Familial Hypercholesterolaemia

Anthony S. Wierzbicki
Consultant in Metabolic Medicine/Chemical Pathology
St. Thomas' Hospital
London SE1 7EH

NICE guidelines for identifying FH

Simon Broome Criteria

- Diagnose a person with **definite FH** if they have:
  - cholesterol concentrations as defined below and tendon xanthomas, or evidence of these signs in a 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 below and at least one of the following:
  - Family history of myocardial infarction (MI): <50 years in second-degree relative or <60 years in first-degree relative.
  - Family history of raised total cholesterol in first- or second-degree relative as per table below.

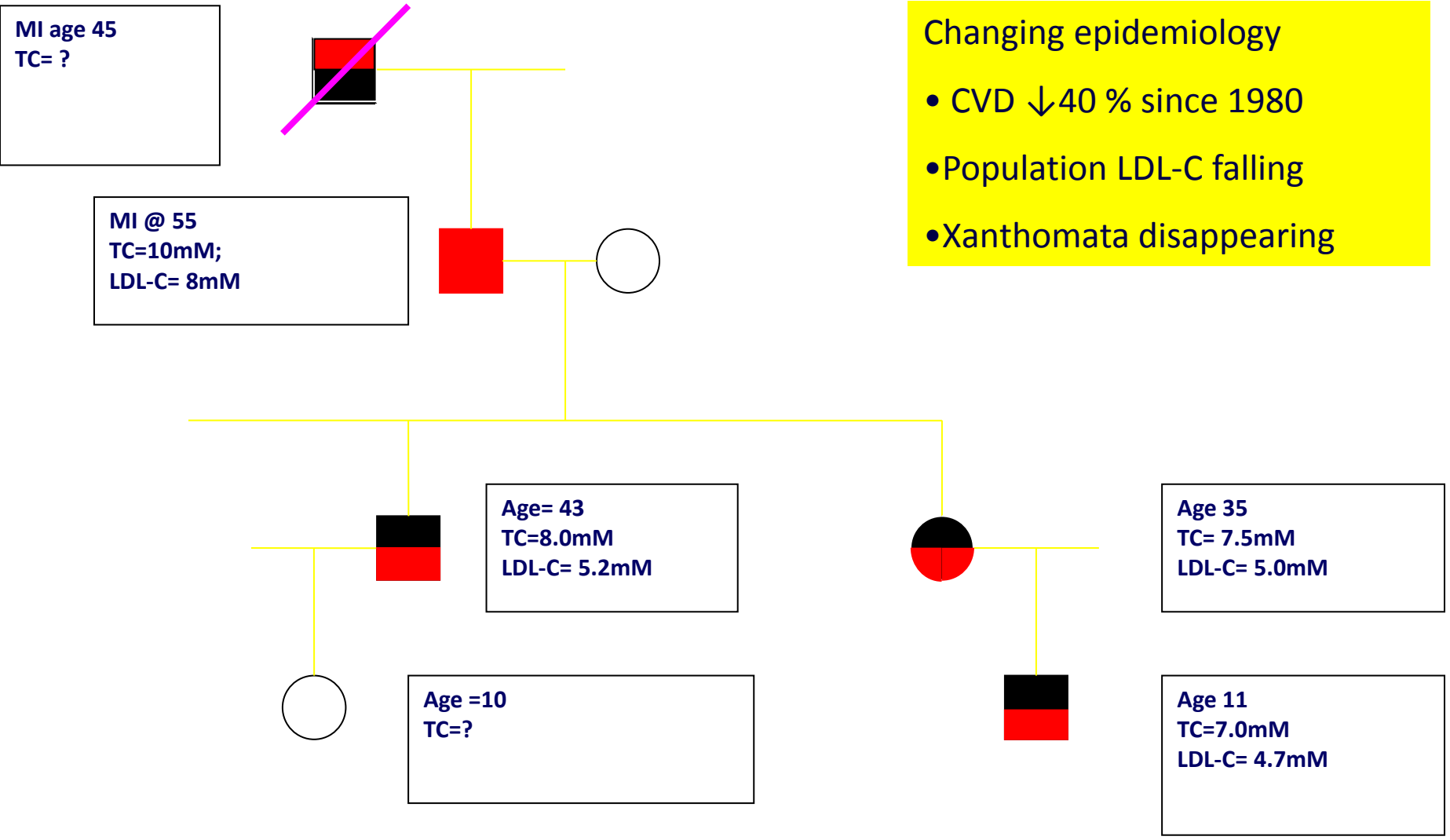
	Total cholesterol	**LDL cholesterol**
Under 16	> 6.7 mmol/L	> 4.0 mmol/L
Adults	> 7.5 mmol/L	> 4.9 mmol/L

Familial hypercholesterolaemia

- 1 in 500 (possibly 1 in 250)
- Autosomal dominant
- LDL receptor defect (chromosome 19)

- Higher incidence in some populations
- Afrikaaners; Quebecois; Lebanese (1%)

FH: typical pedigree



Changing epidemiology

- CVD ↓40 % since 1980
- Population LDL-C falling
- Xanthomata disappearing

Genetics of Familial Hypercholesterolemia

Major Defect

- Low density lipoprotein receptor (LDLR
  - More than 1000 mutations known
    - 85% point mutation; 5% insertion-deletion; 10% splicing

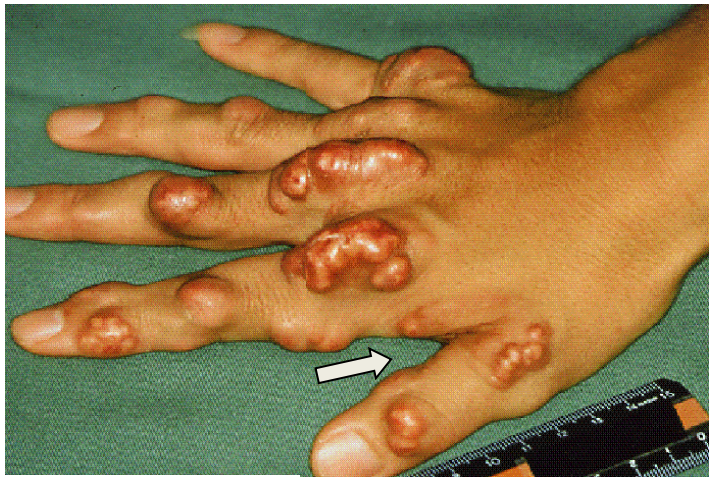
Minor defects

- Familial defective apoB_{100}
  - Defect of ligand not receptor
  - 1 in 20,000
  - Less severe phenotype
- PCSK-9 mutations
  - Controller of LDLR expression
  - Gain of function = FH phenocopy
  - 1 in 40,000
- Recessive FH (LRAP)
  - A variety of defects- best known in Sardinia
  - 1 in 10^6
  - Mild phenotype

Homozygous FH

- Rare: 1 in 10^6
- TC > 16mmol/L
- Signs:
  - Tendon xanthomata, tuberose xanthomata, arcus
- Poor statin response (0-30% ΔLDL)
  - As less residual LDLR function
- Life expectancy (untreated) = 33 years
  - CHD common by age 20
- Treatment
  - Drug therapy
  - Apheresis
  - Liver transplantation

Homozygous Familial Hypercholesterolaemia (FH)



Tendon xanthomas in homozygous FH
-pathognomic = finger web xanthomata

Identifying Heterozygous FH:

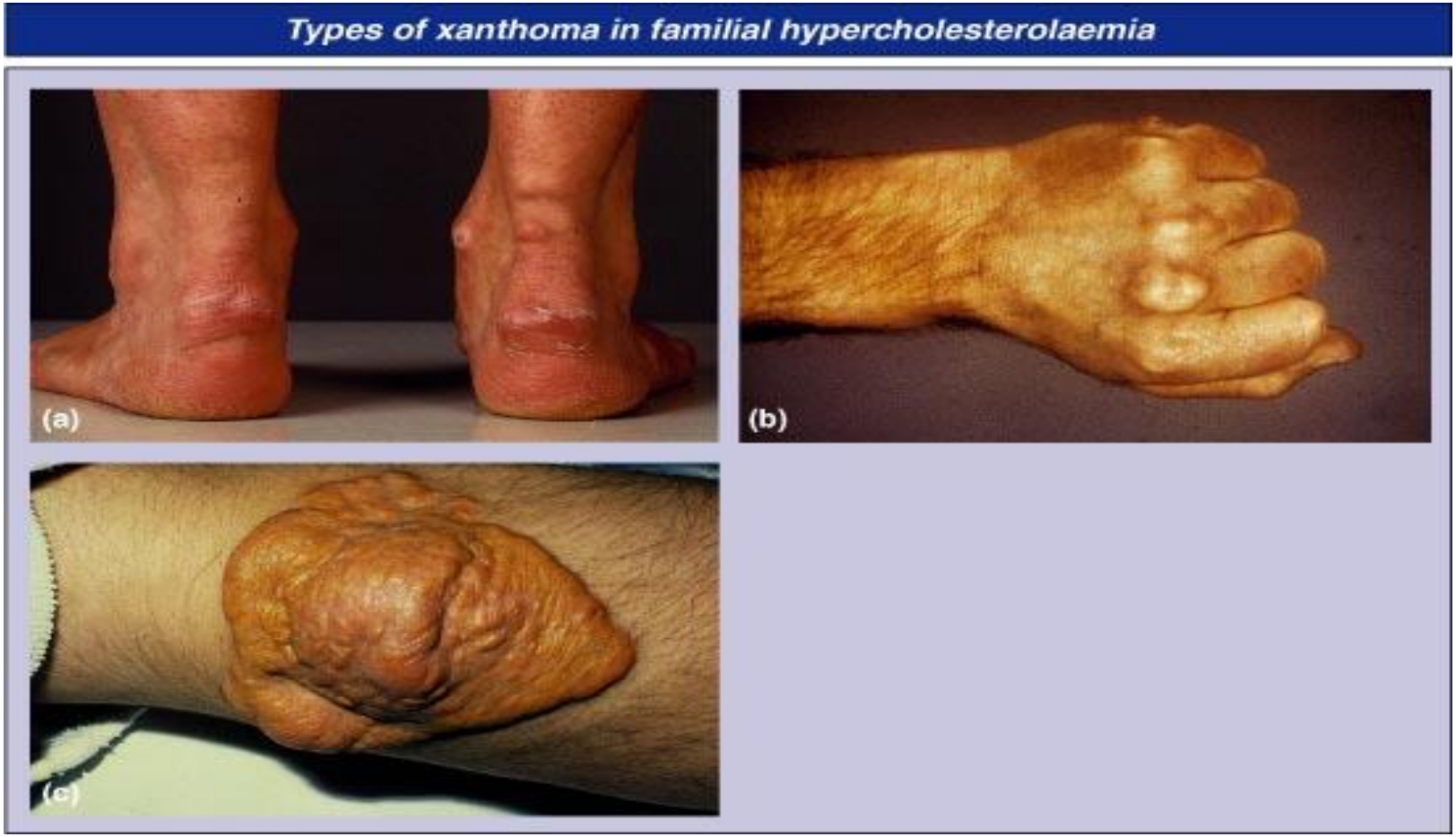
- <25% cases identified.
- There are other causes of premature myocardial infarction / raised LDL-cholesterol.
  - 9p21 CHD locus
  - Post-menopause LDL-C rise
  - High CHO diets/ excess alcohol lead to raised LDL-C

- Overlap with 'normal' population.
  - 12% UK population have FHx CHD
    - 2-3% have CHD <65 years old.
  - 2-15% UK population have cholesterol >7.5 mmol/L.
- Prevalence of tendon xanthoma / CHD falling.

