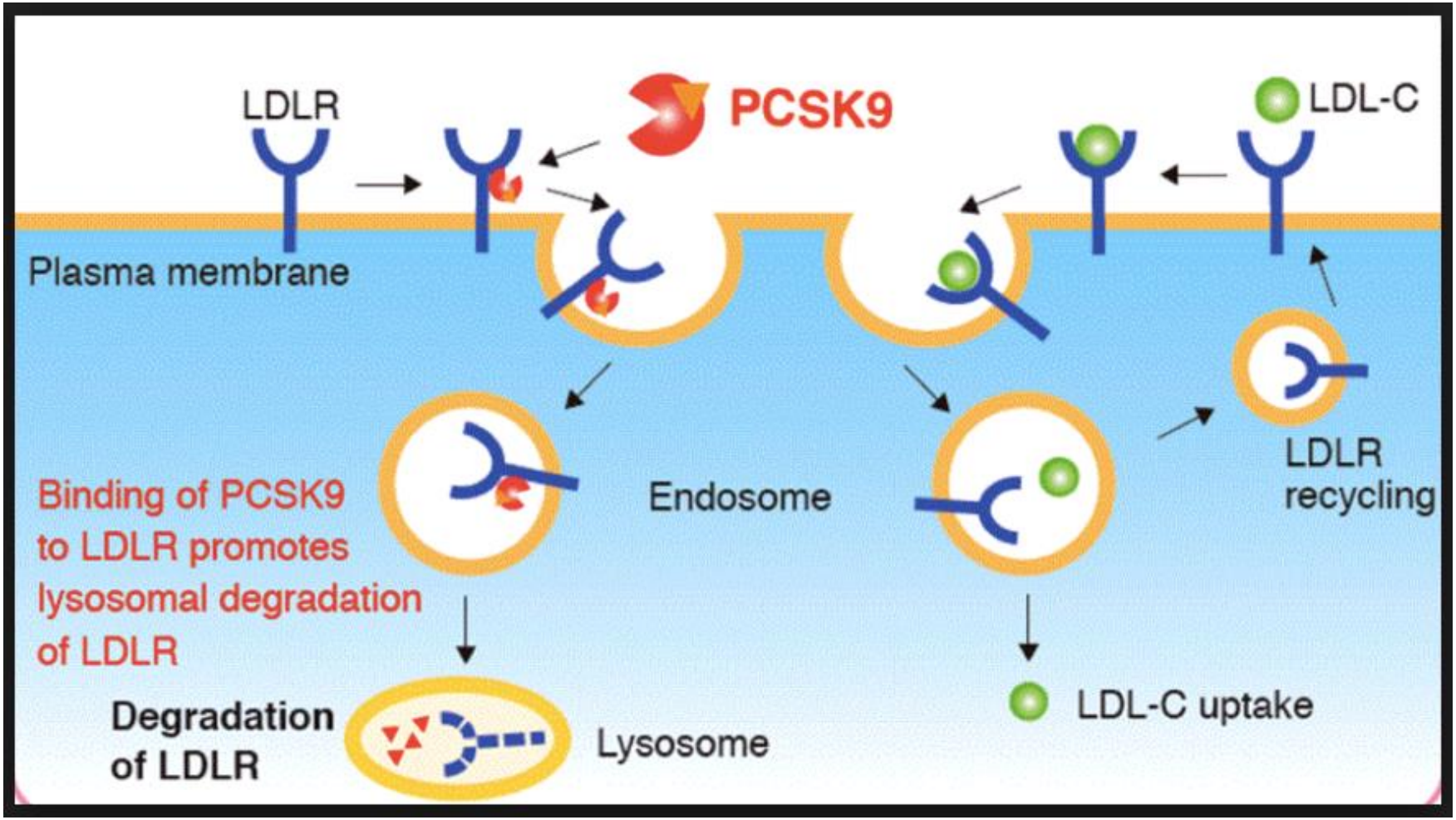


Simon Broome UK FH Registry papers; Athero, 1999

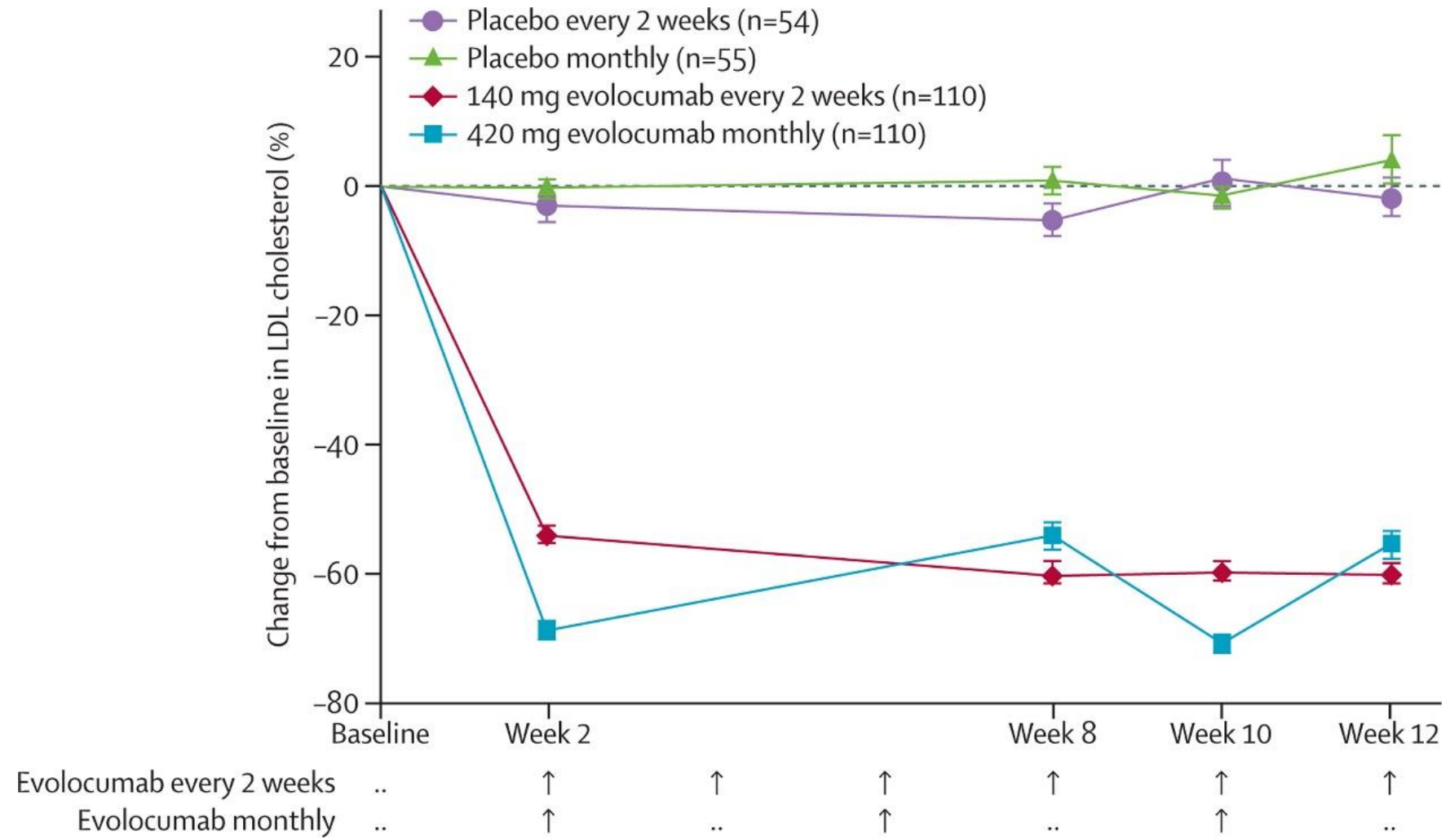
LDL-lowering in women

- 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**

PCSK-9 inhibitors

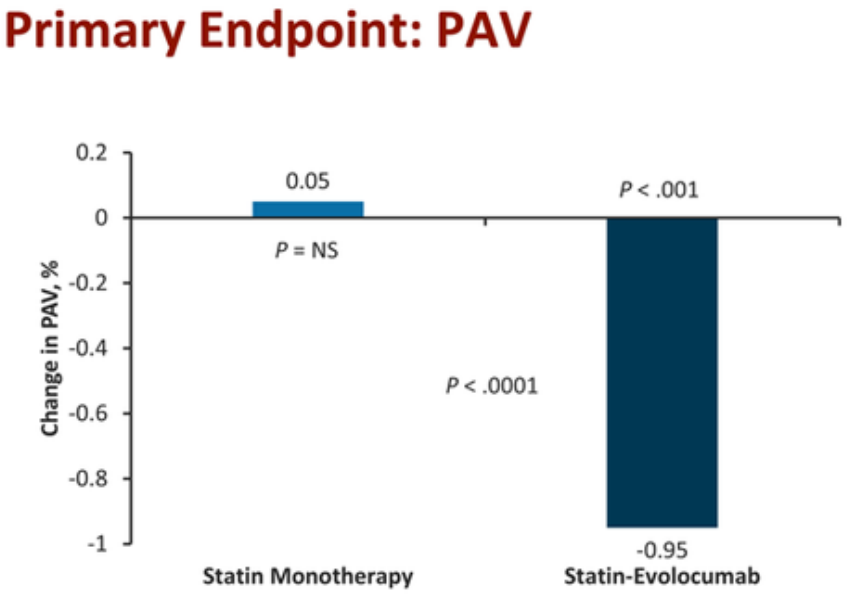


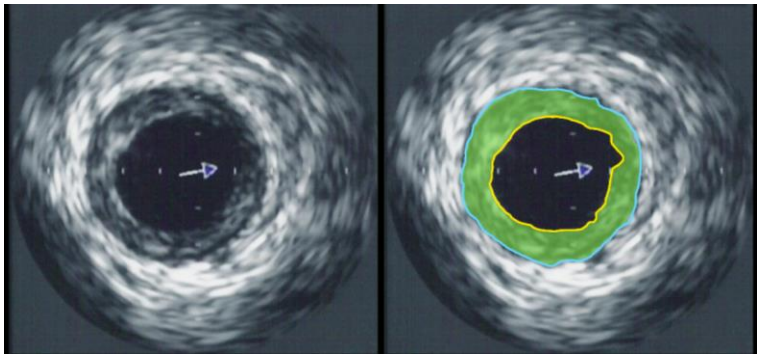
PCSK-9 inhibition in FH



Raal et al, Lancet. 2014

Effect on the coronaries





Yellow = lumen
Blue = external elastic membrane
Green = atheroma

Nicholls et al, JAMA, 2016

PCSK-9 inhibition and NICE

	Without CVD	With CVD	
