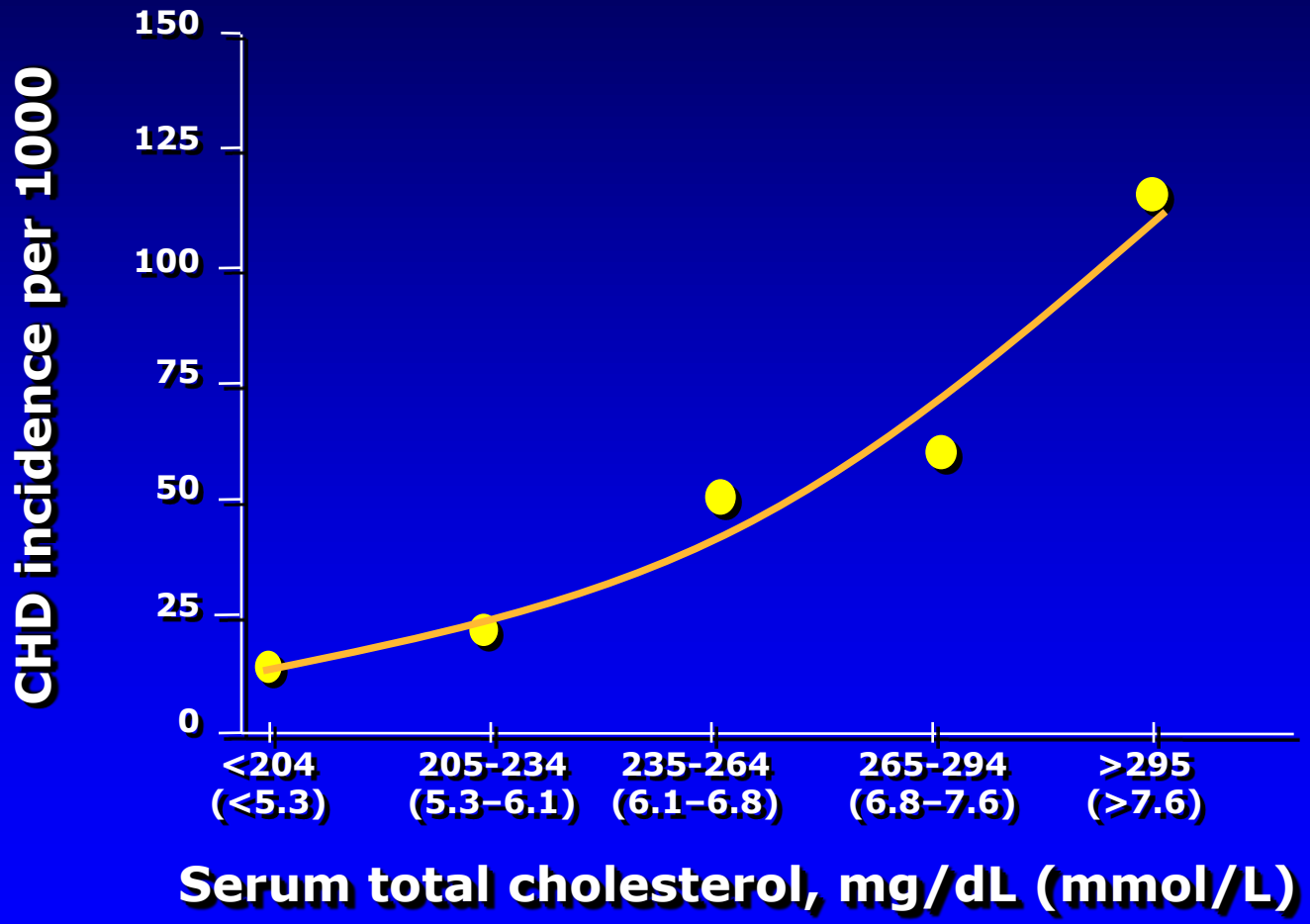
Lipids
What's new (and what's not)

Overview

- Background evidence
- Obesity
- Guidelines
- Treatment options
- Pragmatic lipidology
- Side effects
- Familial Hypercholesterolaemia
- Cases
- Summary