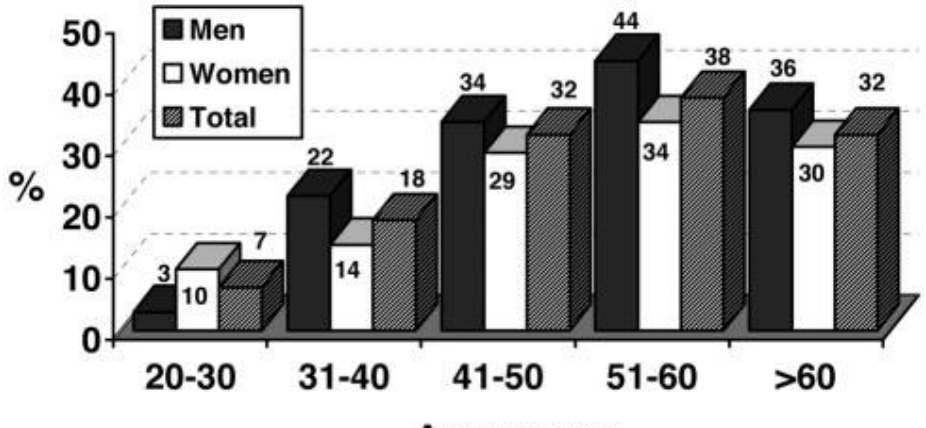
Heterozygous Familial Hypercholesterolaemia

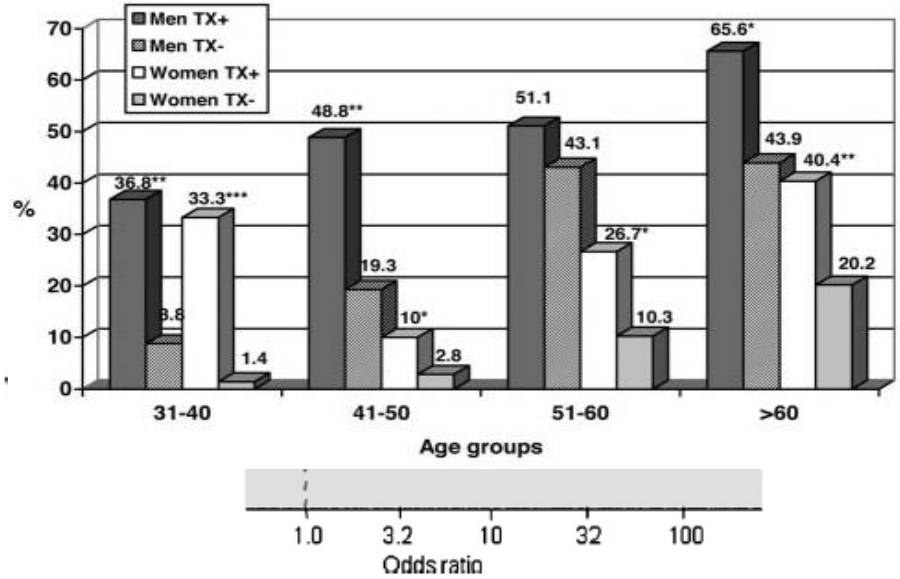
- Presentation
  - TC > 7.5 mmol/L LDL > 4.7 mmol/L
- Physical signs
  - tendon xanthomata (30%)
  - arcus
- CHD age range 20-75 (highly variable)
  - Clinical diagnostic criterion :
    - CHD < age 60yrs