		High risk of CVD [1]	Very high risk of CVD [2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL–C concentration	Recommended only if LDL–C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL–C concentration is persistently above 3.5 mmol/litre
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL–C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL–C concentration is persistently above 3.5 mmol/litre	

Lipoprotein apheresis

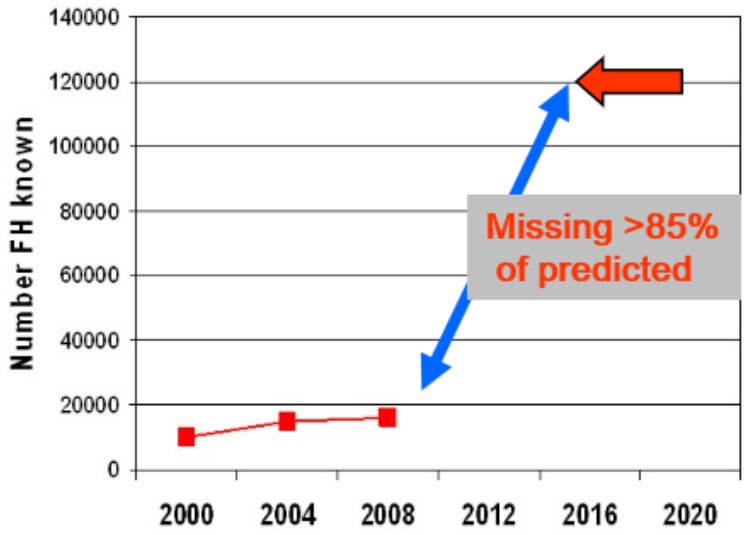
- LA should be considered in patients with heterozygous FH with CHD who cannot achieve LDL cholesterol targets or have progressive disease despite maximal drug therapy