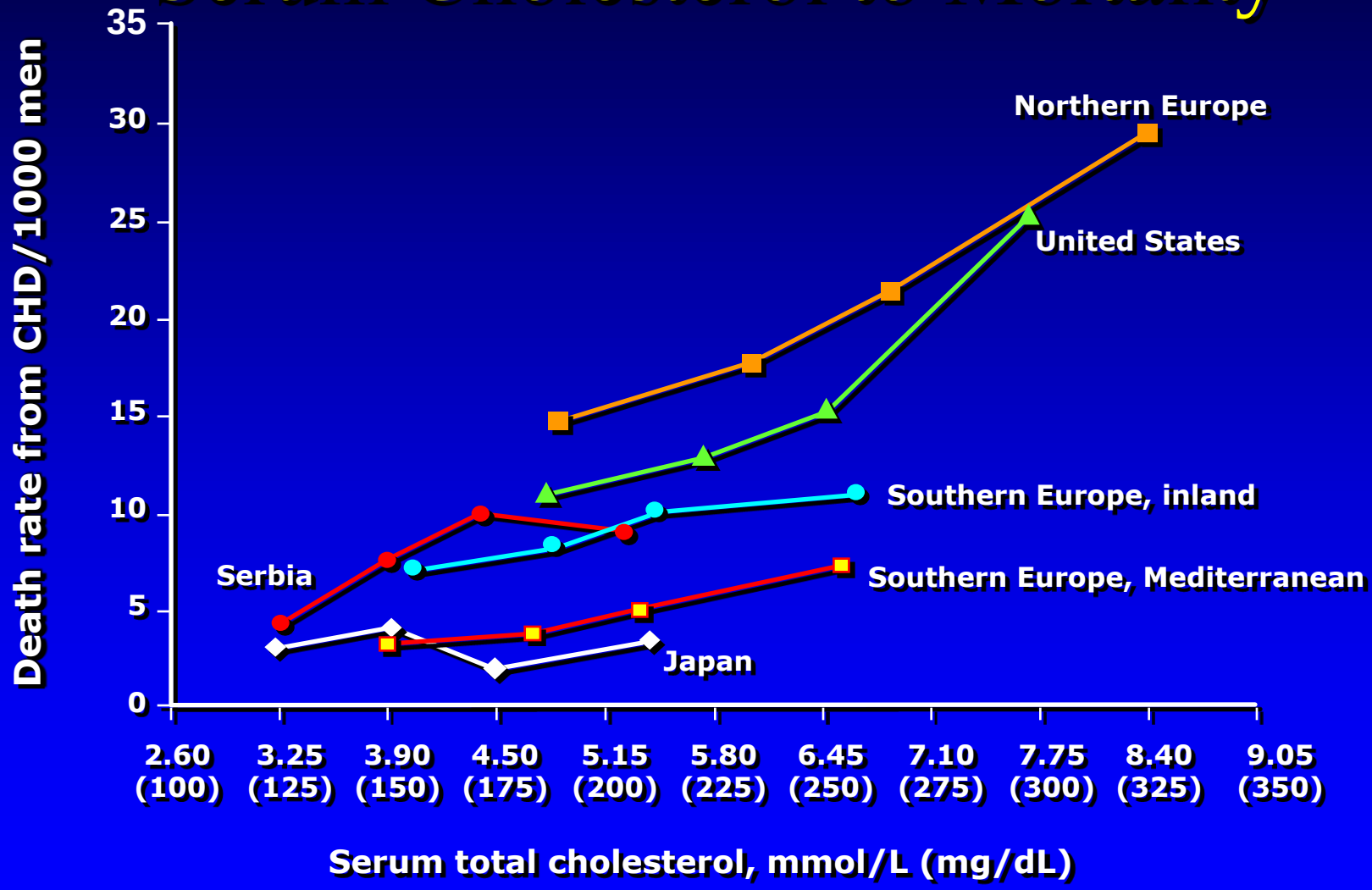
Background evidence

The Framingham Study: Relationship Between Cholesterol and CHD Risk



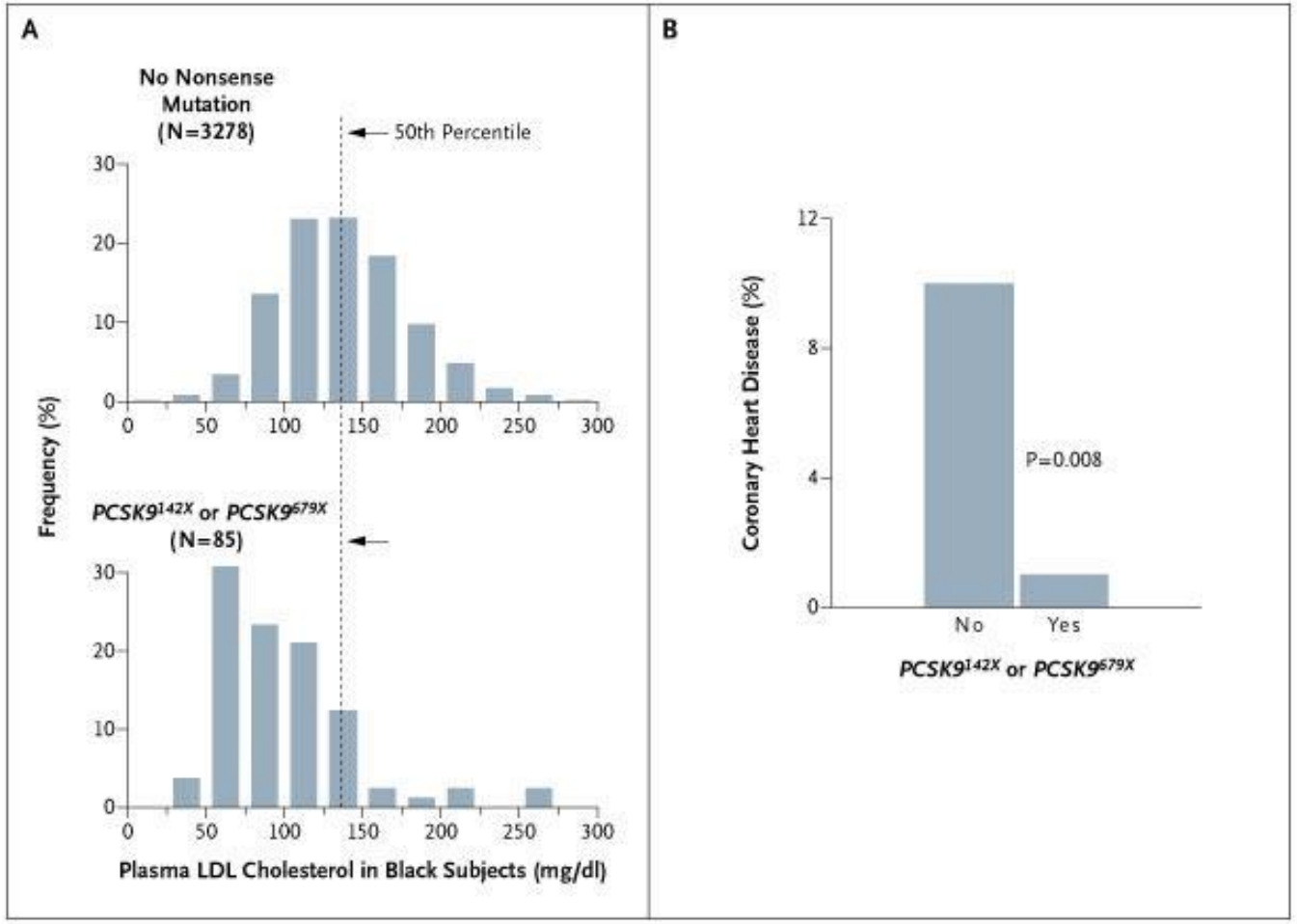
Adapted from Castelli WP. *Am J Med* 1984;**76**:4–12

Seven Countries Study: Relationship of Serum Cholesterol to Mortality