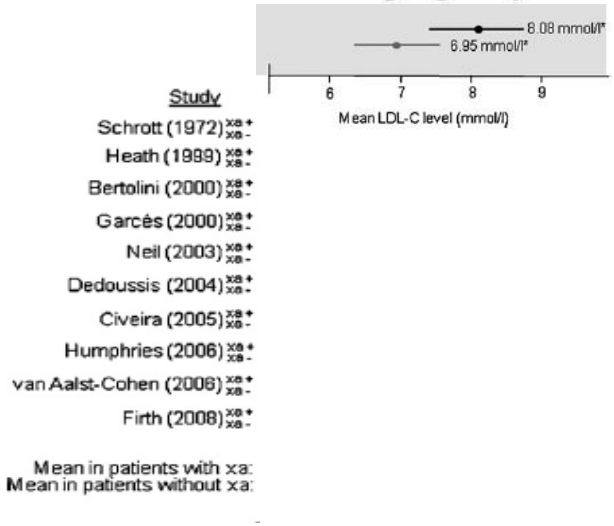
Clinical signs of FH



FH: tendon xanthomata & risk

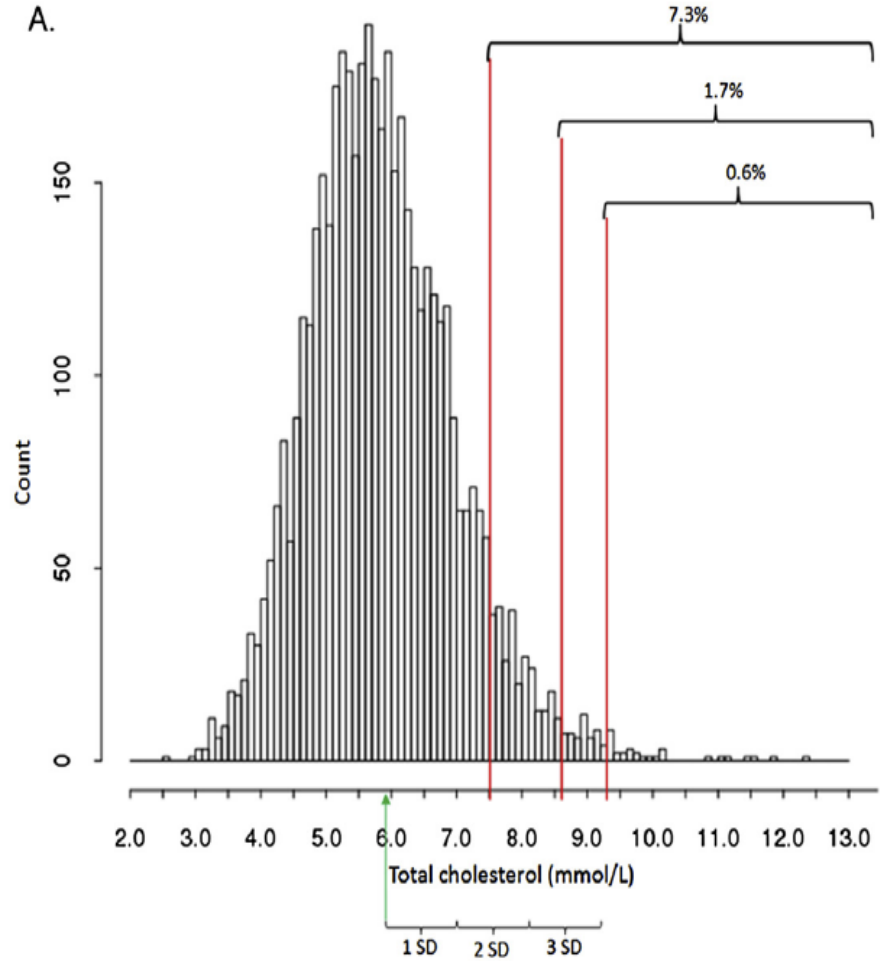




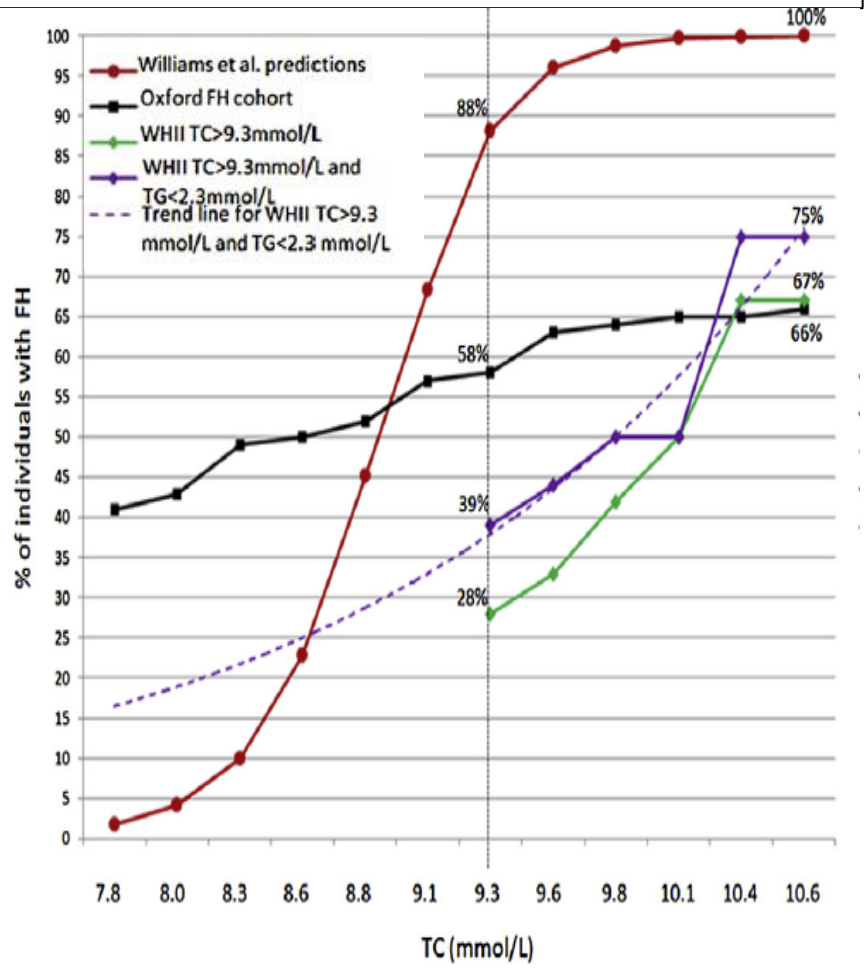


FH screening by lipid cut-offs

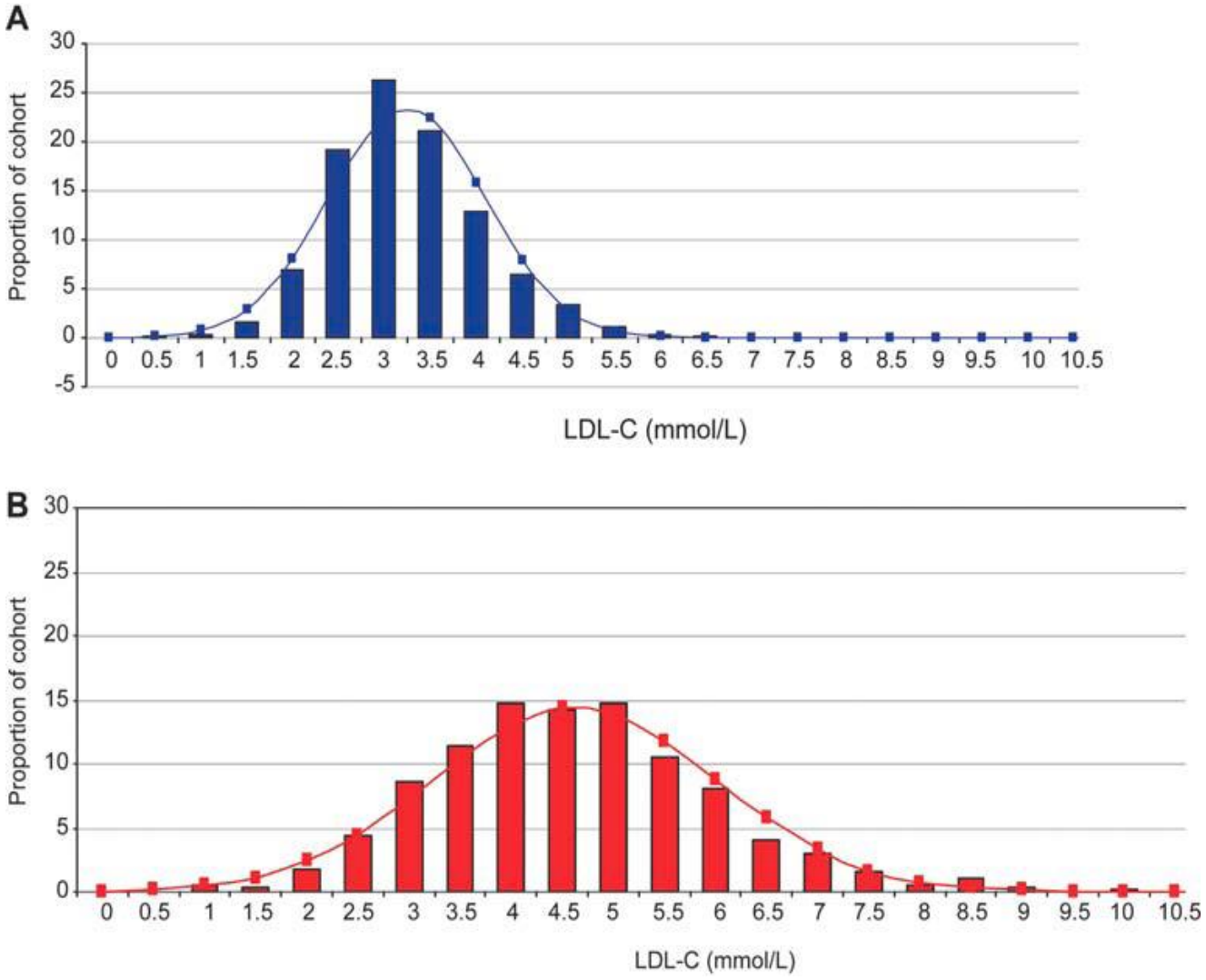
Population lipid distribution



FH detection by cohorts



LDL-C distributions in FH and the general population

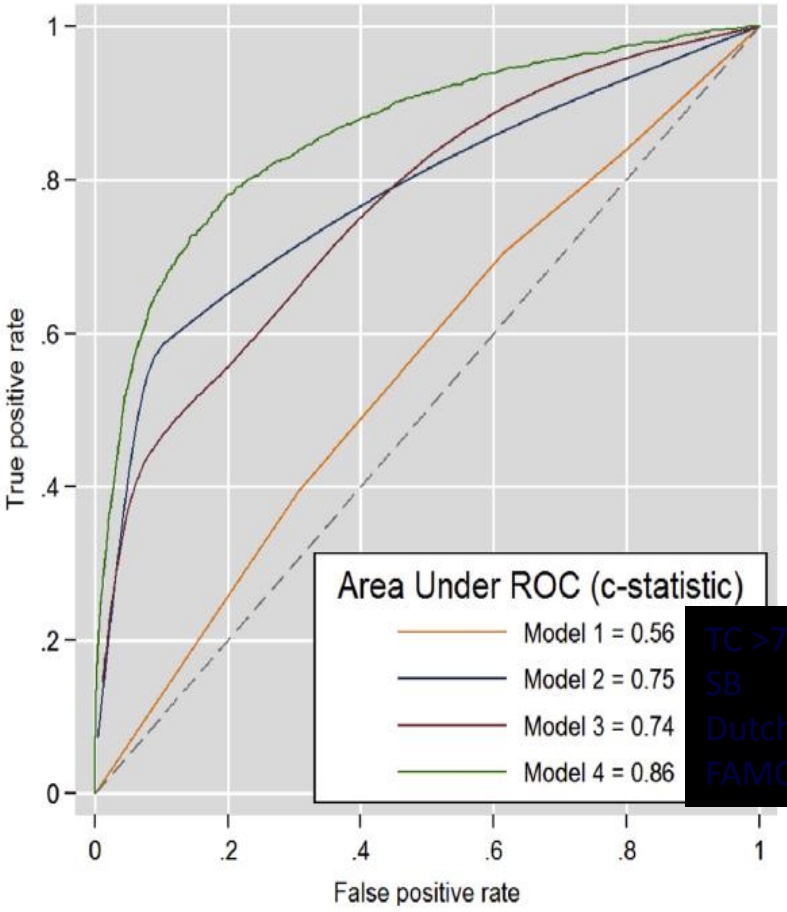


FAMCAT FH tool

Inputs for FAMCAT

- Highest TC or LDL-C
- Age
- TG
- Drug therapies
  - Type; class, dose
- Family history
  - FH
  - MI
  - Lipids
- DM
- CKD

ROC curves for FH tools

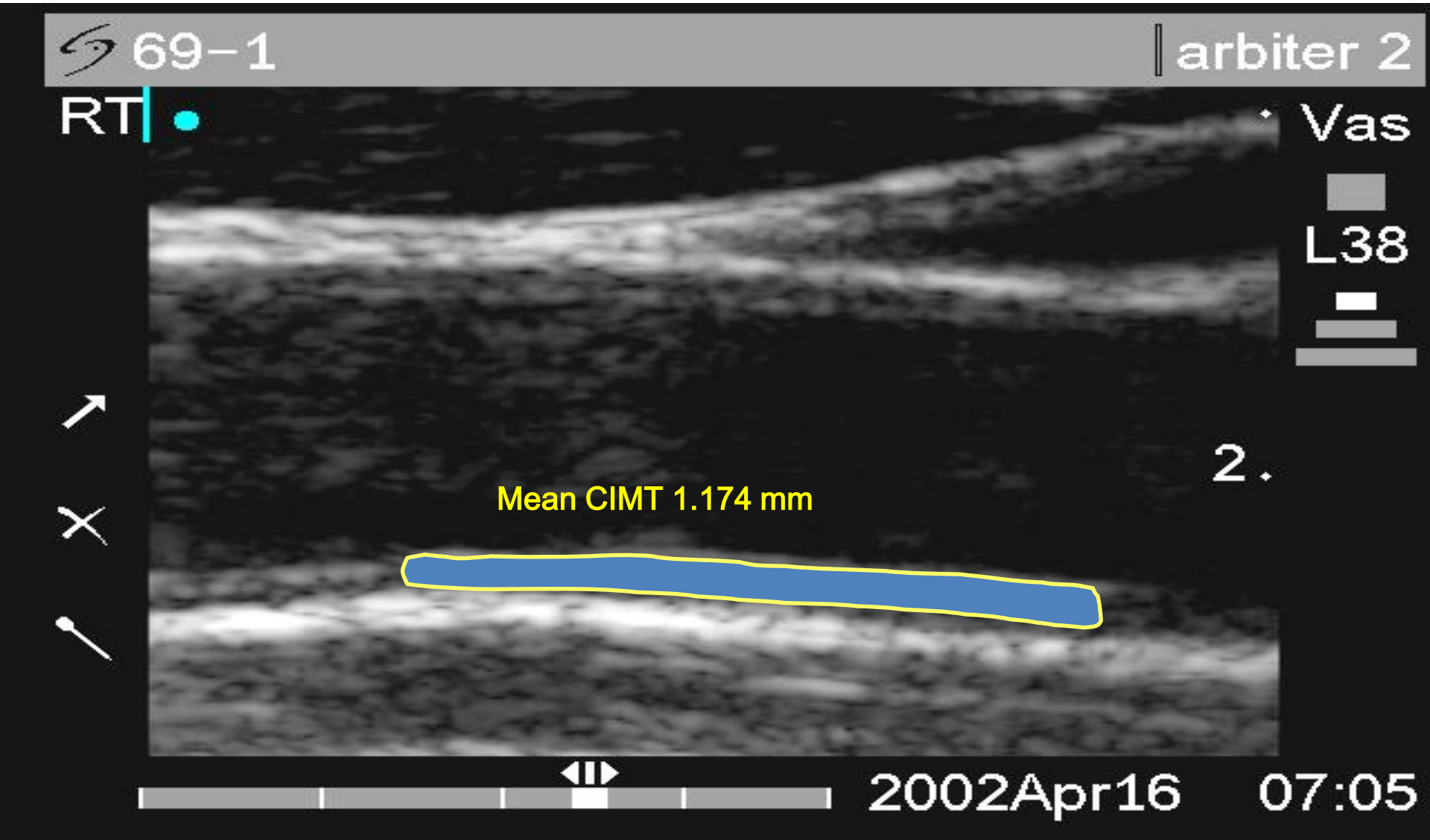


FH: additional stratifying markers

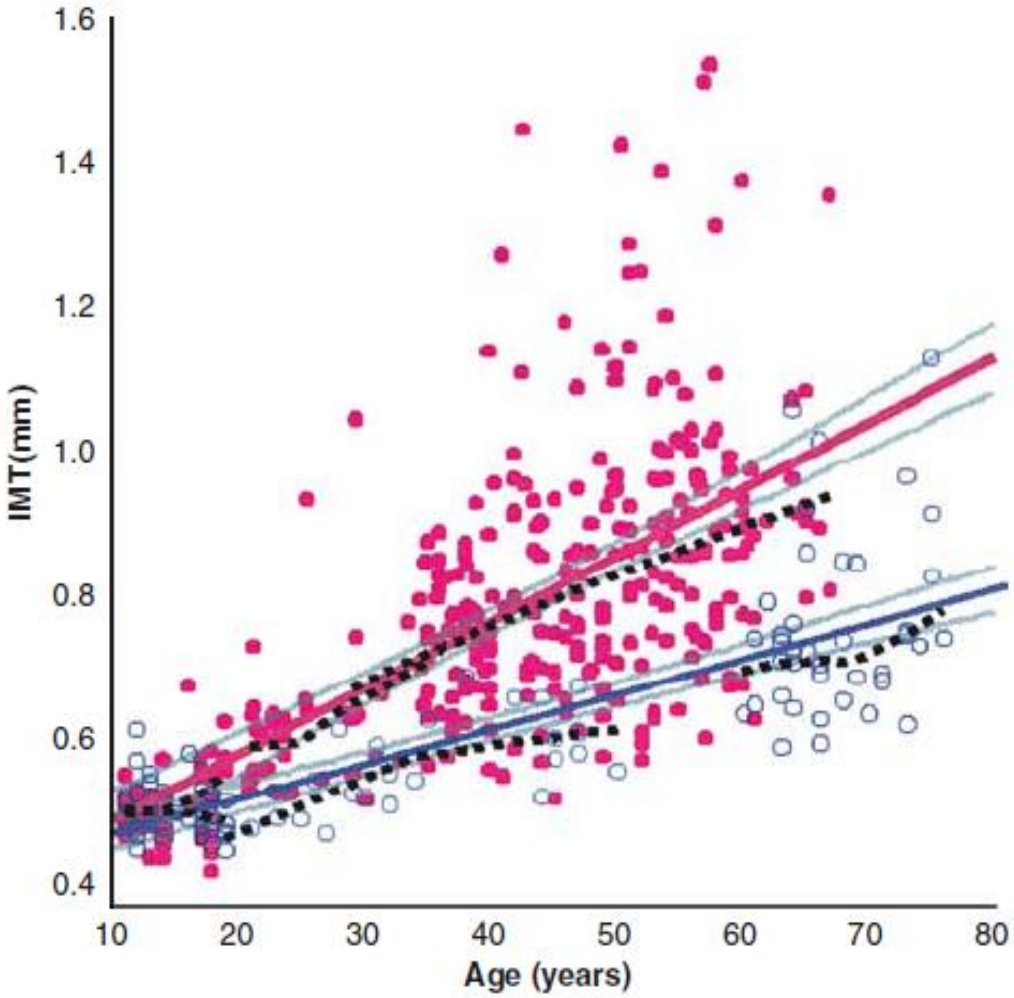
- Presence of tendon xanthomata
- Absolute LDL-C level
  - Best definition with TC >9.3 (LDL-C > 7mmol/L)
- Severity of family history of CHD
- GP database screening
  - FAMCAT risk scoring*

- Lipoprotein (a) > 50mg/dL
  - Familial Atherosclerosis Trial
- Imaging atherosclerosis
  - Carotid intima-media thickness
  - Coronary artery calcium score

What Is Carotid Intima Media Thickness (CIMT)?