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

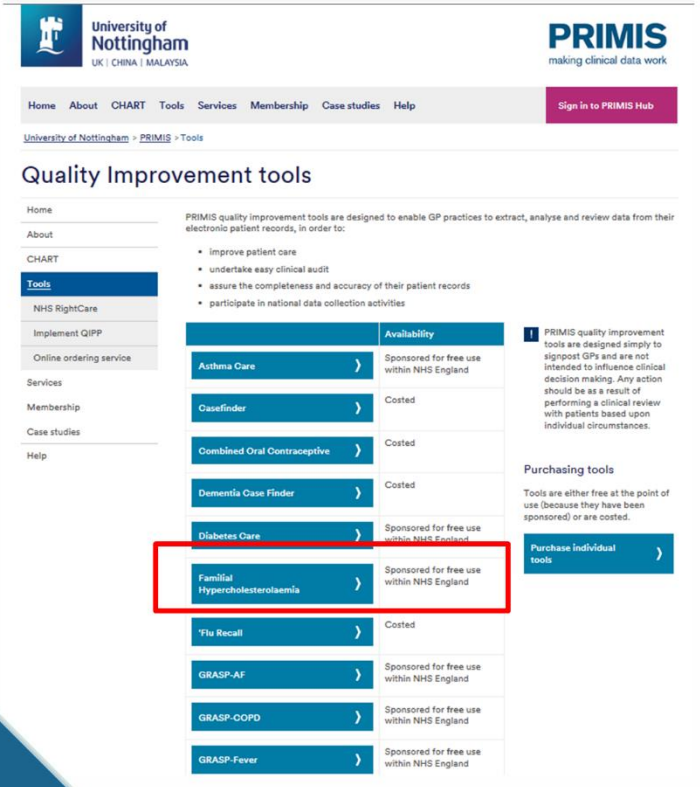
PRIMIS Familial Hypercholesterolaemia FH Case-Finder tool

https://www.nottingham.ac.uk/primis/

The FHC tool is designed to help practices case find patients who may have FH and also may be missing a coded diagnosis

FHC tool is quick and simple to run within practices, and free to download for any PRIMIS registered users.

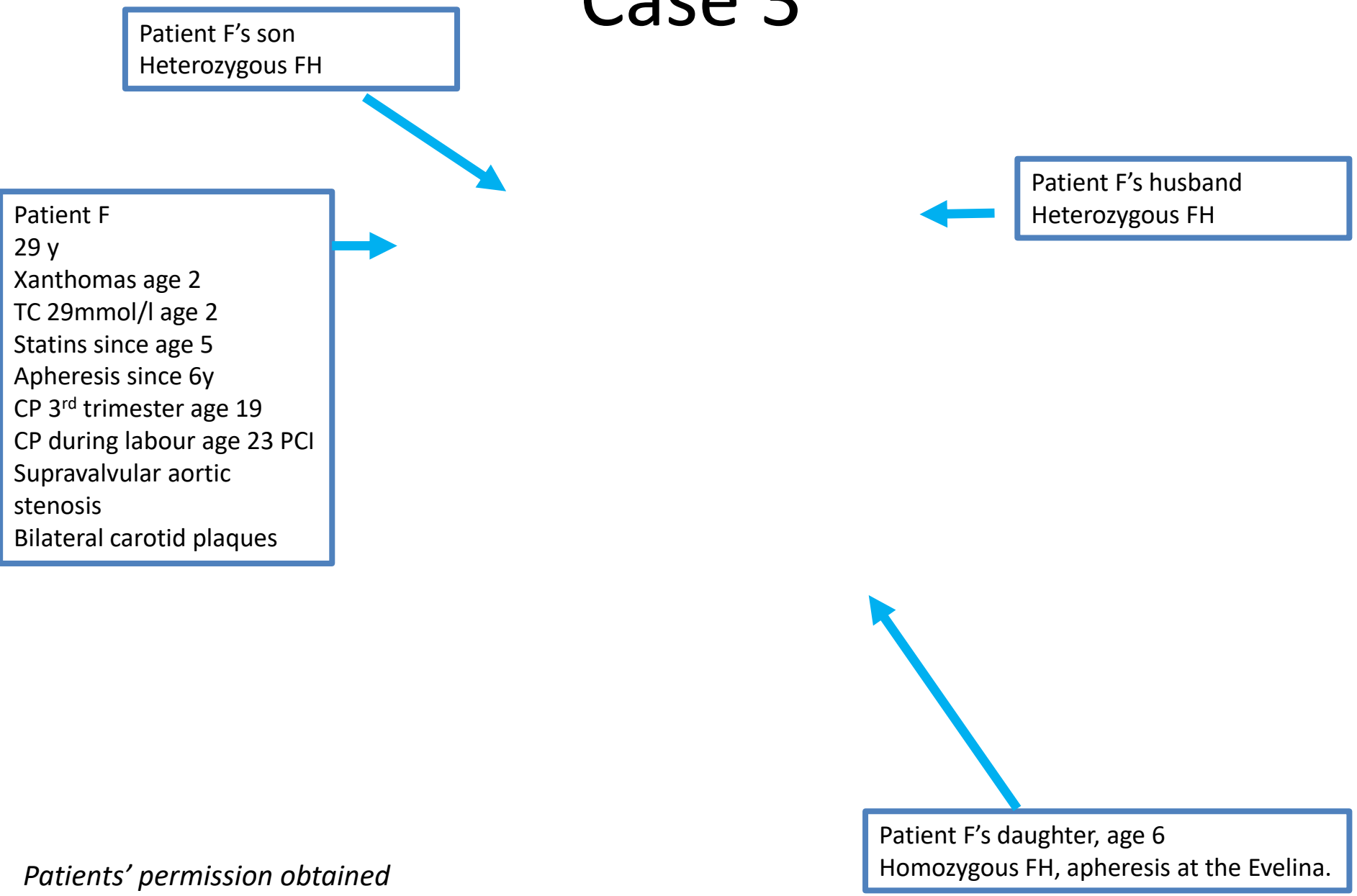
Developed in collaboration with the **Primary Care Stratified Medicine (PRISM) research group** (formerly the Applied Genetics and Ethnicity Research Group) at the University of Nottingham. This tool is based on the FAMCAT algorithm[1] developed by academics in the Applied Genetics and Ethnicity research group