Adapted from Verschuren WM *et al. J Am Med Assoc* 1995;**274**(2):131–136

Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a PCSK9^{142X} or PCSK9^{679X} Allele



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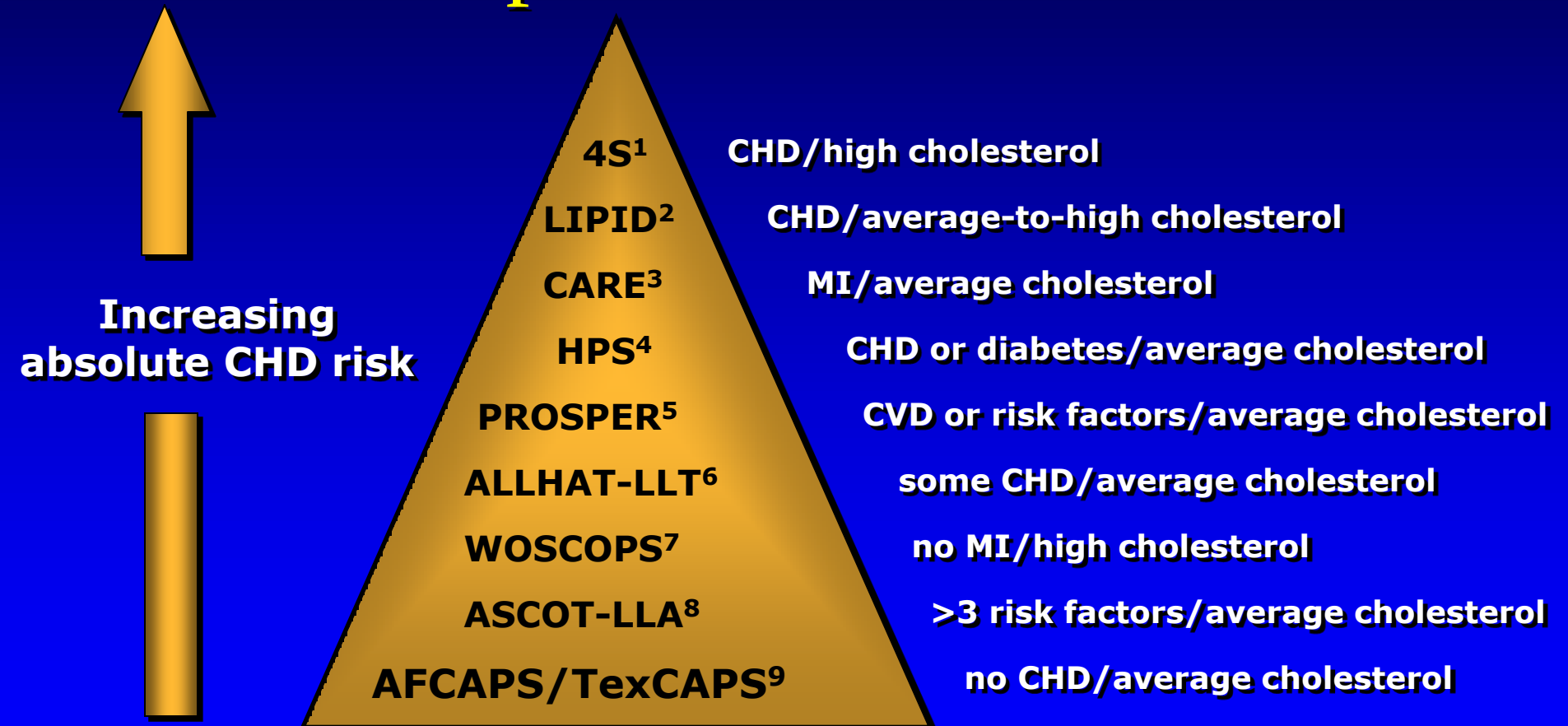
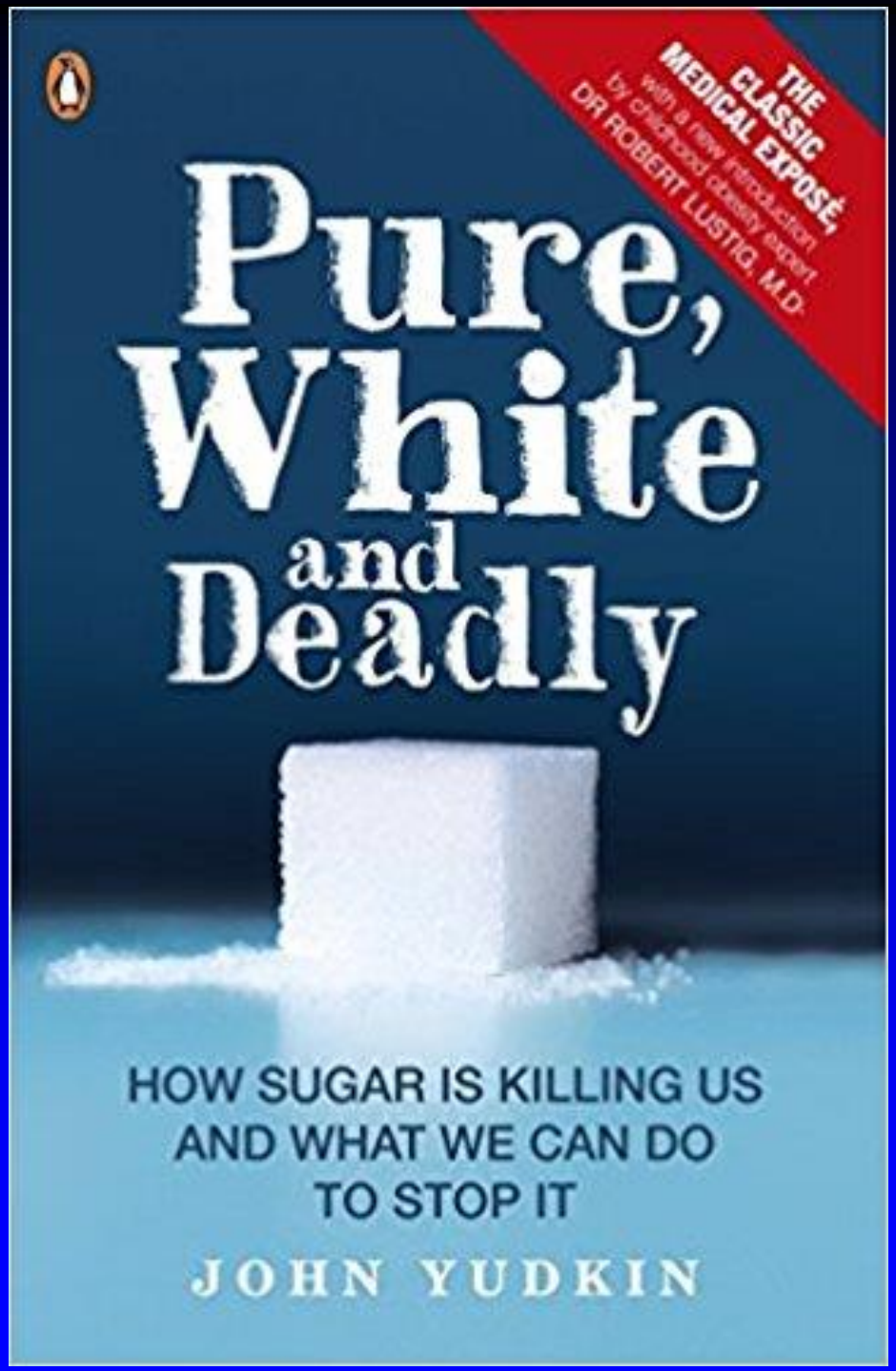
Cohen, J. et al. N Engl J Med 2006;354:1264-1272