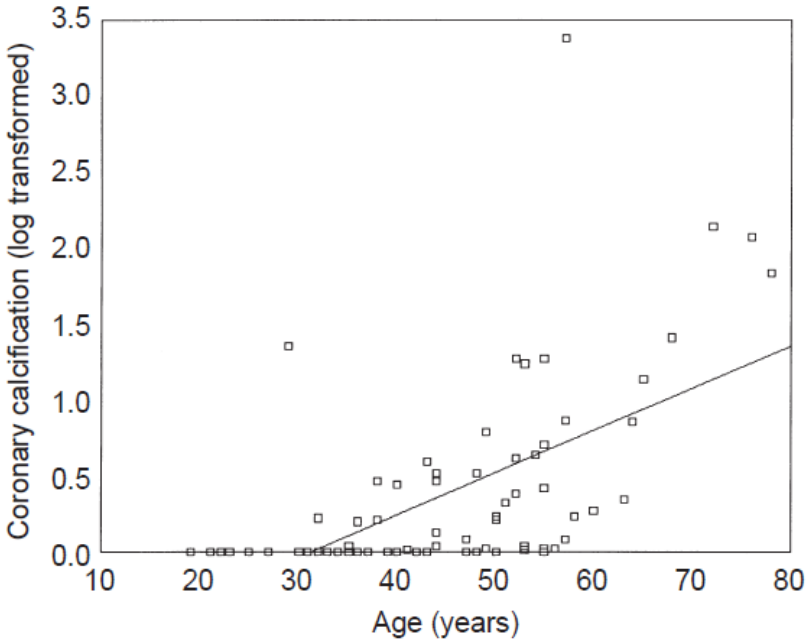


cIMT in FH and controls

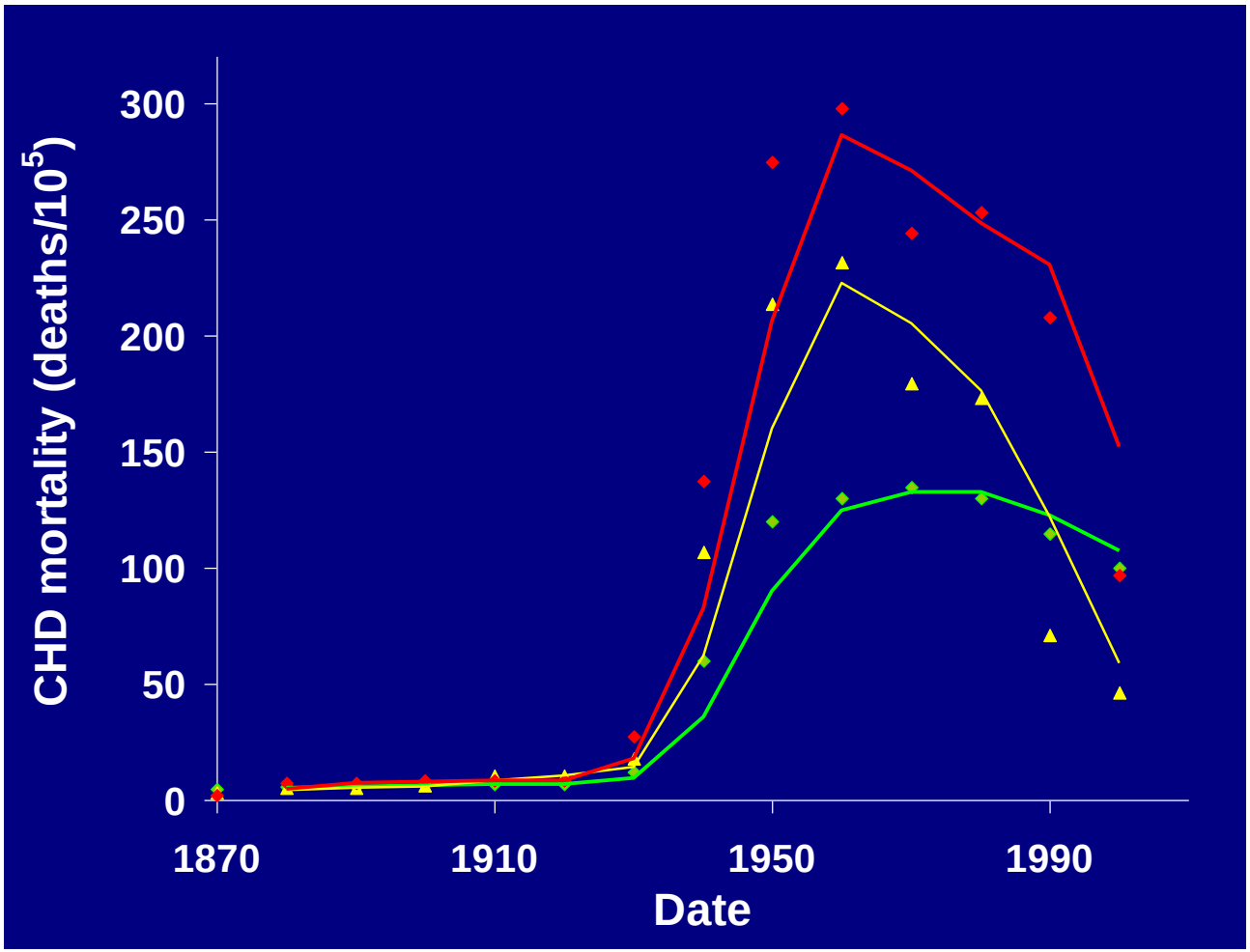


FH: CACS and medical history of CHD

	Coronary heart disease		
	Yes	No	$P <$
Numbers	24	56	
Age (years)	55.3 (11.7)	38.8 (10.6)	0.001
U-cholesterol (mmol L^{-1})	10.2 (2.2)	9.7 (2.1)	0.08
T-cholesterol (mmol L^{-1})	7.3 (2.1)	8.3 (1.8)	0.05
BMI (kg m^{-2})	25.6 (3.3)	24.5 (5.7)	0.06
CC (mm^3 $year^{-1}$)	50.3 (101.1)	3.1 (6.2)	0.001
AC (mm^3 $year^{-1}$)	46.2 (46.3)	11.7 (22.9)	0.001
Sex (% male)	62.5	44.6	0.15
Hypertension (%)	12.5	5.4	0.36
Smoking (%)	83.3	53.5	0.02



Changing mortality of CHD in the last century



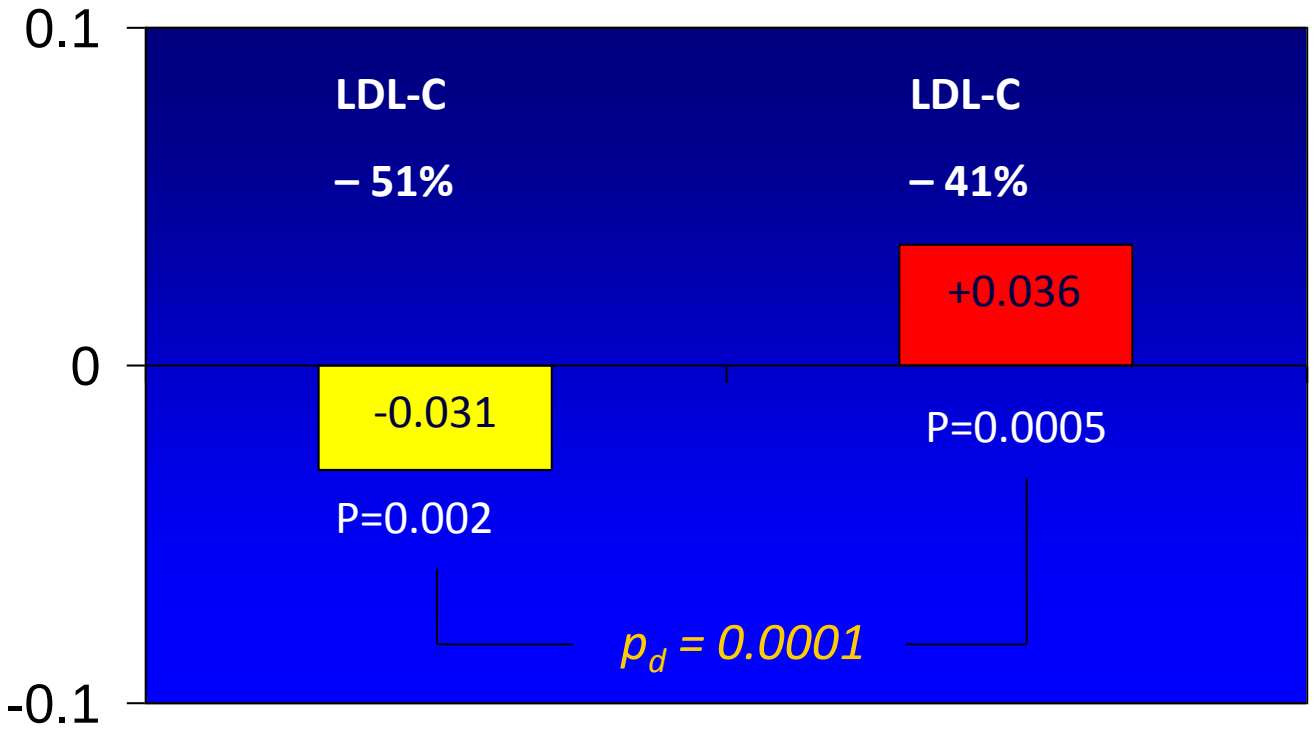
FH Treatment

- Statin
  - Regression of carotid IMT at TC < 6mmol/L (ASAP study)
- Cholesterol absoption inhibitor
  - ezetimibe
- Resin/bile acid sequestrant
  - cholestyramine
- Apheresis

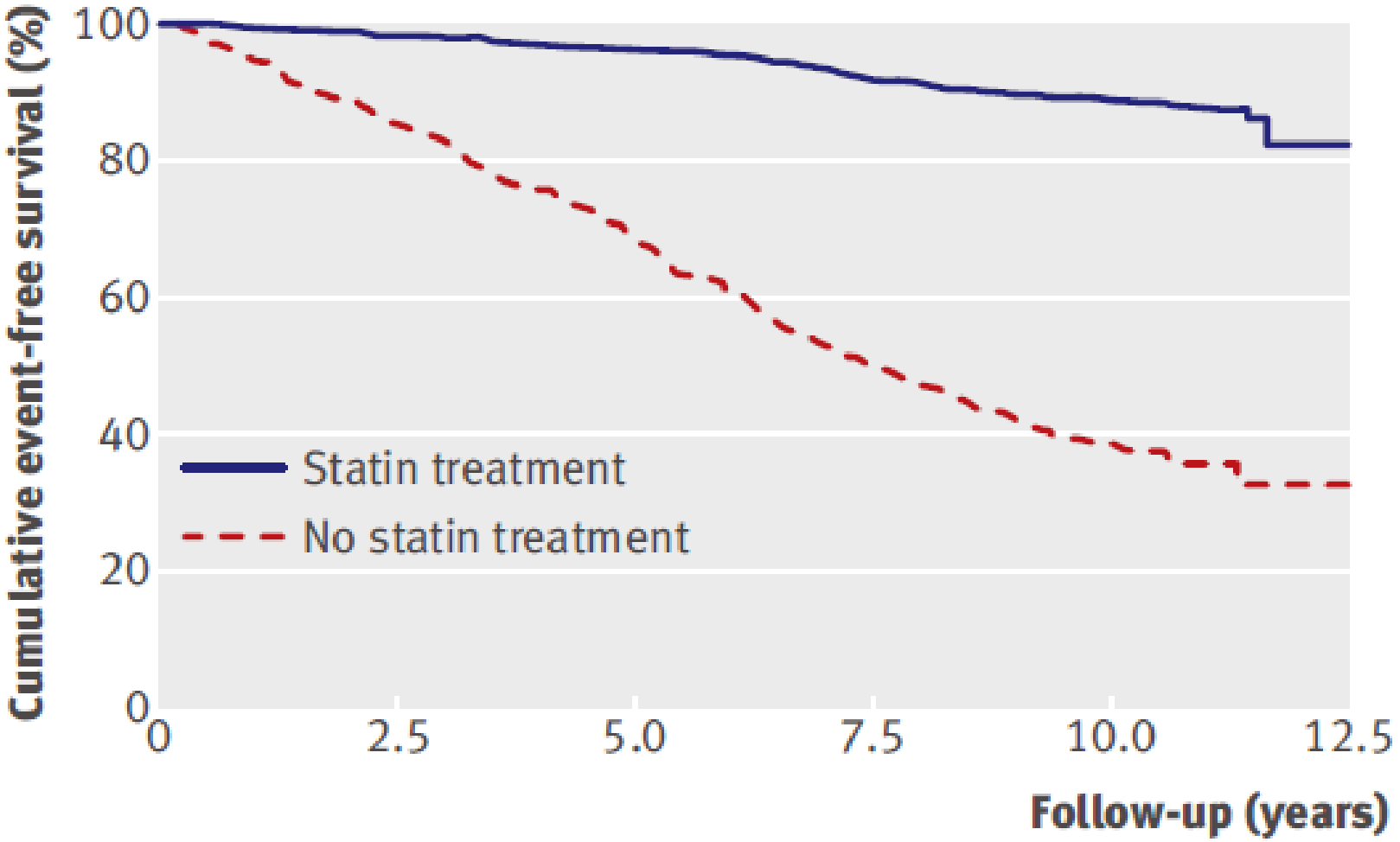
NICE FH Guideline (CG71) - Treatment

- Potent Statin preferred
- Reduce LCL-C> 50% from baseline
  - non-FH: CVD (+)
    - atorvastatin 80mg (approx LDL-C 2mmol/L)
  - non-FH : CVD (-)
    - CVD risk > 10%/decade then atorvastatin 20mg
- Ezetimibe combination with Statin (TA 132)
- Intolerance/Contraindication to statins
  - consider any statin dose, ezetimibe or a fibrate