1. •Visit website •Register
2. •Download •Tool •Instructions
3. •Run search •Report

Homozygous FH

Case 3



Patients' permission obtained

Homozygous FH

- Cholesterol 15-30 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

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

- Homozygous FH
- Before and after 6 years of apheresis

Format

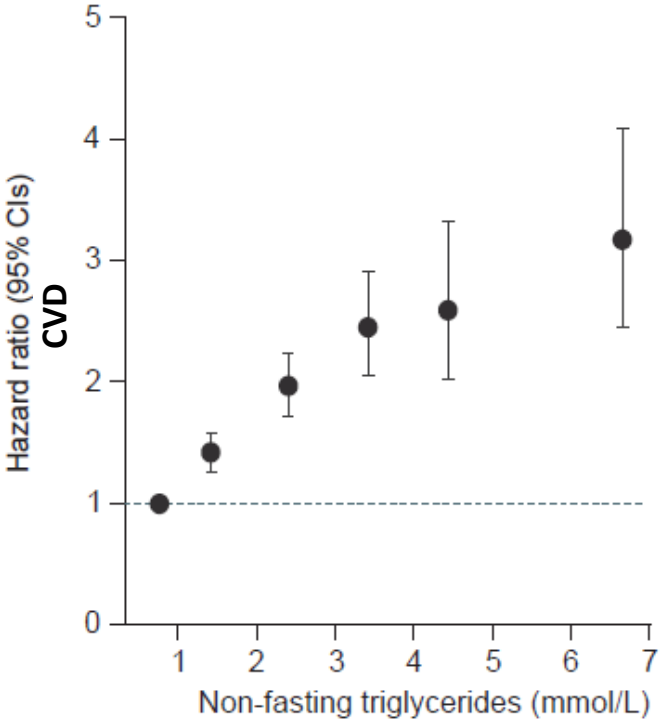
1. **CV Risk and lipid lowering**
2. **Familial Hypercholesterolaemia**
3. **Hypertriglyceridaemia**
4. **Lipoprotein(a)**

Case 4

- 25 year old lady
- TC 5.2 mmol/l
- **TG 14.1 mmol/l**
- HDL 1.1 mmol/l
- non-HDL 4.1 mmol/l

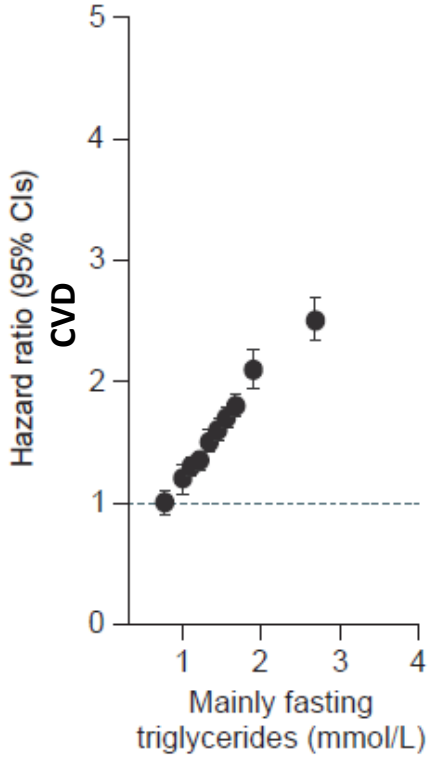
- HbA1C 31 mmol/mol
- BMI 22
- Tee total
- No meds