Key Statin Trials and Spectrum of Risk



What else?

- Sugar
  - Increasing evidence that the amount of refined sugar in the diet is linked to obesity
  - Too much emphasis on fat alone and insufficient emphasis on a sensible diet
- Dietary advice
  - Not too much, mostly plants
  - Count the legs
- Come back Professor Yudkin all is forgiven


THE CLASSIC MEDICAL EXPOSÉ
with a new introduction by childhood obesity expert DR ROBERT LUSTIG, M.D.
Pure, White and Deadly
HOW SUGAR IS KILLING US AND WHAT WE CAN DO TO STOP IT
JOHN YUDKIN

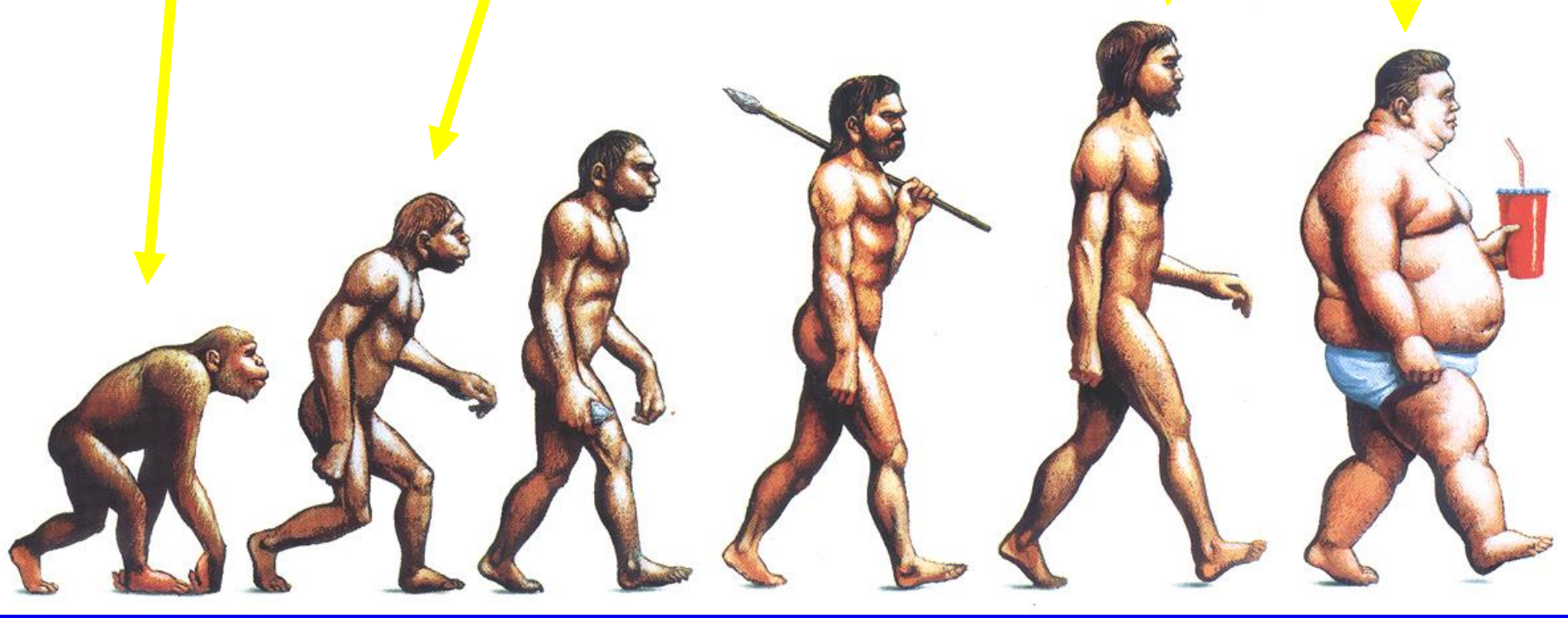
The evolution of man

Banker

Surgeon

GP

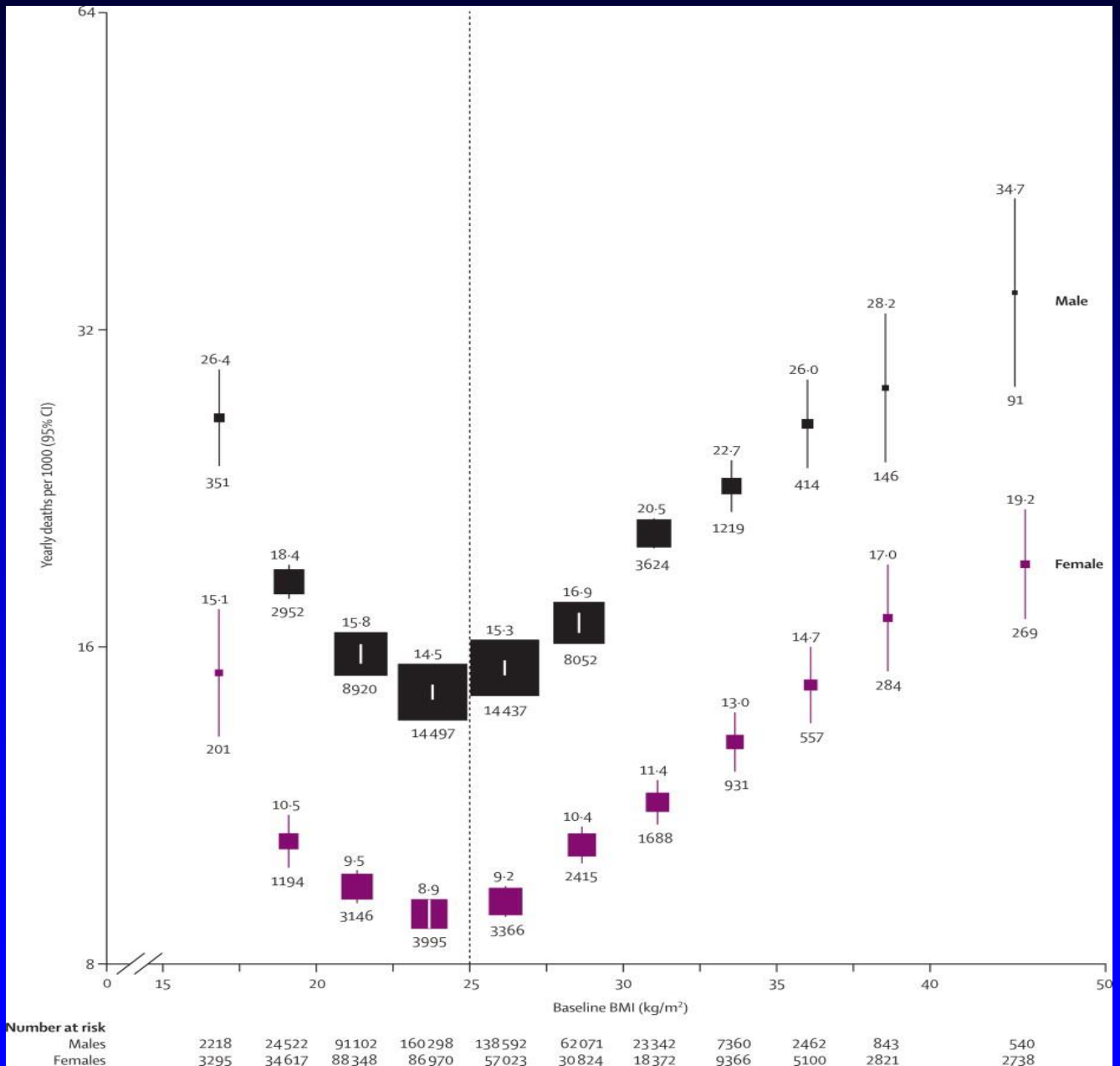
Patient



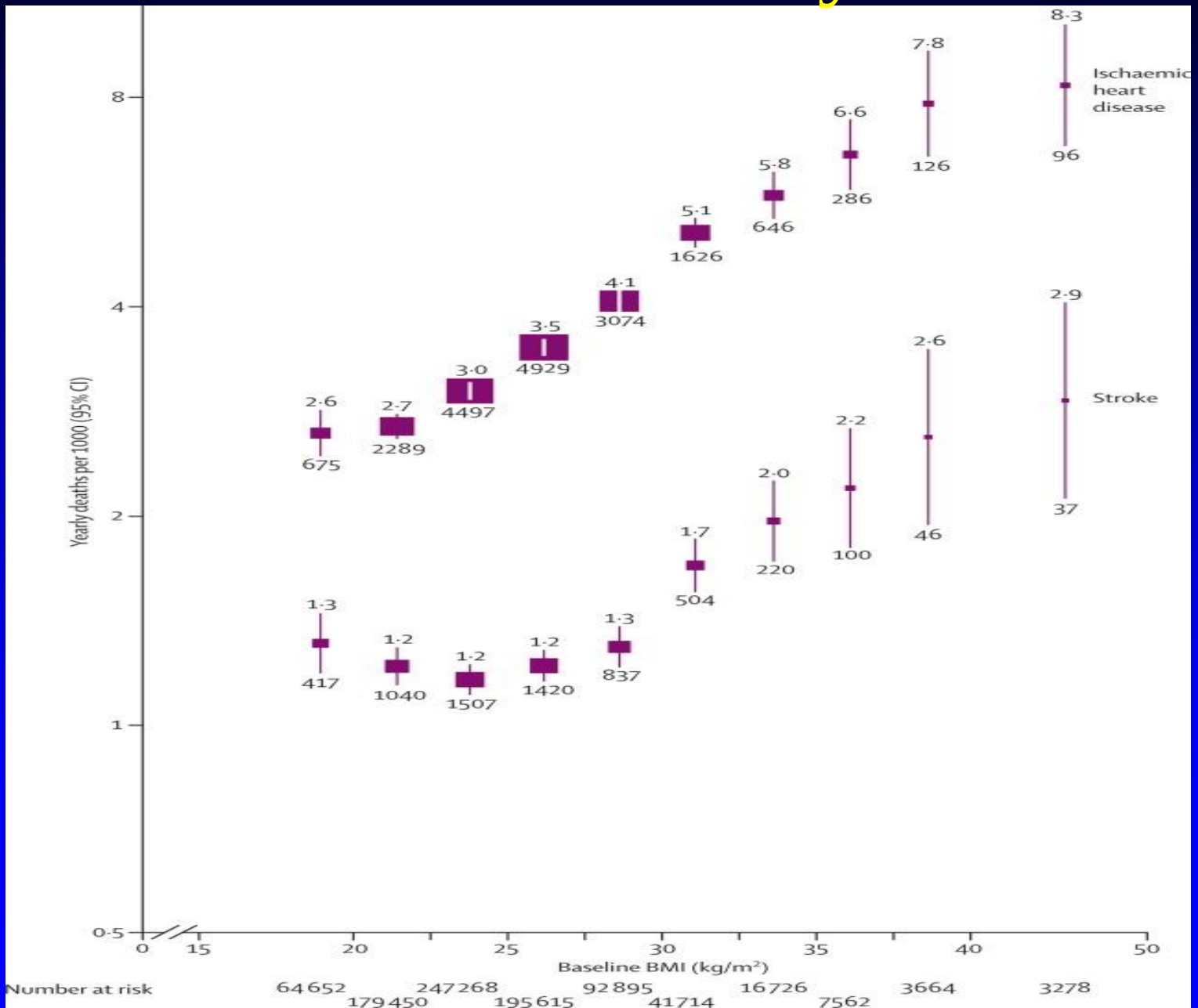

Green Giant Fresh

Obesity

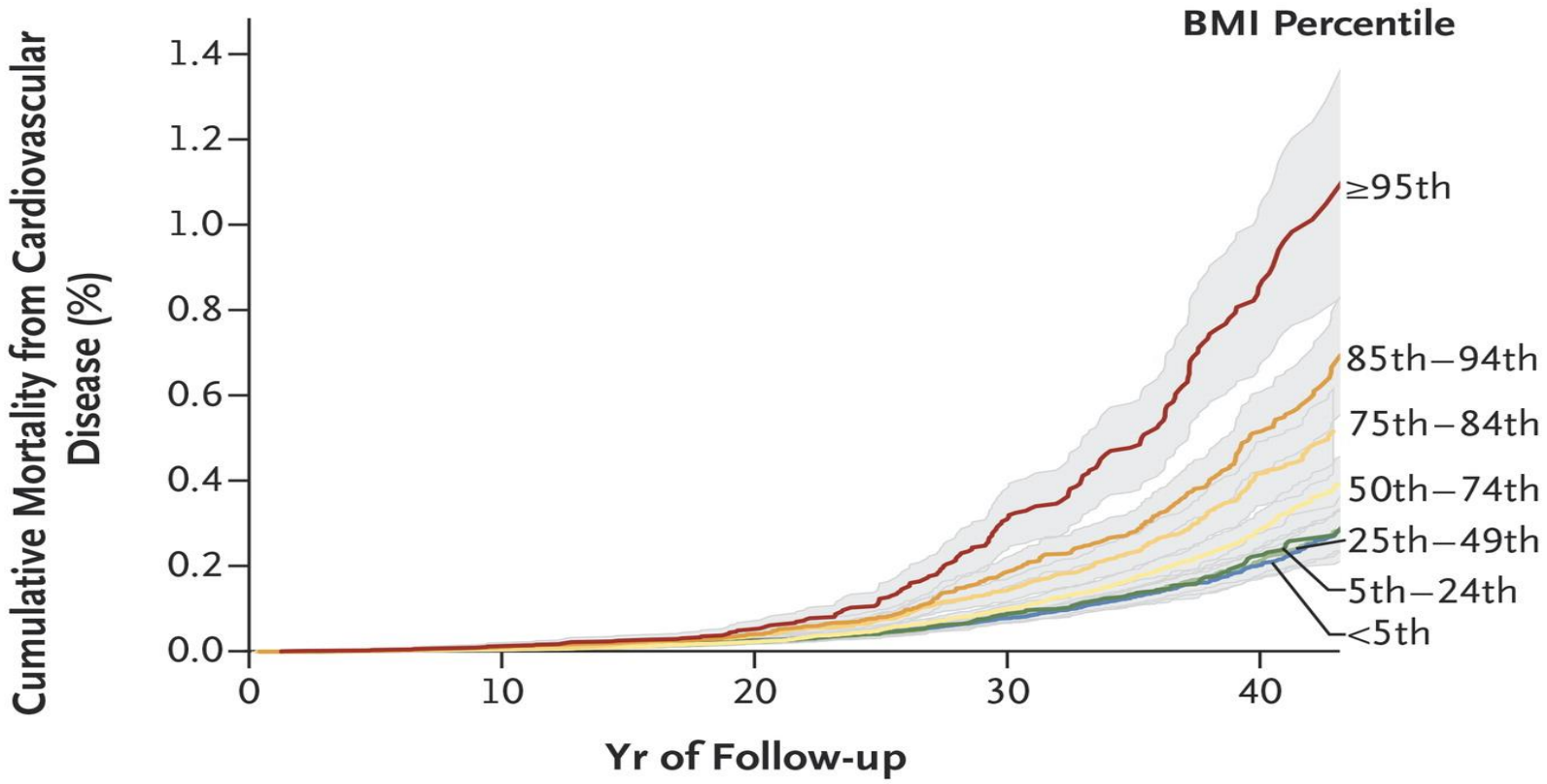
All cause mortality



CVD mortality



Body-Mass Index (BMI) during Adolescence and Subsequent Cardiovascular Mortality.



No. at Risk

Participants at risk	1,712,018	1,042,018	540,636	160,145
Cumulative person-yr	17,201,301	30,718,320	38,472,521	41,926,636
Cumulative cardiovascular deaths	185	609	1,577	2,676

Twig G et al. N Engl J Med 2016;374:2430-2440.

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Guidelines

Guidelines

- Guideline groups from Europe, UK and US have taken the same evidence base and produced different guidelines

ESC

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
≥5 to <10, or high-risk	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice and drug treatment for most	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high-risk	Lifestyle advice, consider drug	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

NICE

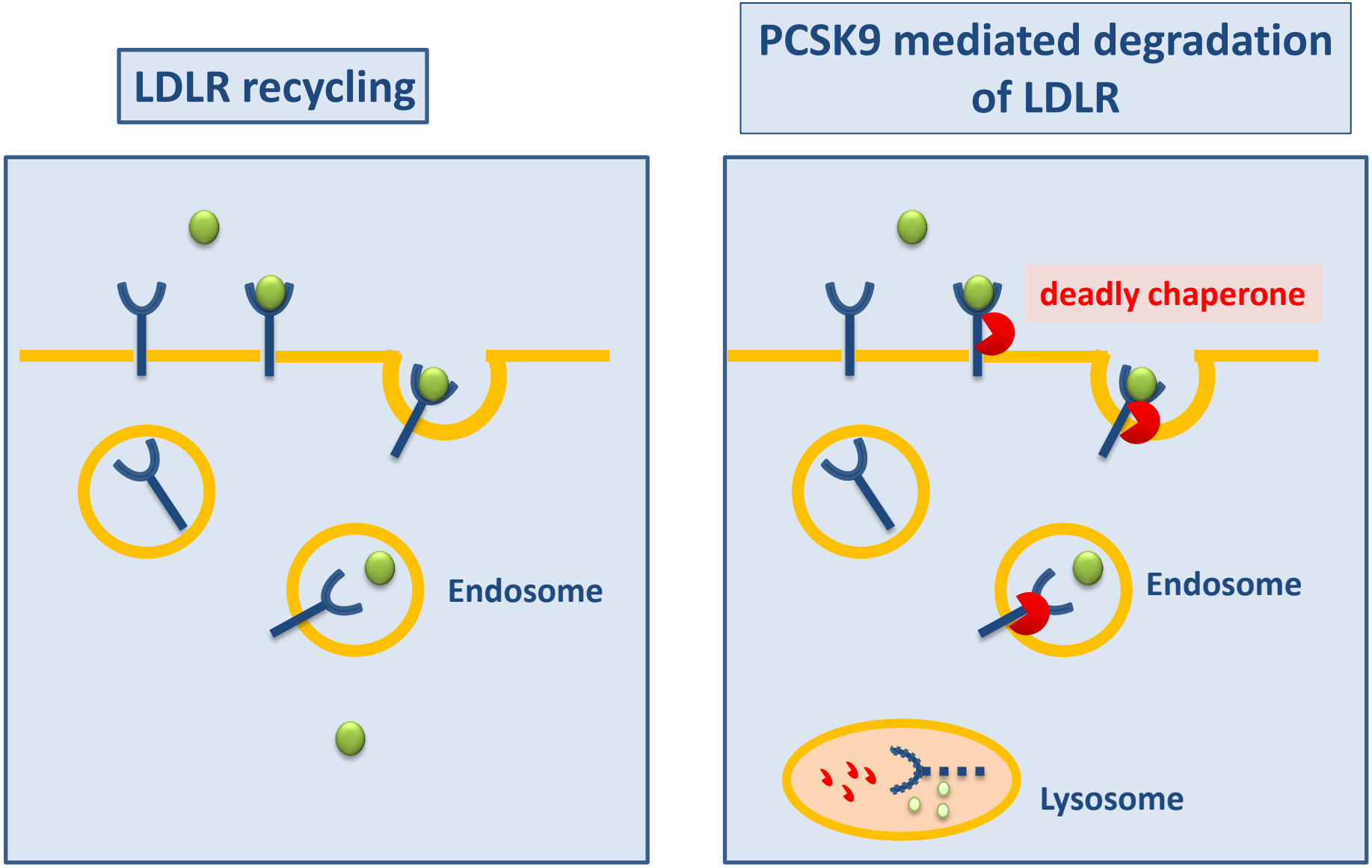
- Before
  - 20% risk intervention by QRISK
  - LDL target of 3.0 mmol/L
- After - NICE guidelines [CG181] Published date: July 2014 Last updated: July 2016
  - 10% risk intervention by QRISK2
  - Use non-HDL cholesterol
  - 40% reduction in non-HDL cholesterol

Treatment options

Treatment options