ASAP: cIMT in Familial Hypercholesterolaemia Primary endpoint

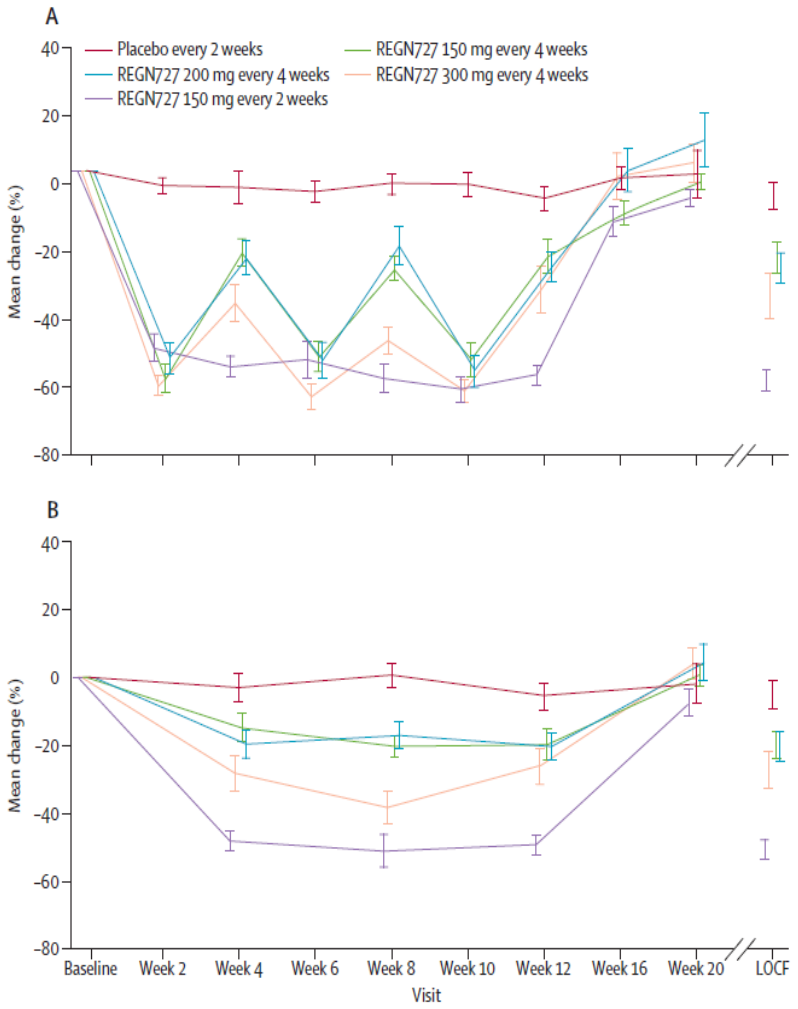


Treatment of familial hypercholesterolaemia



Effects of PSCK-9 inhibition on LDL-C & apoB

- PSCK-9 function
  - Down-regulate LDLR
- PSCK-9 inhibitors
  - Small molecule
  - Antibody
    - alirocumab; evolocumab; bococizumab:
    - LDL-C↓ 17-65%
  - Antisense
    - ISIS-BMS PCSK-9; SPC-5001



Alirocumab

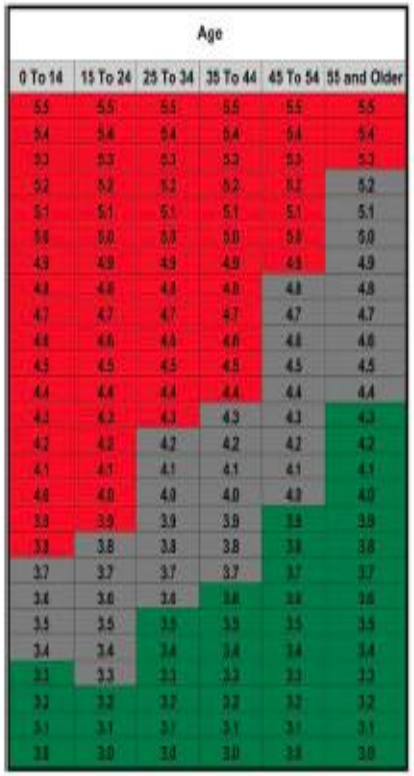
Stein EA et al; Lancet 2012; 380 : 29

Family Screening

- Arrange to review all direct family members
- Screen for family mutation
  - Check LDL-C in relatives
- Enter second degree relatives into wider family screening programme

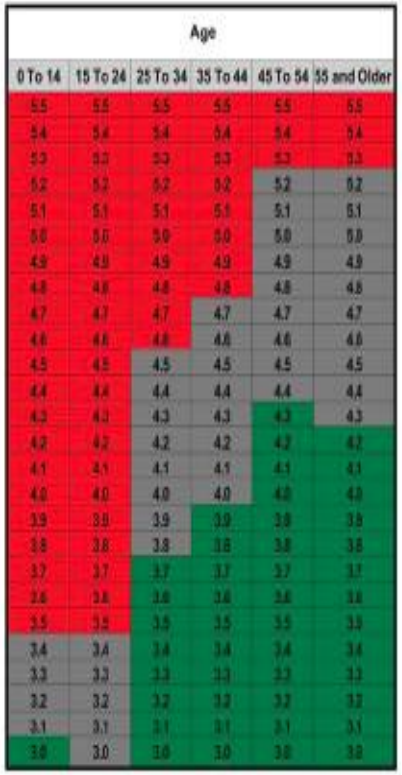
Cut-offs for FH screening in families

A



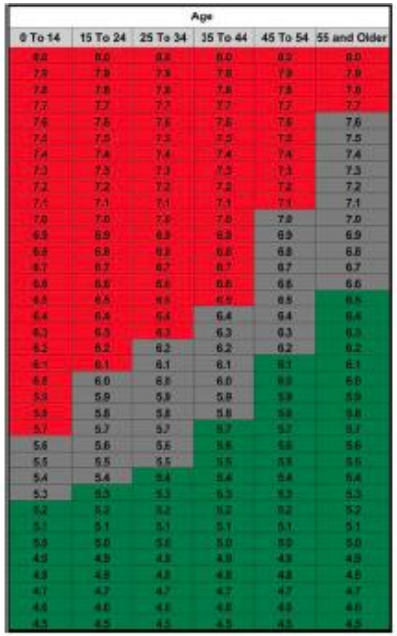
Age					
0 To 14	15 To 24	25 To 34	35 To 44	45 To 54	55 and Older
5.5	5.5	5.5	5.5	5.5	5.5
5.4	5.4	5.4	5.4	5.4	5.4
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2
3.1	3.1	3.1	3.1	3.1	3.1
3.0	3.0	3.0	3.0	3.0	3.0

B



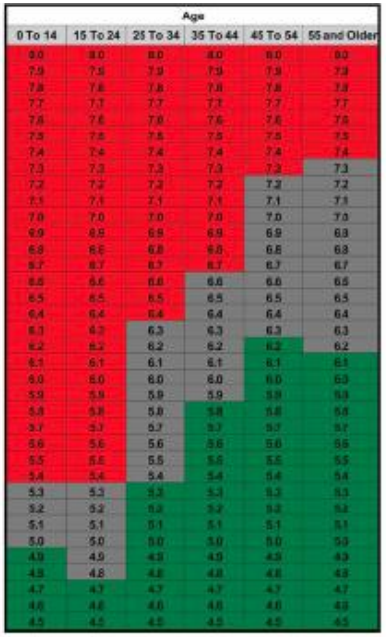
Age					
0 To 14	15 To 24	25 To 34	35 To 44	45 To 54	55 and Older
5.5	5.5	5.5	5.5	5.5	5.5
5.4	5.4	5.4	5.4	5.4	5.4
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2
3.1	3.1	3.1	3.1	3.1	3.1
3.0	3.0	3.0	3.0	3.0	3.0

C



Age					
0 To 14	15 To 24	25 To 34	35 To 44	45 To 54	55 and Older
8.0	8.0	8.0	8.0	8.0	8.0
7.9	7.9	7.9	7.9	7.9	7.9
7.8	7.8	7.8	7.8	7.8	7.8
7.7	7.7	7.7	7.7	7.7	7.7
7.6	7.6	7.6	7.6	7.6	7.6
7.5	7.5	7.5	7.5	7.5	7.5
7.4	7.4	7.4	7.4	7.4	7.4
7.3	7.3	7.3	7.3	7.3	7.3
7.2	7.2	7.2	7.2	7.2	7.2
7.1	7.1	7.1	7.1	7.1	7.1
7.0	7.0	7.0	7.0	7.0	7.0
6.9	6.9	6.9	6.9	6.9	6.9
6.8	6.8	6.8	6.8	6.8	6.8
6.7	6.7	6.7	6.7	6.7	6.7
6.6	6.6	6.6	6.6	6.6	6.6
6.5	6.5	6.5	6.5	6.5	6.5
6.4	6.4	6.4	6.4	6.4	6.4
6.3	6.3	6.3	6.3	6.3	6.3
6.2	6.2	6.2	6.2	6.2	6.2
6.1	6.1	6.1	6.1	6.1	6.1
6.0	6.0	6.0	6.0	6.0	6.0
5.9	5.9	5.9	5.9	5.9	5.9
5.8	5.8	5.8	5.8	5.8	5.8
5.7	5.7	5.7	5.7	5.7	5.7
5.6	5.6	5.6	5.6	5.6	5.6
5.5	5.5	5.5	5.5	5.5	5.5
5.4	5.4	5.4	5.4	5.4	5.4
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5

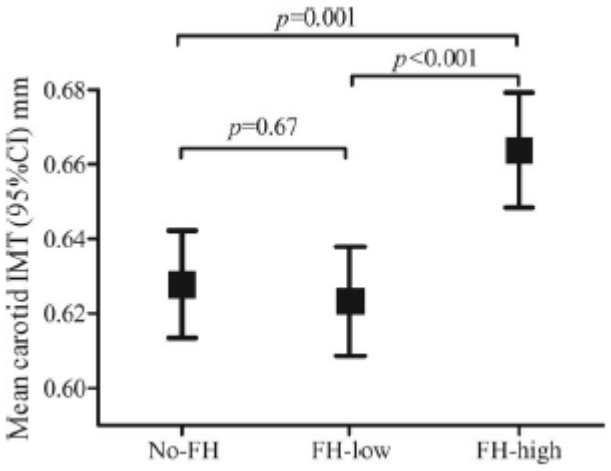
D



Age					
0 To 14	15 To 24	25 To 34	35 To 44	45 To 54	55 and Older
8.0	8.0	8.0	8.0	8.0	8.0
7.9	7.9	7.9	7.9	7.9	7.9
7.8	7.8	7.8	7.8	7.8	7.8
7.7	7.7	7.7	7.7	7.7	7.7
7.6	7.6	7.6	7.6	7.6	7.6
7.5	7.5	7.5	7.5	7.5	7.5
7.4	7.4	7.4	7.4	7.4	7.4
7.3	7.3	7.3	7.3	7.3	7.3
7.2	7.2	7.2	7.2	7.2	7.2
7.1	7.1	7.1	7.1	7.1	7.1
7.0	7.0	7.0	7.0	7.0	7.0
6.9	6.9	6.9	6.9	6.9	6.9
6.8	6.8	6.8	6.8	6.8	6.8
6.7	6.7	6.7	6.7	6.7	6.7
6.6	6.6	6.6	6.6	6.6	6.6
6.5	6.5	6.5	6.5	6.5	6.5
6.4	6.4	6.4	6.4	6.4	6.4
6.3	6.3	6.3	6.3	6.3	6.3
6.2	6.2	6.2	6.2	6.2	6.2
6.1	6.1	6.1	6.1	6.1	6.1
6.0	6.0	6.0	6.0	6.0	6.0
5.9	5.9	5.9	5.9	5.9	5.9
5.8	5.8	5.8	5.8	5.8	5.8
5.7	5.7	5.7	5.7	5.7	5.7
5.6	5.6	5.6	5.6	5.6	5.6
5.5	5.5	5.5	5.5	5.5	5.5
5.4	5.4	5.4	5.4	5.4	5.4
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5