HyperTG and CVD



N=93410 (cardiac events=7183)
Median follow-up 6 years

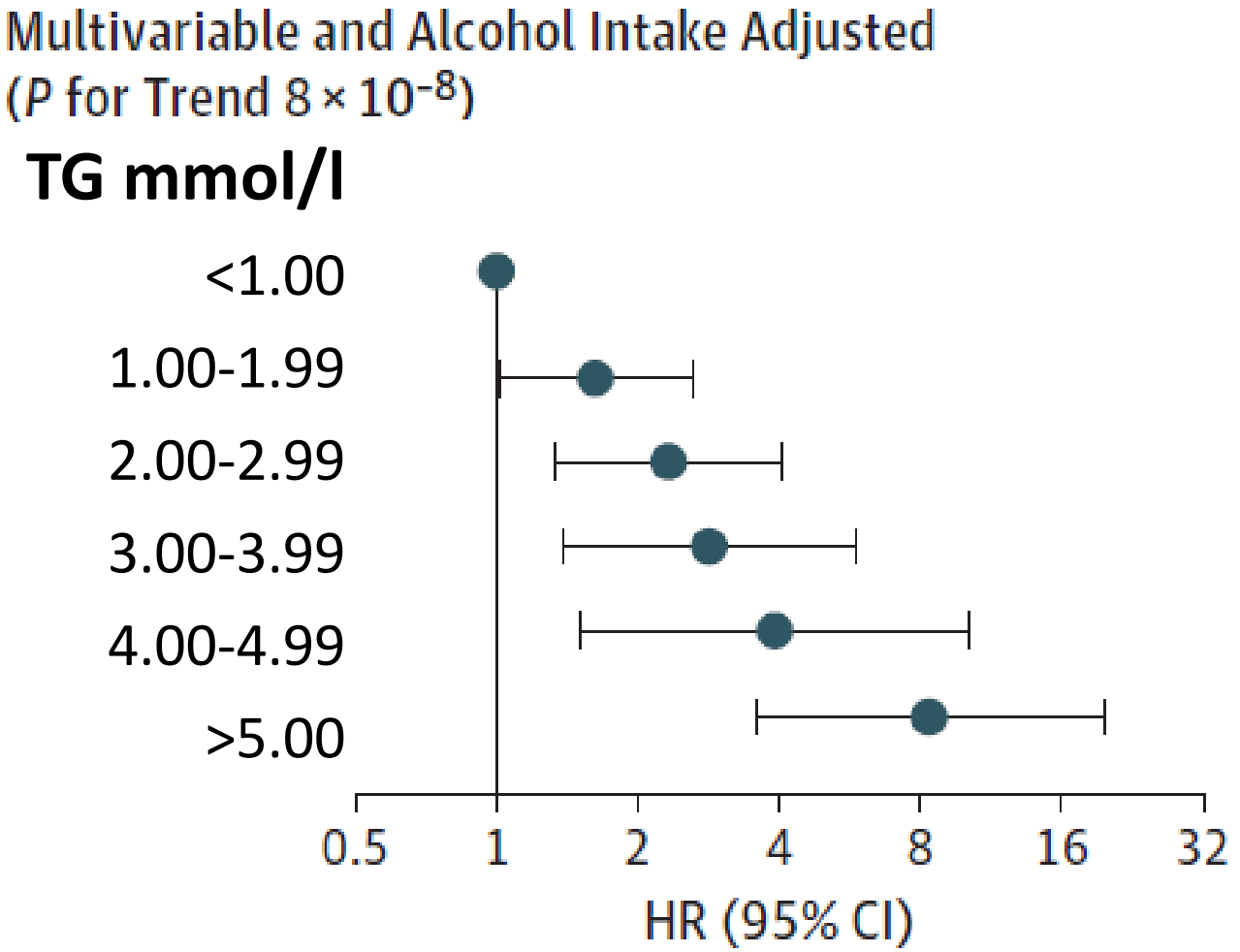
Copenhagen City Heart Study and
Copenhagen General Population Study



N=302430 (cardiac events=12785)
Median follow-up 8 years

Emerging Risk Factors Collaboration

HyperTG and acute pancreatitis

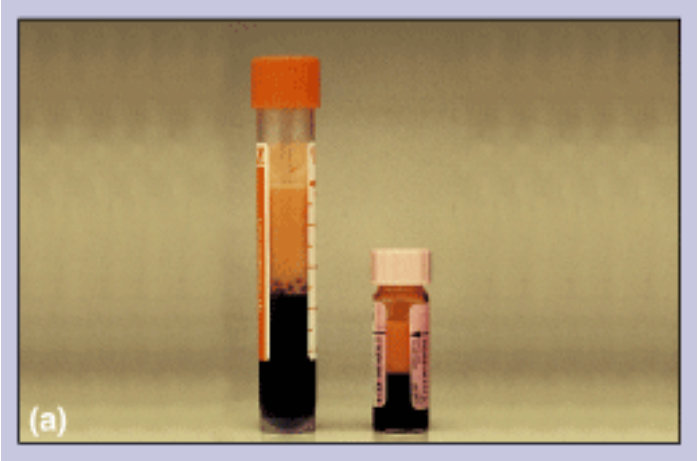


JAMA intern med 2016

Primary

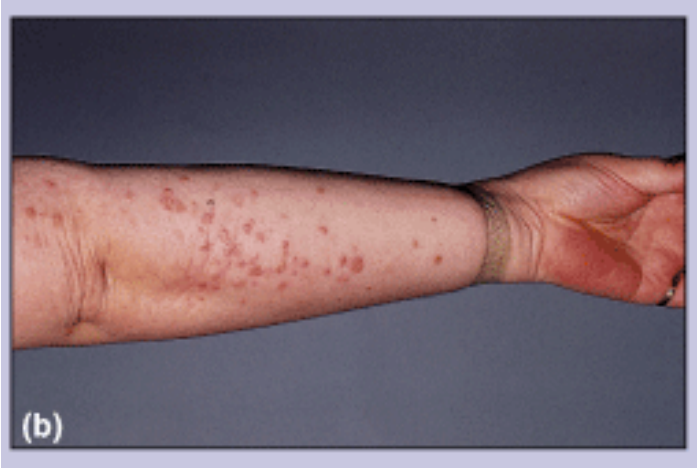
TG only

- Familial chylomicronaemia syndrome
- Familial HyperTG



Mixed

- Familial dysbetalipoproteinaemia
- Familial combined hyperlipidaemia



With permission from Prof GR Thompson

TG response to a meal..

Assumptions:

- Complete digestion and absorption of dietary fat
- Clearance is zero (e.g. LPL deficiency)
- Ignore VLDL production
- Fasting triglycerides are 4 mmol/L
- Plasma volume of 3 L
- 1 mol triglycerides ≈ 885 g

Take-away meal: Triglyceride content	
• Double hamburger with cheese	42 g
• French fries (large)	30 g
• Chocolate triple thick shake (supersize)	28 g

Total meal is 100 g of triglyceride → 113 mmol

Change in triglycerides: 113 mmol of triglyceride / 3 L plasma volume: 37.66 mmol/L

Triglycerides can rise from 4 mmol/L to over 40 mmol/L

Cholesterol consumed: 255 mg (≈ 0.7 mmol)

Blom et al, 2014

Secondary causes of hyperTG

Condition	Comments
Obesity	Mild hypertriglyceridaemia frequent in metabolic syndrome Increased waist circumference highly predictive of mild hypertriglyceridaemia
Diet	See Box 1 for the effect of dietary fat in patients with lipolytic defects
Diabetes mellitus	Most common secondary cause in our experience Controlling diabetes mellitus often lowers TGs substantially
Alcohol	Alcohol can increase VLDL synthesis Pancreatitis risk from alcohol and TGs
Renal disease	Mild hypertriglyceridaemia frequently seen in uremia
Pregnancy	Increased VLDL production may expose lipolytic effect Pancreatitis has high fatality rate in pregnancy
Paraproteins	May inhibit lipolytic proteins
Autoimmune disorders	Systemic lupus erythematosus (SLE) may generate auto-antibodies to LPL
Other disorders	Glycogen storage disorders may have mild hypertriglyceridaemia