- Statins
- No nicotinic acid
- Ezetimibe is now accepted
  - RCT evidence from Improve-IT
- PCSK9 inhibitors

PCSK9 mechanism of action



	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	

[1] High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; chronic heart disease; ischaemic stroke; peripheral arterial disease.
[2] Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Pragmatic lipidology

Presentation

- Family history of premature CVD or sudden death
  - Males <55, females <65 (<60)

- Incidental finding
  - Opportunistic check
  - Health screening
  - Investigation of chest pain

- Presentation with clinical sequelae of hyperlipidaemia
  - Myocardial infarction/PVD/CAS/CVA
  - Acute pancreatitis
  - Xanthelasma / xanthomata

Classification of hyperlipidaemia

- **Primary**

- **Secondary**
  - Hypothyroidism
  - Diabetes
  - Renal disease
  - Liver disease
  - Alcohol

Baseline investigations on all patients with lipid disorders

- Lipid profile (no longer requirement for fasting) (TC, HDL, non-HDL, LDL,Tg)
- U and E
- LFT and γGT
- Fasting glucose / HbA1c
- TFT
- Urine dipstick

Initial assessment

- Exclude secondary causes of dyslipidaemia
  - Consider the possibility of familial hypercholesterolaemia if total cholesterol > 7.5 mmol/L and family history of premature (<60) heart disease
- Can you classify the hyperlipidaemia?
- ? Genetic
- Who needs specialist referral?
  - Specialist referral if TC > 9.0 mmol/L or non-HDL >7.5mmol/L even if no FH
  - Urgent specialist review if TG > 20 mmol/L (unless XS ETOH or poor glycaemic control)

Classification

Chol +++ Type IIA	Chol +++ TG+ Type IIB	Chol ++ TG ++ Type III	Chol +++ TG +++ Type IV	Chol + TG +++	
				Type I	Type V
Familial Hyper-cholesterol-aemia (FH) (1/500)	FH Familial Combined Hyperlipida emia	Type III	Often secondary	Familial Hyper-triglyceridaemia	Polygenic
Polygenic	Polygenic			LPL deficiency Apo CII deficiency	
LDL	LDL VLDL	Increased IDL	VLDL	Chylomicrons	Chylomicrons VLDL

Who to treat ?