The phenotype matters: FH mutations and normocholesterolaemia

	No-FH Group (n=145)	FH-Low Group (n=114)	FH-High Group (n=162)
Male sex	69 (48)	52 (46)	68 (42)
Age, y	42.3±8.7	37.5±8.5	35.2±8.7
Hypertension	14 (10)	8 (7)	10 (6)
Diabetes	1 (1)	…	1 (1)
Smoker ever	73 (50)	51 (45)	66 (41)
Statin use§	5 (3)	25 (22)	111 (69)
Body mass index, kg/m^2	25.7±4.2	25.6±5.1	25.0±4.4
Systolic blood pressure, mm Hg	128±14	124±12	124±13
Lipid profile, mmol/L			
At molecular screening			
LDL-C	3.2±1.0	2.9±0.7	5.2±1.0
pLDL	40 (21–68)	47 (21–64)	97 (95–98)
At study visit			
TC	5.3±1.1	5.3±1.1	6.0±1.5
LDL-C	3.4±1.0	3.4±1.0	4.1±1.4
HDL-C	1.5±0.4	1.4±0.4	1.4±0.4
Triglycerides	0.9 (0.7–1.4)	0.7 (0.5–1.2)	0.7 (0.5–1.1)



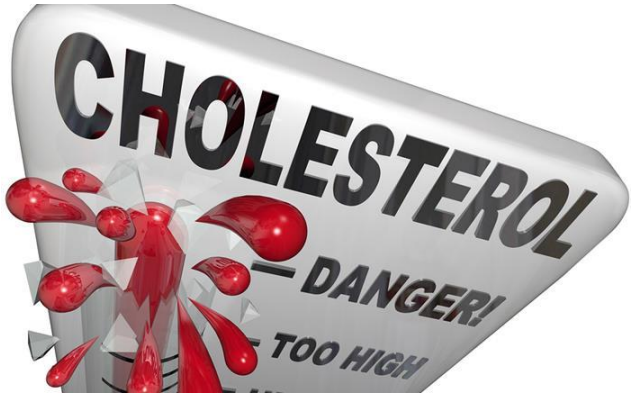
Conclusions

- Screening will find patients with genetic hyperlipidaemias
- FH is at least 1 in 500 UK population
- Family (cascade) screening required
- Statin treatment for FH irrespective of calculated CVD risk
- Combination therapy often needed to reduce LDL-C >50%.

United Kingdom Clinical Pharmacy Association

NHS Southwark
Improving the health and wellbeing of Southwark

LIPID MANAGEMENT
What does NICE really say?



Prof Anthony S. Wierzbicki Metabolic Medicine/Chemical Pathology Guy's & St Thomas' Hospitals	Helen Williams Consultant Pharmacist for CV Disease - South London

What has changed since NICE CG67?

- Implementation of NHS Health checks
- Move of QoF oversight into NICE Quality Standards
- Updated risk calculator systems
  - QRISK2 etc
- Updated lipid risk relationships & measurements
  - ERFC- nonHDL-C
  - VLDL- accuracy of cLDL-C
- Updated meta-analyses of statin trials
  - CTT group
- Updated evidence on combination therapy
  - Fibrates: ACCORD (lipids)
  - Niacin: AIM-HIGH & HPS2/THRIVE
- New prices for off-patent statins- changes TA94 HE model

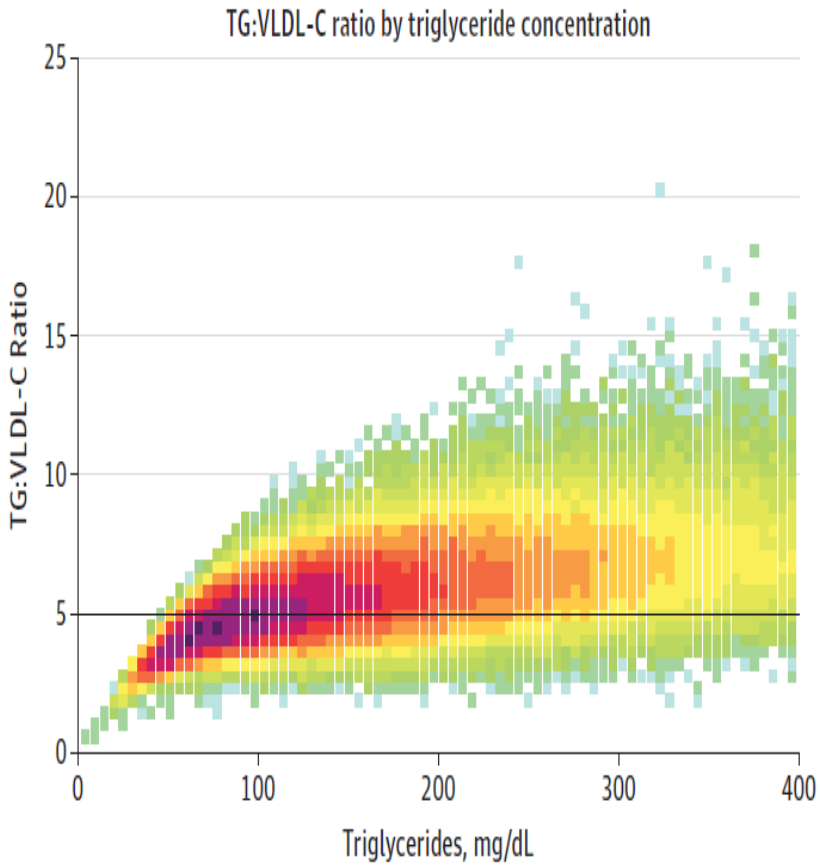
Lipids: screening and the basics

- Initial non-fasting lipid profile
  - TC, TG, HDL-C & nonHDL-C
  - Non-HDL-C = LDL-C + approx 0.8mmol/L
    - i.e. LDL-C 2.00mmol/L = nonHDL-C 2.6 mmol/L
    - i.e. LDL-C 3.00mmol/L – nonHDL-C 3.8mmol/L

- TC >9mmol/L
  - Consider FH even in no family history of CHD
- TG> 20 mmol/L
  - If not alcohol or new DM- refer to Lipid clinic
- TG 11-20mmol/L
  - Rpt in 7 days; consider referral or advice

Changes to lipid efficacy assessment: switch to non-HDL-C

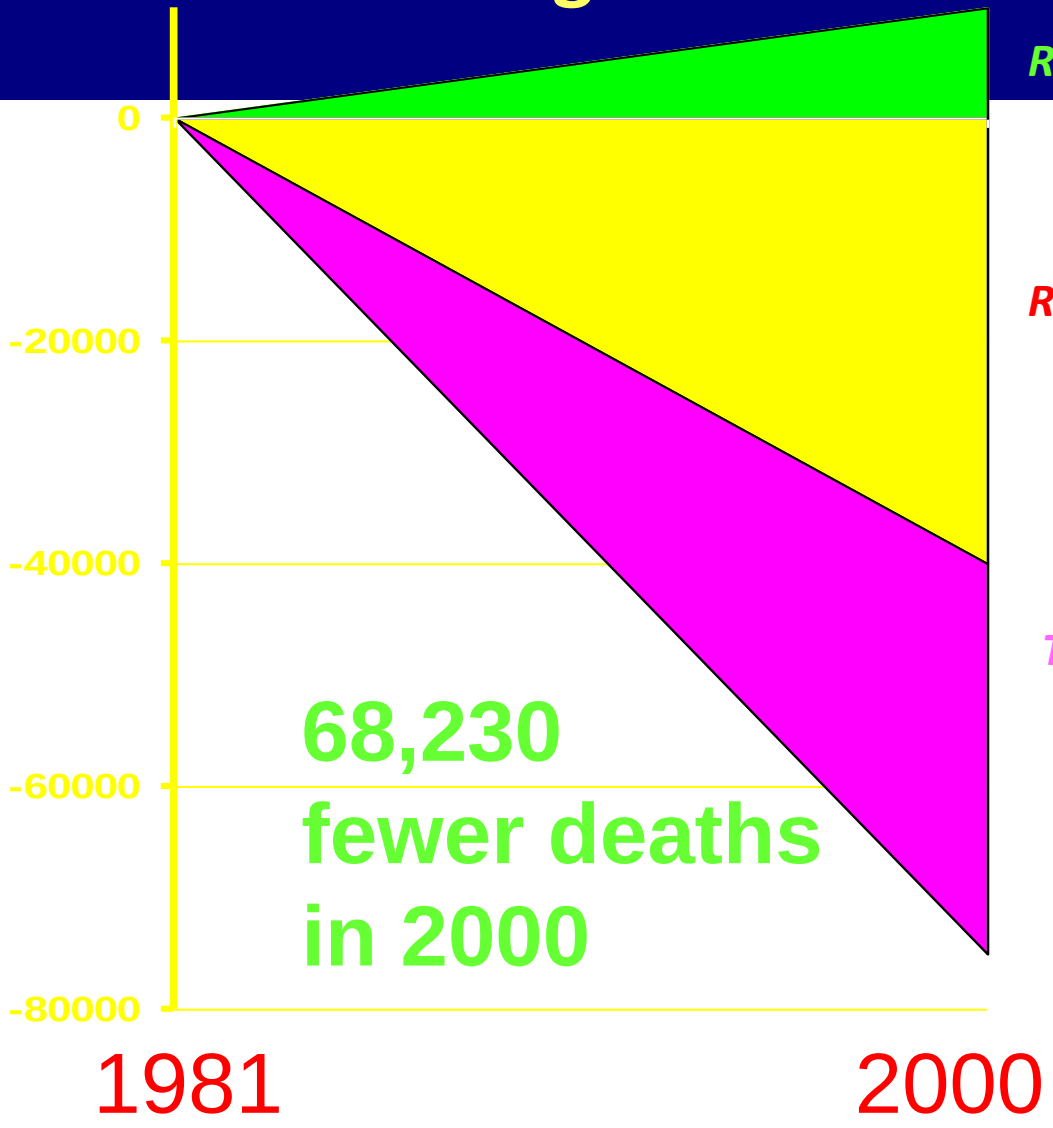
- LDL-C Friedewald
  - Poor calibration
  - Complex adjustment matrix
- Non-HDL-C better for CVD risk
- NHS Health Check
  - Non-Fasting rate
  - DNA rate for fasting
  - Move to HbA_{1c} for DM
- GP workload pressure



CV Risk Assessment Recommendations

- For the primary prevention of CVD in primary care, use a systematic strategy to identify people who are likely to be at high risk
- Prioritise people for a full formal risk assessment if their estimated 10-year risk of CVD is ≥10%
- Use the QRisk2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years (except CKD)

Explaining the fall in coronary heart disease deaths in England & Wales 1981-2000



Risk Factors worse +13%

- Obesity (increase) +3.5%
- Diabetes (increase) +4.8%
- Physical activity (less) +4.4%

Risk Factors better -71%

- Smoking -41%
- Cholesterol -9%
- Population BP fall -9%
- Deprivation -3%
- Other factors -8%

Treatments -42%

- AMI treatments -8%
- Secondary prevention -11%
- Heart failure -12%
- Angina:CABG & PTCA -4%
- Angina: Aspirin etc -5%
- Hypertension therapies -3%

Unal, Critchley & Capewell
Circulation 2004 109(9) 1101

Welcome to the QRISK®2-2014 risk calculator: http://qrisk.org

This calculator is only valid if you do not already have a diagnosis.

Reset | Information | Publications | About | Copyright | Contact Us | Algorithm | Software

About you

Age (25-84): 56
Sex: (•) Male ( ) Female
Ethnicity: White or not stated

UK postcode: leave blank if unknown
Postcode:

Clinical information

Smoking status: non-smoker
Diabetes status: none
Angina or heart attack in a 1st degree relative < 60? ☐
Chronic kidney disease? ☐
Atrial fibrillation? ☐
On blood pressure treatment? ☐
Rheumatoid arthritis? ☐

Leave blank if unknown
Cholesterol/HDL ratio: 5.8
Systolic blood pressure (mmHg): 156

Body mass index
Height (cm): 180
Weight (kg): 96

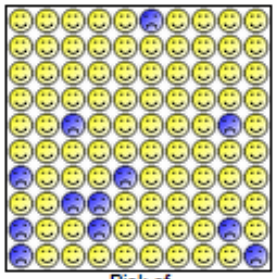
Calculate risk over 10 years. [Calculate risk]

Your results

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

11.5%

In other words, in a crowd of 100 people with the same risk factors as you, 12 are likely to have a heart attack or str



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 29.63 kg/m².