…and drugs

Blom et al, 2014

Drugs associated with hyperTG

Drug	Comments
Oestrogen	Oral oestrogen elevate TGs more than transdermal preparations May cause marked hypertriglyceridaemia in susceptible individuals
Corticosteroids	Variable lipid phenotypes, may cause predominant hypercholesterolaemia
Isotretinion	Severe hypertriglyceridaemia possible Check baseline TGs before therapy and once on treatment
Antiretrovirals	Protease inhibitors, especially ritonavir, most often implicated Hypertriglyceridaemia often severe
Cholestyramine	May aggravate hypertriglyceridaemia Avoid prescription when TGs are increased
Immunosuppressant drugs	Sirolimus frequently implicated
Beta blockers, thiazides	Increase in TGs usually minor
Atypical antipsychotics	Weight gain, insulin resistance and diabetes commonly accompany rise in TGs

Blom et al, 2014

Treatment

- **Acute:**
  - dietary intervention
  - insulin,
  - heparin,
  - plasmapheresis,
  - drug therapy (e.g., fibrates, omega-3 fatty acids and statins)
- **Non-acute:**
  - dietary intervention
  - drug therapy (e.g., fibrates, omega-3 fatty acids and statins)

Format

1. **CV Risk and lipid lowering**
2. **Familial Hypercholesterolaemia**
3. **Hypertriglyceridaemia**
4. **Lipoprotein(a)**

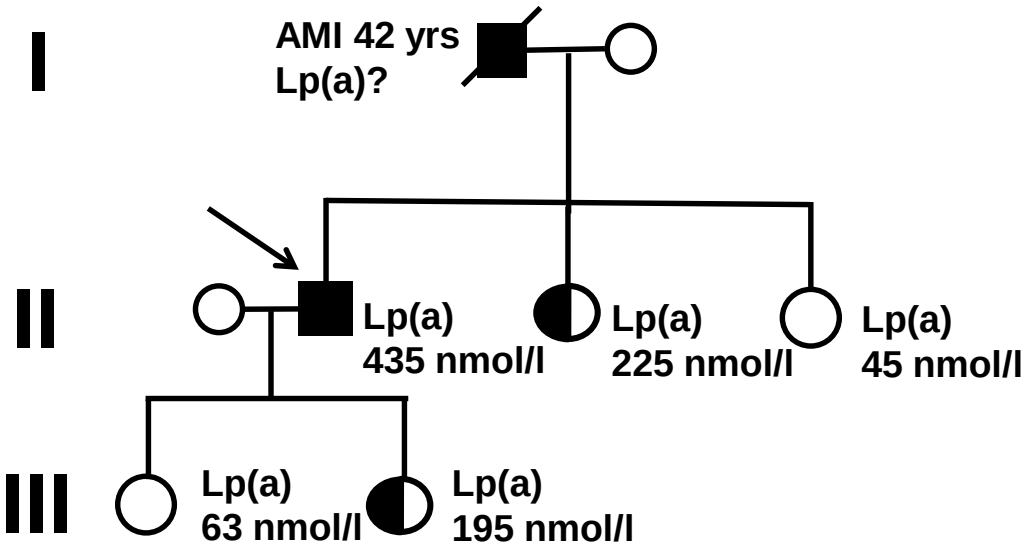
Case 5

36 year old architect
Presented with AMI

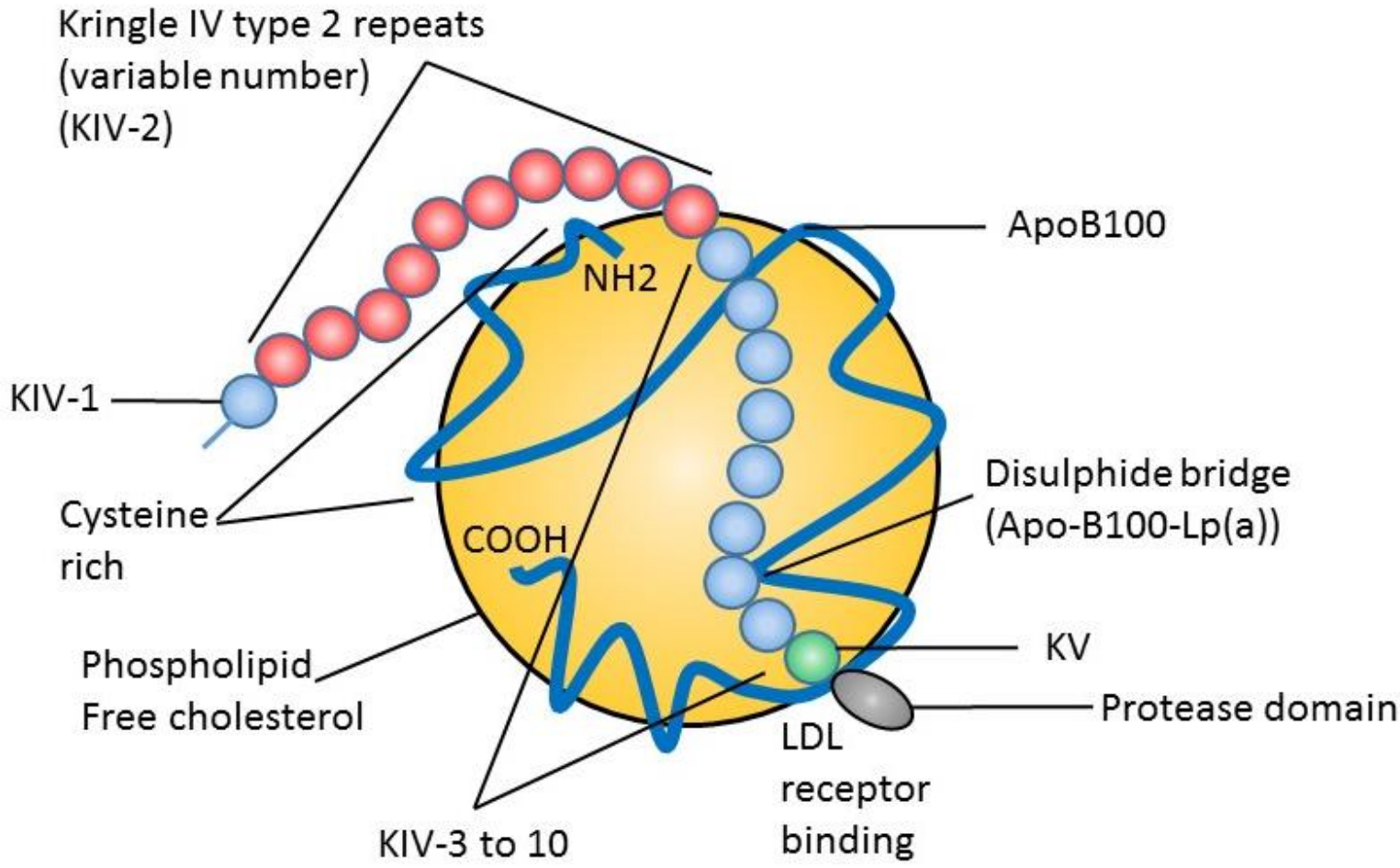
- non-smoker
- runs 5 times per week, cycles