Familial hypercholesterolaemia

Secondary prevention - All patients with established vascular disease

- Angina, MI, PVD,CAS,CVA

Primary prevention (specific groups)

- Type 1 diabetes
- Type 2 diabetes
- CKD (eGFR <60)

Primary prevention

- Depends on risk

Risk scoring
A holistic approach to risk factors

- Various scoring systems
- Predicts 10 year risk of cardiovascular disease
- All utilise the same risk factors
  - Age
  - Gender
  - Blood pressure
  - Total cholesterol or TC/HDL ratio
- NICE specify QRISK 2 (soon 3)
- Recognition that they may under score for some groups

QRISK2-2016

ClinRisk

Welcome to the QRISK®2-2016 risk calculator: https://qrisk.org

This calculator is only valid if you do not already have a diagnosis of coronary heart disease (including angina or heart attack) or stroke/transient ischaemic attack.

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About you

Age (25-84): 64

Sex: ○ Male ◉ Female

Ethnicity: White or not stated

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status: heavy smoker (20 or over)

Diabetes status: none

Angina or heart attack in a 1st degree relative < 60? ☑

Chronic kidney disease (stage 4 or 5)? ☐

Atrial fibrillation? ☐

On blood pressure treatment? ☑

Rheumatoid arthritis? ☐

Leave blank if unknown

Cholesterol/HDL ratio: 6.2

Systolic blood pressure (mmHg): 133

Body mass index

Height (cm): 160

Weight (kg): 62

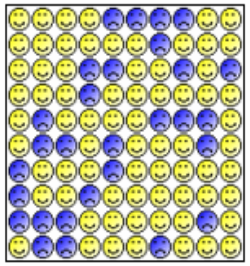
Calculate risk over 10 years. Calculate risk

Your results

Your risk of having a heart attack or stroke within the next 10 years is:

28.7%

In other words, in a crowd of 100 people with the same risk factors as you, 29 are likely to have a heart attack or stroke within the next 10 years.



Risk of heart attack or stroke

Your score has been calculated using estimated data, as some information was left blank.

Your body mass index was calculated as 24.22 kg/m².

How does your 10-year score compare?

Your score

Your 10-year QRISK®2 score	28.7%
The score of a healthy person with the same age, sex, and ethnicity*	8.2%
Relative risk**	3.5
Your QRISK® Healthy Heart Age***	81

* This is the score of a healthy person of your age, sex and ethnic group, i.e. with no adverse clinical indicators and a cholesterol

Side effects

Side effects

- Side effects do occur in statin therapy
- The current debate is ill-informed by statements that say
  - No one in clinical trials had side effects
  - Side effects occur in 10-20%
- Side effects have a strong psychological component

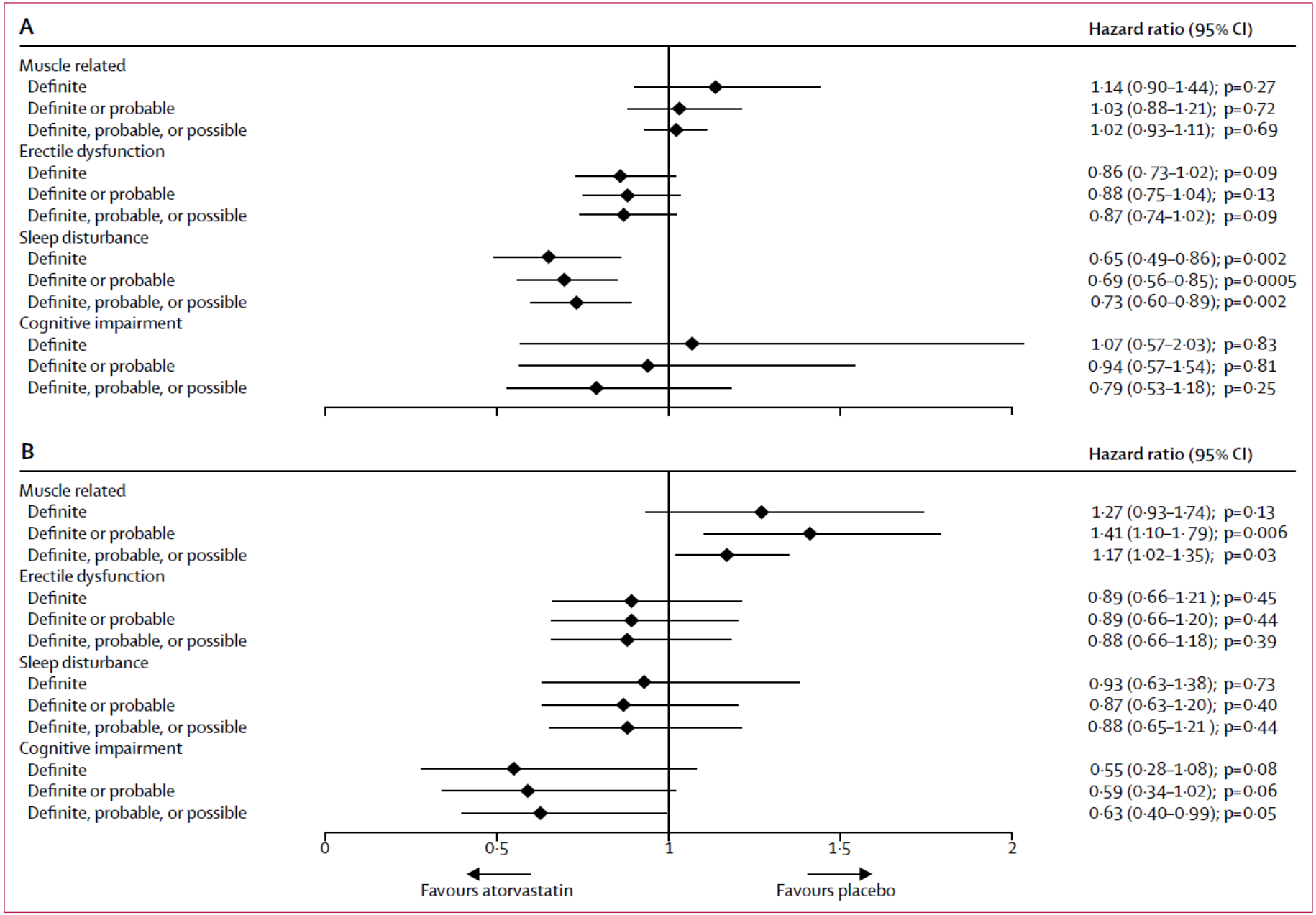


Figure 2: Risk of adverse events of interest in the (A) blinded randomised phase and (B) non-blinded non-randomised phase, grouped according to adjudication certainty

How well can we extrapolate from clinical trial studies?

Clinical trial data

- Well screened, highly selected patients
- Frequent and intensive monitoring
- Good compliance

Real life practice

- Unselected patients
- Co-morbidities
- Polyphramacy
- Variable understanding and drug compliance
- Monitoring may be problematic

What to do

- Prove that it is due to the statin
  - Did the side effect stop when the statin stopped
- Exclude hypothyroidism, Vitamin D deficiency and muscle disease (check CK)
- Replete Vitamin D if deficient
- Re-challenge at a lower dose
  - Stop if the side effect occurs
    - Stop for one week – does it go away
    - Re-challenge - does it come back

Then

- Try a low dose of a different statin
- Try once weekly Rosuvastatin 5mg with dose escalation
  - Twice a week
  - Three times a week
  - Alternate days
- Then add ezetimibe

Familial hypercholesterolaemia

- A diagnosis of FH should be made using the Simon Broome criteria, which include a combination of family history, clinical signs (specifically tendon xanthomata), cholesterol concentration and DNA testing

- Diagnose a person with definite familial hypercholesterolaemia (FH) if they have:
  - cholesterol concentrations as defined in table 1 and tendon xanthomas, or evidence of these signs in first- or second-degree relative or
  - DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.
- Diagnose a person with possible FH if they have cholesterol concentrations as defined in table 1 and at least one of the following.
  - Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative.
  - Family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative or greater than 6.7 mmol/l in child, brother or sister aged younger than 16 years.