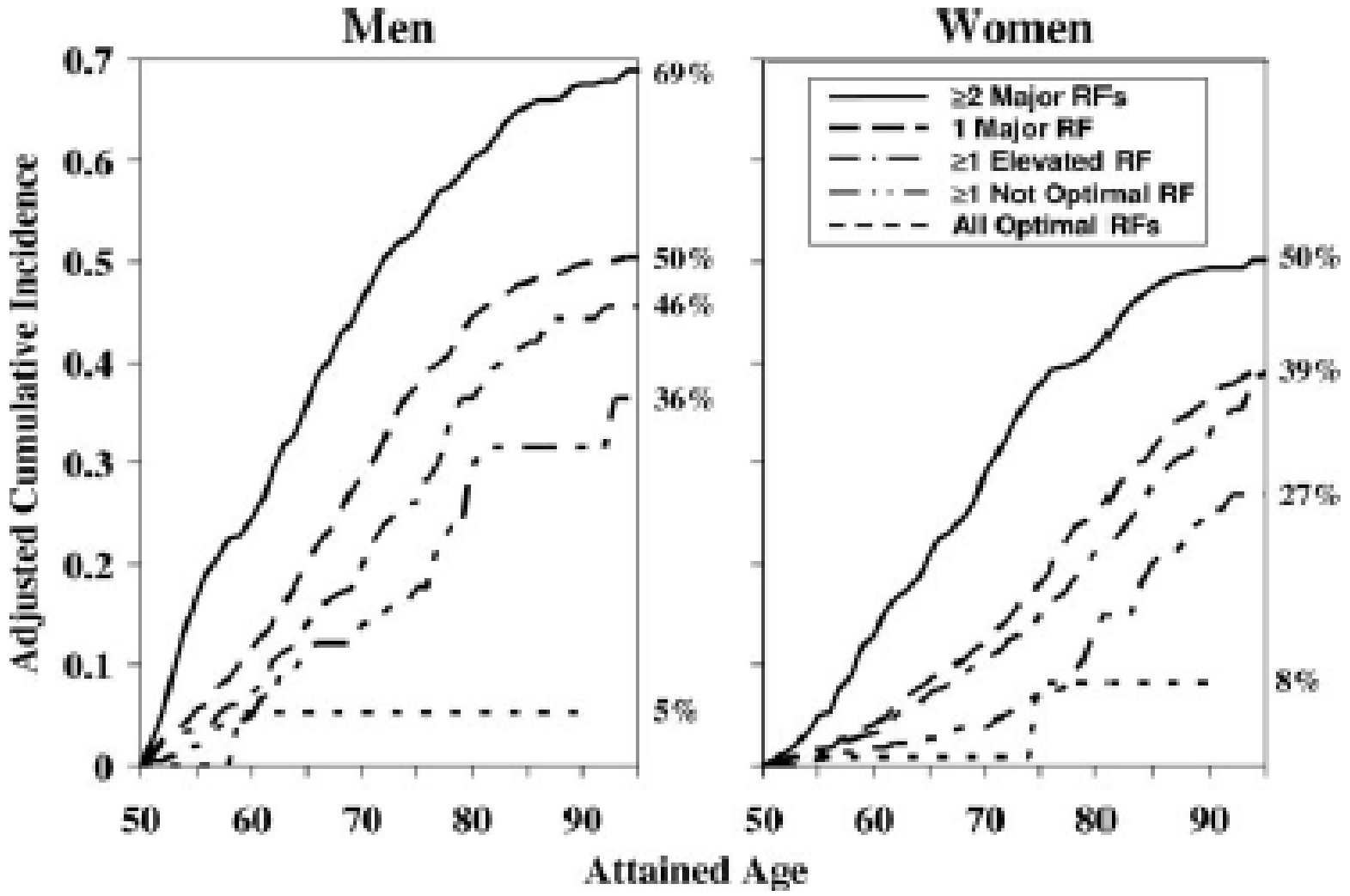
How does your 10-year score compare?

Your score

Your 10-year QRISK®2 score	11.5%
The score of a typical person with the same age, sex, and ethnicity*	9.7%
Relative risk**	1.2
Your QRISK® Heart Age***	59

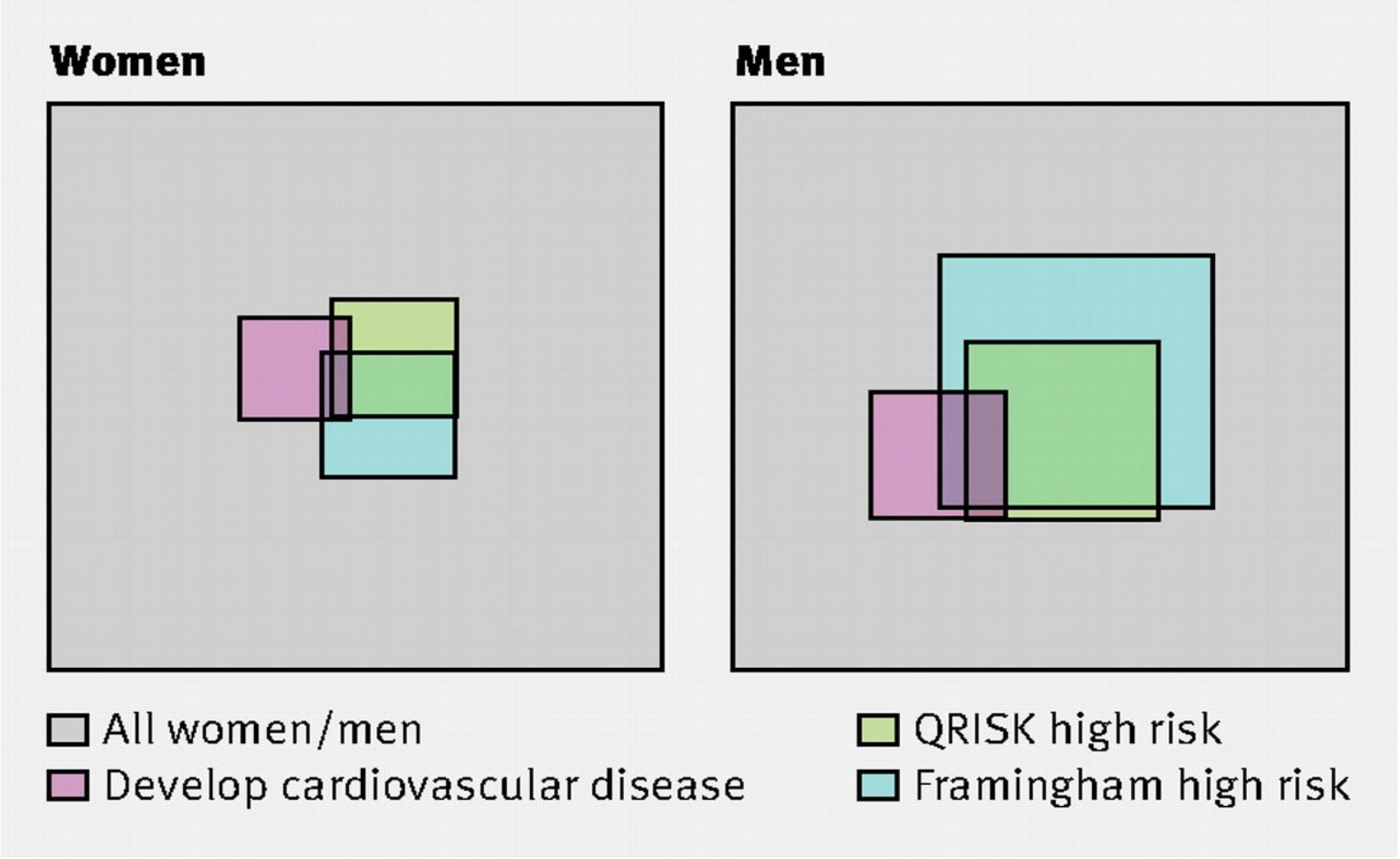
* This is derived from all people of your age, sex and ethnic group, whatever their clinical information.
** Your relative risk is your risk divided by the typical person's risk.
*** Your QRISK® Heart Age is the age at which a typical person of your sex and ethnicity has your 10-year QRISK®2 score.

Framingham study
lifetime risk: 2 CVD RFs matter



Lloyd-Jones D et al; Circulation 2006 : 113 ; 791

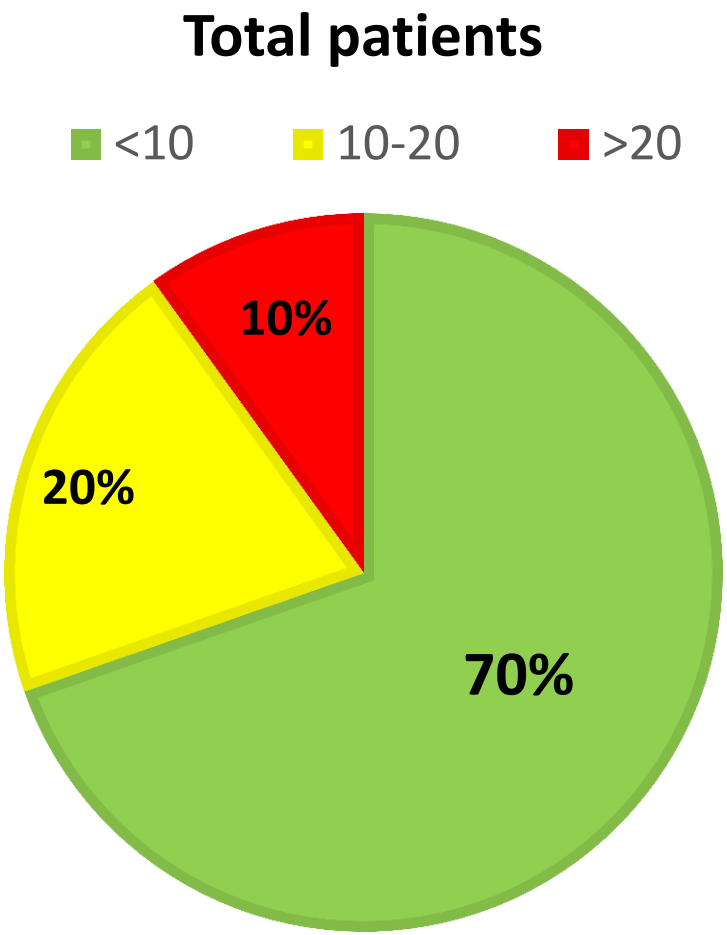
Limitations of CVD risk calculation: 20% threshold