- TC 4.2 mmol/l
- TG 1.1 mmol/l
- HDL 1.2 mmol/l
- non-HDL 3.0mmol/l
- HbA1C 24 mmol/mol

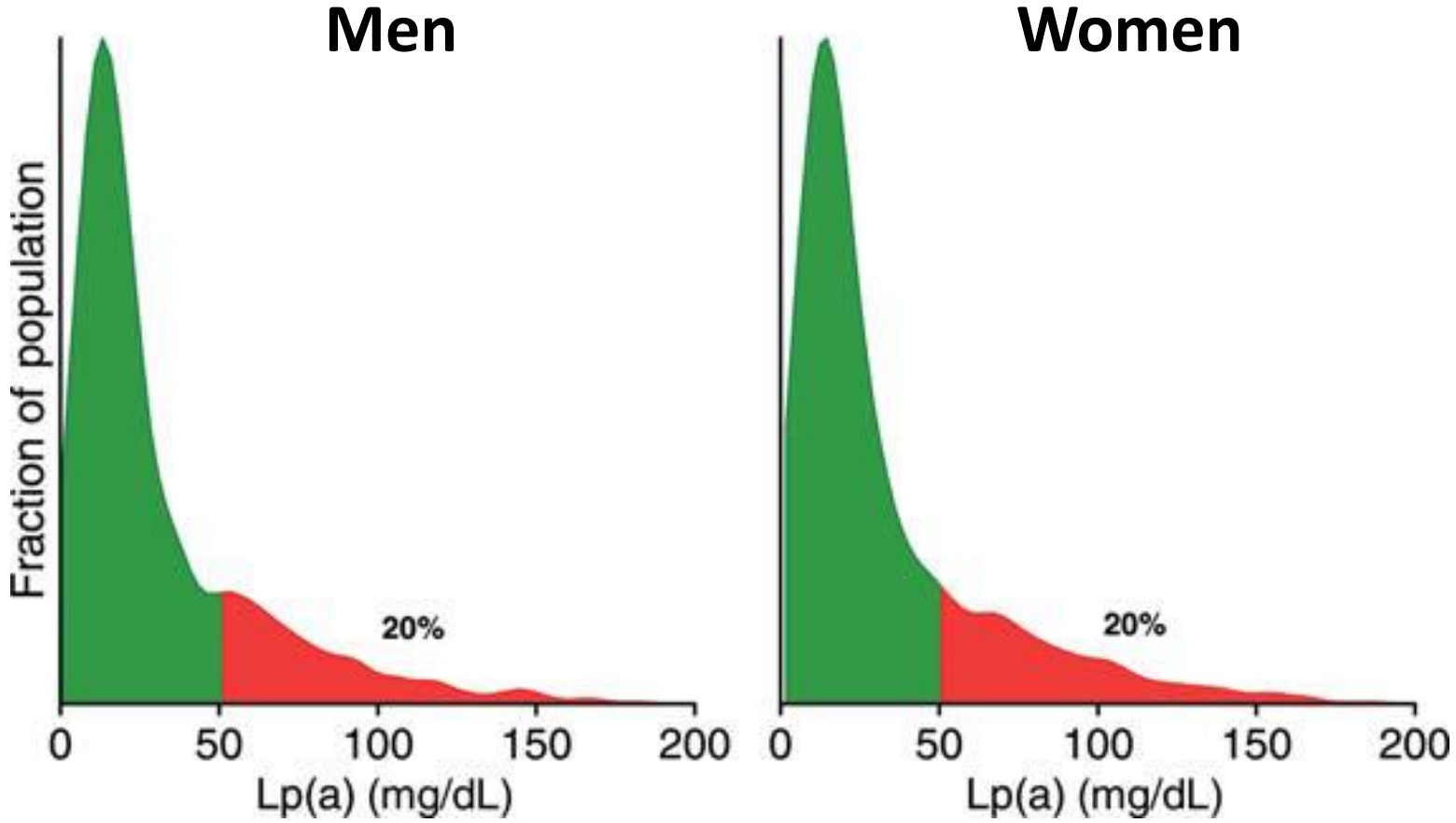
- BP 124/84



Lipoprotein(a)