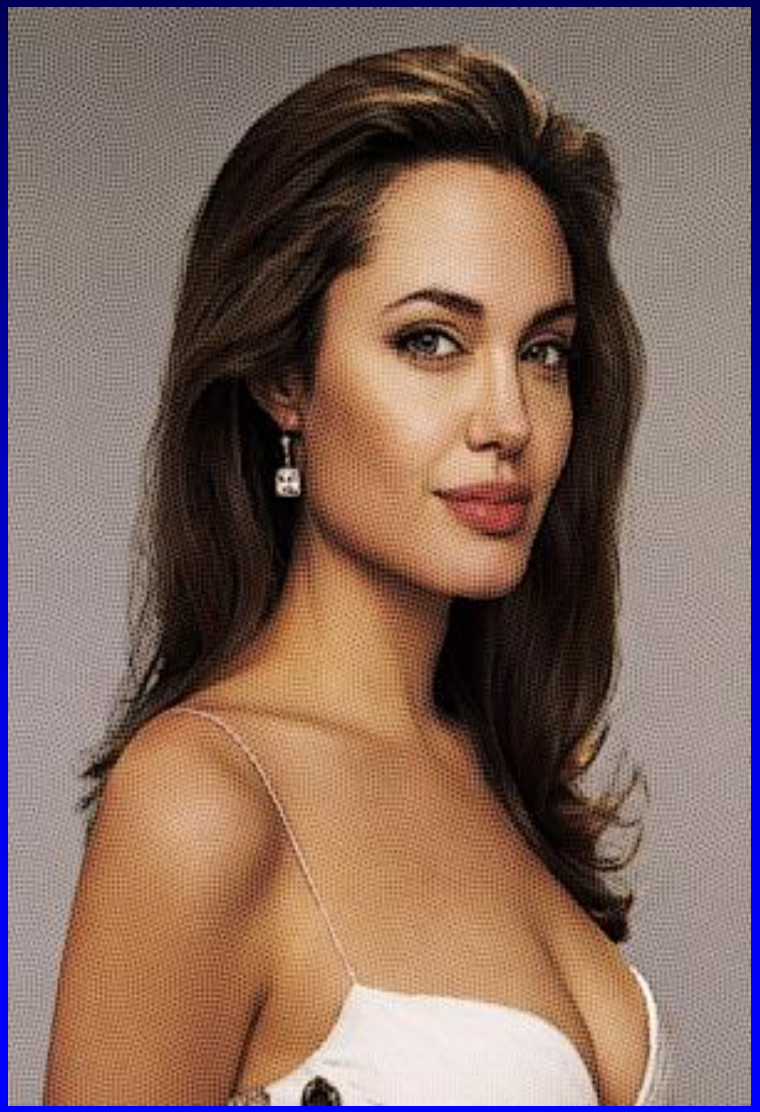
	Total cholesterol	**LDL-C**
Child/young person	> 6.7 mmol/l	> 4.0 mmol/l
Adults	> 7.5 mmol/l	> 4.9 mmol/l

What does this really mean?

- Genetic testing is required for FH diagnosis
- This is (relatively) cheap and will get cheaper and is essential for cascade testing
- It is only required if treatment decisions are uncertain or cascade testing is contemplated

Cases

Case studies - typical patients



Case

- Female 55 years
  - Referred with TC of 7.9 mmol/L
  - FH of IHD
- Details of history
  - Brother had AMI age 66 and was a heavy smoker
- Non smoker having never smoked
- Weight 55 kg, BMI 20
- BP 110/70
- No medication
- Caucasian genes

Investigations

- TC 8.0 mmol/L
  - HDL 3.5 mmol/L
  - Tg 1.1 mmol/L
  - LDL 4.0 mmol/L
  - TC/HDL ratio 2.3
- Risk score?

Investigations

- TC 8.0 mmol/L
- HDL 3.5 mmol/L
- Tg 1.1 mmol/L
- LDL 4.0 mmol/L
- Tc/HDL ratio 2.3
- Risk score – 2.7% QRISK2 and <1% by HeartSCORE
- Additional data
  - CRP 0.4 mg/L(High risk >3)
  - Lp(a) <20 (high risk >300)

Case

- Male 55 years
- TC 6.5 mmol/L
- FH IHD
- Details of history
  - Father had AMI age 64, smoker
  - Brother had CABG age 59, smoker
- Smoker 20/day from age 20
- Weight 70 kg BMI 29.1
- BP 150/95
- Asian genes

Investigations

- TC 6.5 mmol/L
  - HDL 0.7 mmol/L
  - Tg 1.1 mmol/L
  - LDL 5.3 mmol/L
  - TC/HDL ratio 9.3
- Risk score?

Investigations

- TC 6.5 mmol/L
  - HDL 0.7 mmol/L
  - Tg 1.1 mmol/L
  - LDL 5.3 mmol/L
  - TC/HDL ratio 9.3
- Risk score 54.2$ QRISK2 and 8-13% HeartSCORE
  - Increase by 50% for ethnicity
  - Increase by 50% for FH IHD
- Note that the non-smoking risk is still 34.4% by QRISK2 4-7% HeartSCORE so enters the treatment band due to ethnicity and FH

Investigations

- CRP 6 mg/L (high risk >3)
- Lp(a) 450 mg/L (>300 high risk)

Case

- Female 55 years
- TC 15.0 mmol/L
- Tg 27.4 mmol/L
- Glucose 35.5 mmol/L
- HbA1c 120 mmol/mol
- Panic Panic Panic

Case

- Treatment
  - Manage diabetes
    - Metformin initially 500mg bd then 1000mg bd

Case

- 1 month later
  - TC 6.5 mmol/L
  - Tg 2.2 mmol/L
  - HDL 1.0 mmol/L
  - LDL 4.5 mmol/L
  - Glucose 6.9 mmol/L
  - HbA1c 82 mmol/mol
- Add atorvastatin 20 mg od

Case

- Male 46
- TC 12.1 mmol/L
- Tg 35.2 mmol/L
- Glucose 4.5 mmol/L
- HbA1c 23 mmol/mol
- LFT including GGT – normal
- TFT - normal

Case

- BMI 26.9
- Lipoprotein electrophoresis
  - Type III pattern
- Apo E genotype
  - E2/E2
- Rx
  - Fenofibrate micronised 160 mg od

Case

- 3 months later

- TC 5.2
- Tg 1.1
- HDL 1.5
- LDL 3.2

Case

- Female
- 52 years
- TC 13.4 mmol/L
- Tg 4.9 mmol/L
- HDL 1.8 mmol/L
- Non HDLC 11.6 mmol/L

Case

- Referred urgently as FH
- Commenced on Atorvastatin 40mg
- Severe myalgia – stopped statin (an avid Daily Mail reader)

Case

- CK – 850 U/L
- Vitamin D - <17 nmol/L
- Statin induced myopathy?
- Glucose 7.1 mmol/L
- HbA1c 32 mmol/mol
- LFT
  - ALT 65U/L (<40)
  - GGT 85 U/L (<40)
- BMI 29.9

Case

- **BUT**
- fT4 3.2 nmol/L
- TSH 134.2 mu/L

- Thyroxine 50 > 75 > 100 mcg/L

Case

- 6 months later

- TC 5.2 mmol/L
- Tg 0.8 mmol/L
- HDL 2.2 mmol/L
- LDL 2.6 mmol/L

- But what was she most pleased about
- BMI 26.8

Familial hyperlipidaemia implementation of clinical guidelines

- A family history should always be obtained from an individual being investigated for FH to determine if a dominant pattern of inheritance is present

Case

- Male 41 years
- FH IHD – father had quadruple bypass age 65 on a background of familial hypercholesterolemia
- Lipid profile

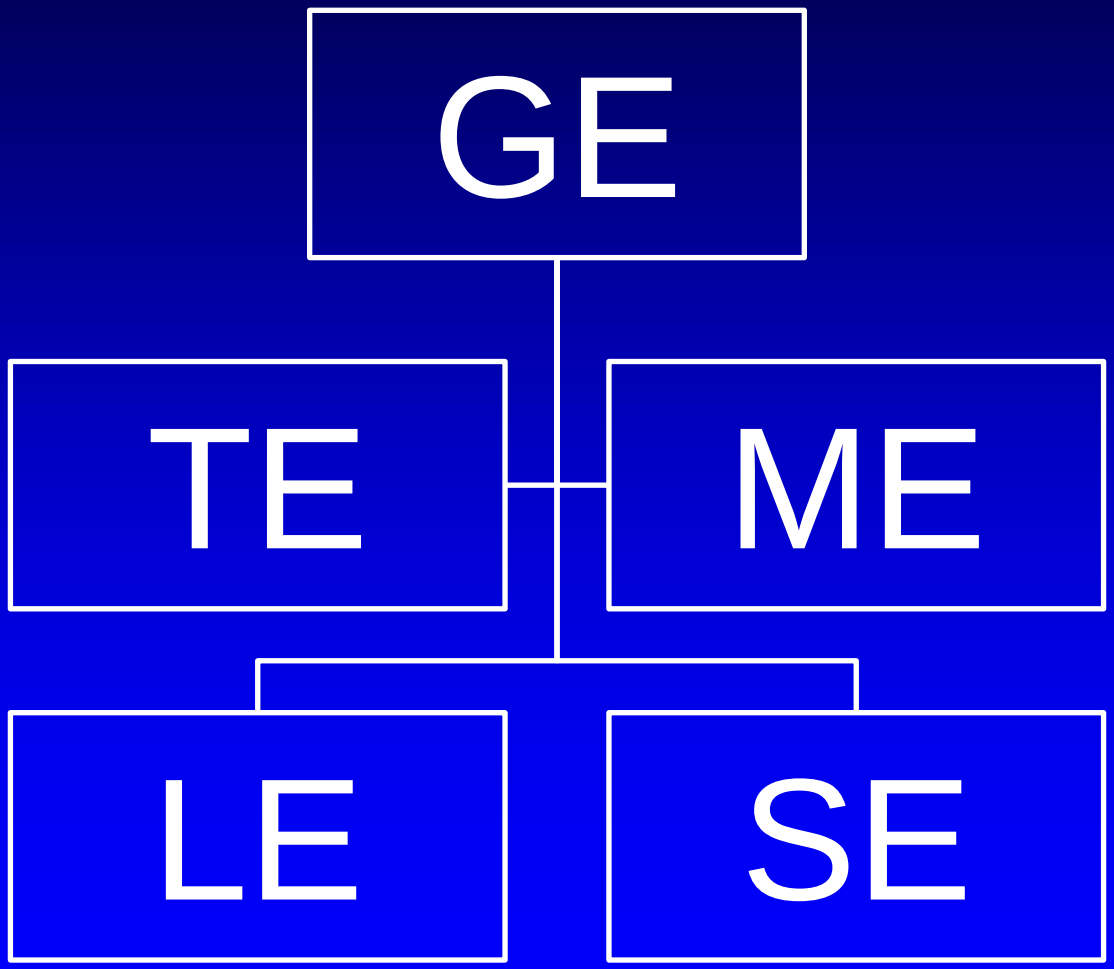
Total cholesterol	Trigs	HDL	LDL	Non-HDL	Apo a	Apo b	S-CRP
5.4	2.9	0.84	3.3	4.5	1.11	1.14	0.7

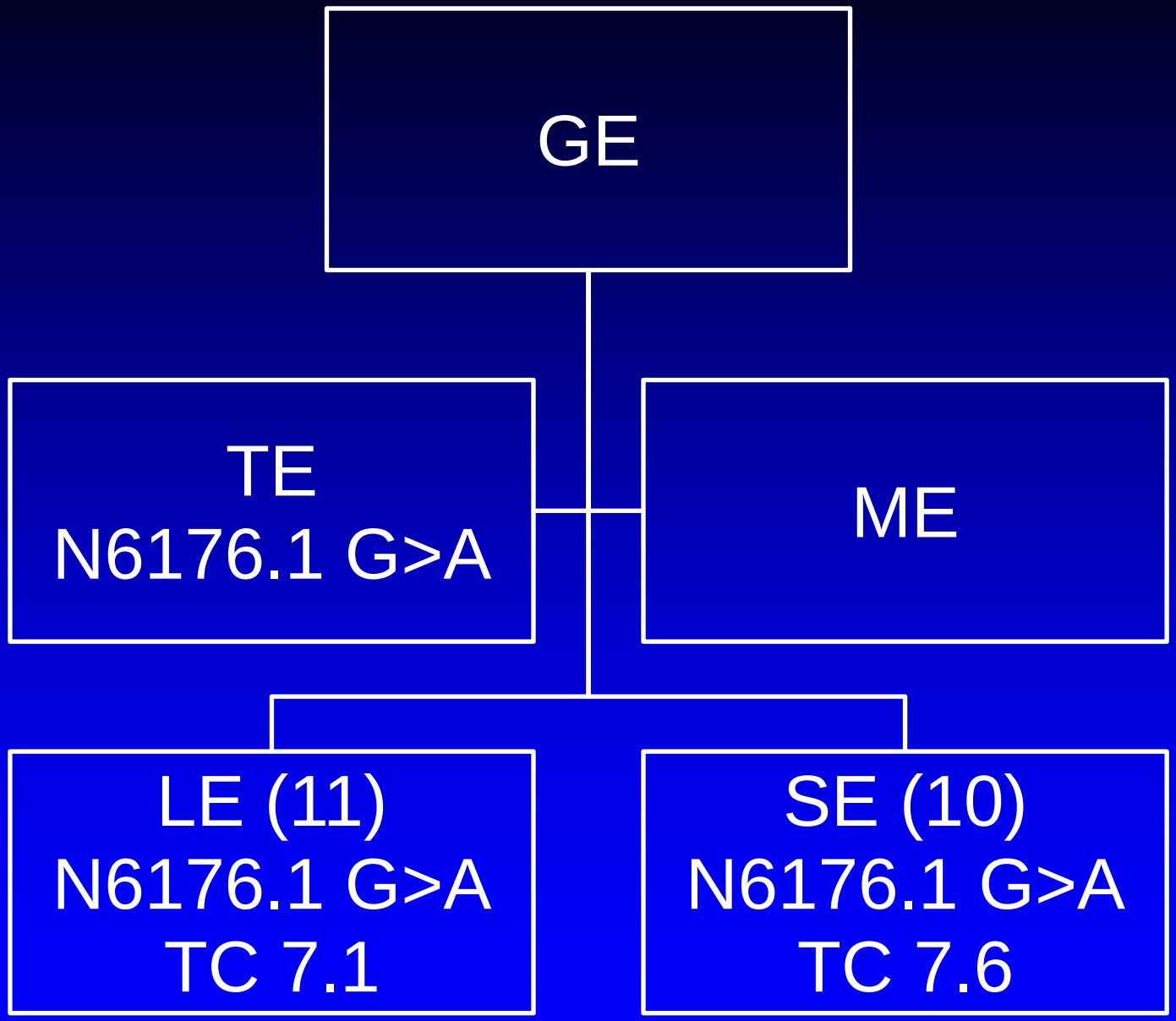
Treat?

- Splice mutation of LDLR N6176.1 G>A
- Yes

1. HDL raising
2. LDL lowering
3. Both

What next




GE
TE
N6176.1 G>A
ME
LE (11)
N6176.1 G>A
TC 7.1
SE (10)
N6176.1 G>A
TC 7.6

Treatment

- Both boys started on simvastatin 10mg

Learning points

- Paternal diagnosis on the basis of LDLR mutation
  - Treatment indicated
- Boys detected by cascade screening
  - NICE guidelines
- All patients with FH IHD and TC >7.5 should be reviewed
- All LDLR mutation positive should be tested

Conclusion

- Lipid lowering therapy will have clinical benefits in all groups
- Risk/benefit must may favourable
- Risk reduction must be greater that the risk of co-morbid conditions
  - Therapy was a success but the patient died
- Clinical judgement is required

Paul's guide to lipids

- Its never THAT urgent (except very high triglycerides)
- You do not have to fast to do cholesterol
- Never believe one reading always do two (preferably 3)
- Risk factor management before pills (death cures smoking) and Benecol drinks do work.
- Do risk stratification first
- Look at the HDL
- Look at the TC and Tg and think
- Tg >5
  - Exclude secondary causes
  - Refer