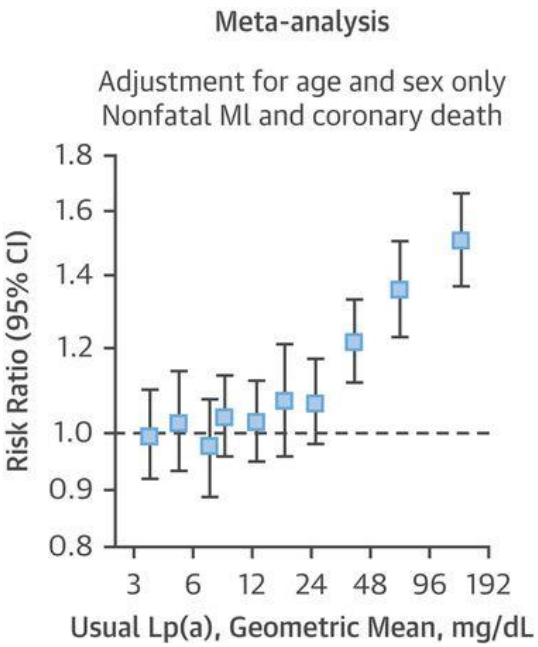


Lp(a) distribution

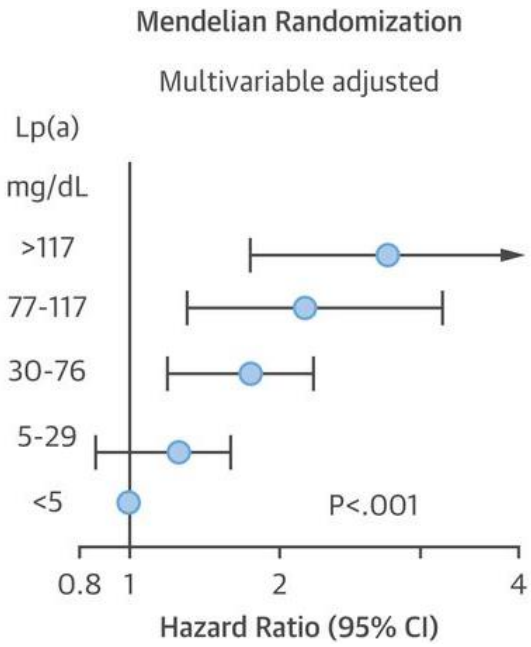


Kamstrup JAMA 2009

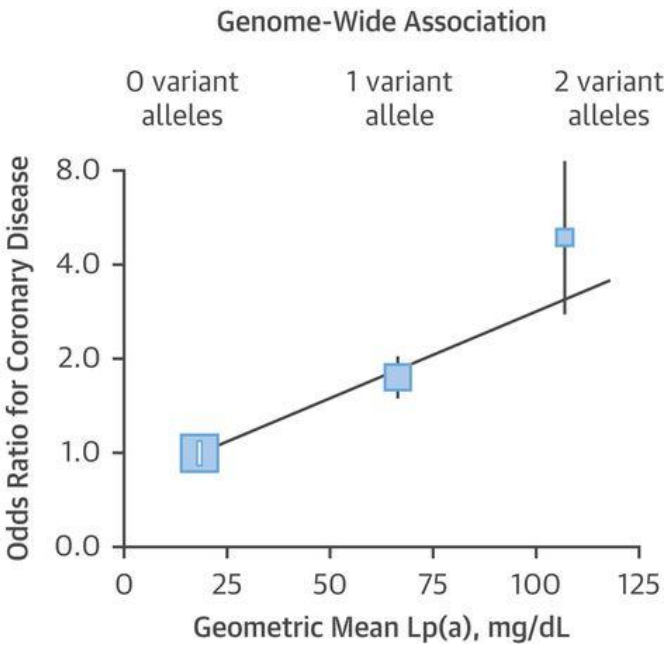
Lp(a) and CV risk



ERF Collab JAMA 2009



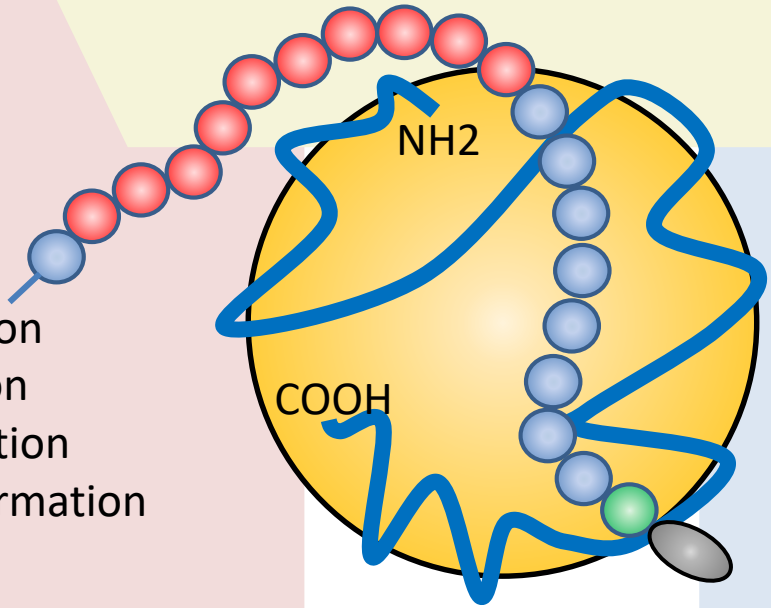
Kamstrup JAMA 2009



Clarke NEJM 2009

Lp(a) Pathophysiology

Pro-inflammatory
↑ oxidised phospholipids
↑ monocyte trafficking
↑ monocyte cytokine release



Proatherogenic
↑ arterial infiltration
↑ SMC proliferation
↑ foam cell formation
↑ necrotic core formation

Prothrombotic
↓ plasminogen activation
↓ fibrin degradation
↑ platelet aggregation

Treatment of Lp(a)

The management of patients with raised lipoprotein(a) levels (> 90 nmol/l), should include:

- 1) reducing residual atherosclerotic risk
- 2) controlling dyslipidaemia and
- 3) consideration of:
    - a) aspirin therapy
    - b) lipoprotein apheresis

When and whom to refer:

- Patients with familial hyperlipidaemias
- Patients who fail to respond adequately to diet and first-line drug therapy
- Patients with severe hypertriglyceridaemia who are at risk of pancreatitis
- Patients for whom there is any uncertainty about diagnosis

Take home messages:

- Lipids are a key target in CVD prevention and statins are the first line drugs
- Consider FH in patients with TC>7.5mmol/l or LDL>4.9mmol/l
- Raised TG- think: Acute risk: Pancreatitis and Chronic risk: CVD
- Consider raised Lp(a) as a mediator of CV risk