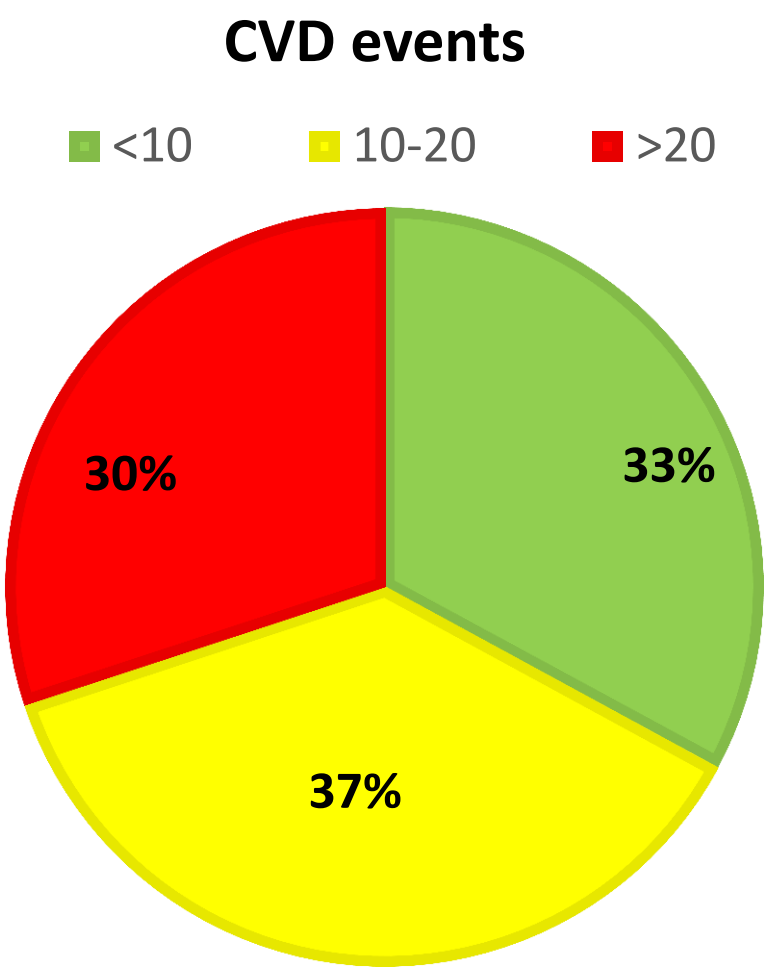


Jackson, R. et al. BMJ 2009;339:b2673

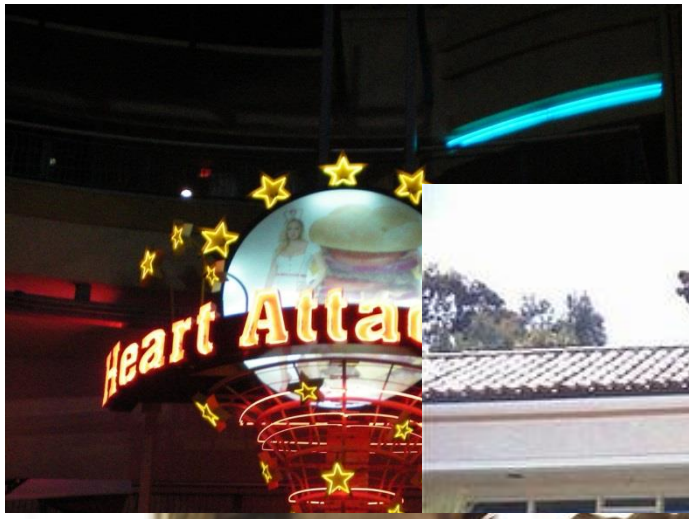
Jackson RD et al; BMJ 2009; 339: b2673

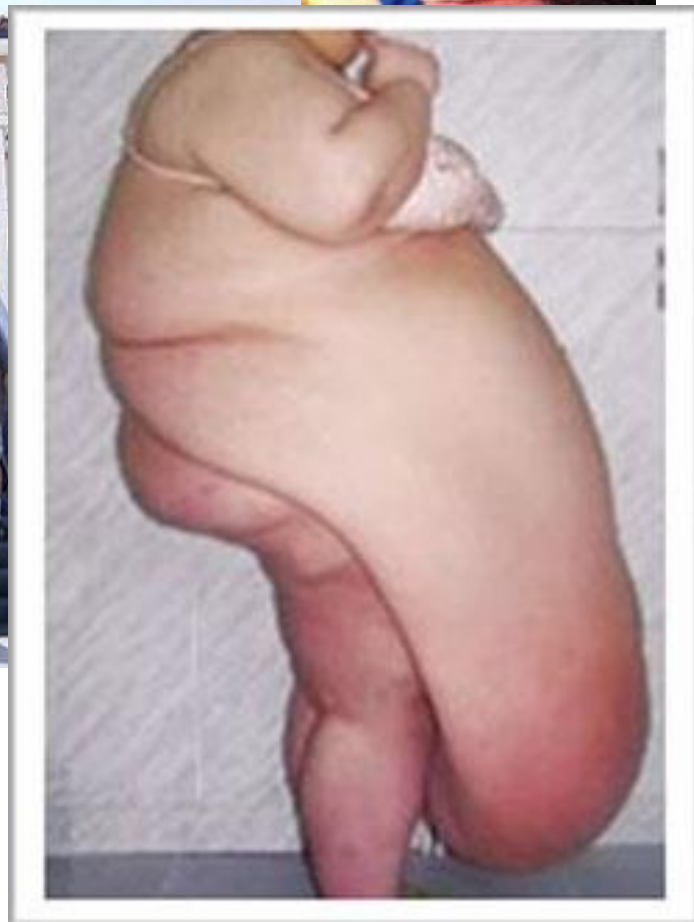
THIN Cohort: Consequences of changing to 10% risk from 20%





Lifestyle





Dietary interventions

- Dated studies
- Poor Evidence
- Modern evidence
  - PREDIMED underpowered
- Conclusions
  - Total fat intake < 30% of energy intake,
  - Saturated fats < 7% of energy intake,
  - Dietary cholesterol < 300 mg/day
  - Saturated fats replaced by MUFA or PUFA fats.
  - No role for plant sterols

Eat food, not too much; mostly plants.

Michael Pollan (2009)

MRFIT- the personalised lifestyle intervention trial

Endpoint	Number of Men With Event (%)		HR	95% CI	*P*
	SI	UC			
Overall composite CVD endpoint					
Nonfatal or fatal CVD	581 (9.0)	652 (10.1)	0.89	0.79–0.99	0.04
Nonfatal and fatal composite CVD endpoints					
Nonfatal CVD	460 (7.2)	529 (8.2)	0.87	0.76–0.98	0.02
Fatal CVD	139 (2.2)	146 (2.3)	0.95	0.76–1.20	0.68
Components of composite CVD endpoint not shown in lower half of Table 2*					
Fatal or nonfatal stroke	**49**	**41**	**1.20**	**0.79–1.81**	**0.40**
Nonfatal stroke	36	30	1.20	0.74–1.95	0.46
Fatal stroke	13	11	1.18	0.53–2.64	0.68
Impaired renal function†	**9**	**11**	**0.82**	**0.34–1.97**	**0.65**
Other fatal CVD	**10**	**10**	**1.00**	**0.42–2.40**	**0.99**

Stamler J et al; JAHA 2012; 1 : e 003640

N=12866

Lipid Lowering Treatment

- When a decision is made to prescribe a statin use a statin of high intensity and low acquisition cost

- Before starting lipid modification therapy for the primary prevention of CVD, take at least sample to measure a full lipid profile.

- A fasting sample is not needed

- Exclude familial lipid disorders or secondary causes of dyslipidaemia

Defining recommendations

Targets	Drug-based
• Consistent with epidemiology • Rare in clinical trials • Traditional output • Focused on single risk factor • Set on 50th centile • Requires multiple monitoring	• Consistent with trials – Exception limits defined • Common trial design • Novel output • Focused on overall risk • Centile-independent • Minimal monitoring required

Comparing statin intensity

US comparison

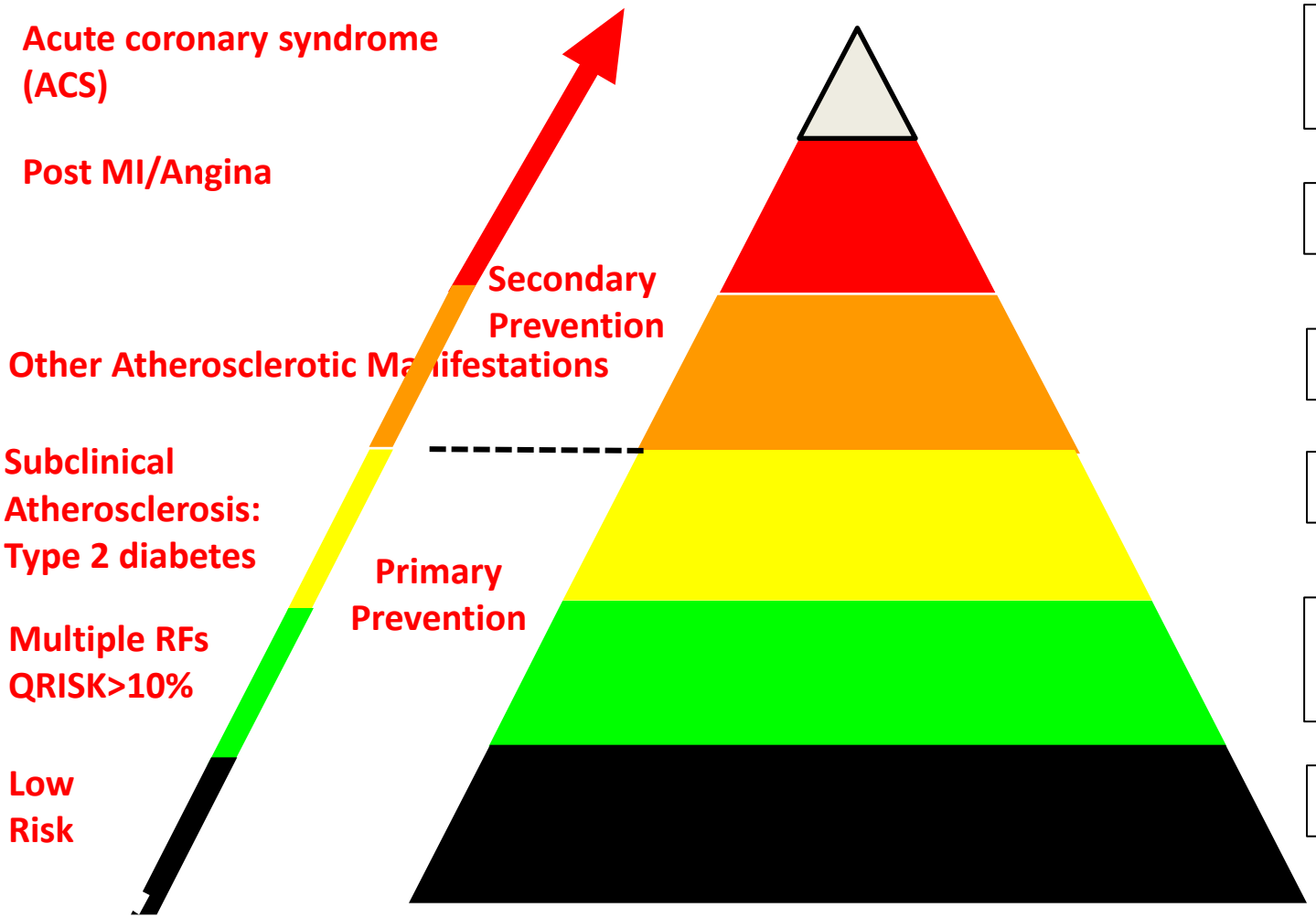
Statin Therapy	Daily Dose		
	High-Intensity†	Moderate-Intensity‡	Low-Intensity§
Atorvastatin	40‖–80 mg	10 *(20)* mg	–
Rosuvastatin	20 *(40)* mg	*(5)* 10 mg	–
Simvastatin	–	20–40 mg¶	*10 mg*
Pravastatin	–	40 *(80)* mg	10–20 mg
Lovastatin	–	40 mg	20 mg
Fluvastatin	–	*80 mg (Fluvastatin XL)*	*20–40 mg*
Fluvastatin	–	40 mg**	–
Pitavastatin	–	*2–4 mg*	*1 mg*
	>50%	30-50%	<30%

NICE lipids comparison

Low intensity	Medium intensity	High intensity
Fluvastatin 20 mg	*Atorvastatin 10mg*	*Atorvastatin 20mg*
Fluvastatin 40 mg	*Fluvastatin 80 mg*	*Atorvastatin 40 mg*
Pravastatin 5 mg	*Rosuvastatin 5 mg*	*Atorvastatin 80 mg*
Pravastatin 10 mg	*Simvastatin 20 mg*	*Rosuvastatin 10 mg*
Pravastatin 20 mg	*Simvastatin 40 mg*	*Rosuvastatin 20 mg*
Pravastatin 40 mg		*Rosuvastatin 40 mg*
Simvastatin 10 mg		*Simvastatin 80 mg*
<30%	31 - 40%	>40%

Stone NJ et al; Circ 2014; 129 : S1-S45; Rabar S et al; BMJ 2014; 349 :g4356

NICE –CG 181 Continuum of CVD Risk and its treatment



Atorva 80mg (+ Eze 10mg)

Atorva 80mg

Atorva 80mg

Atorva 20+ mg

Lifestyle then Atorva 20mg

Lifestyle

Courtesy of CD Furberg.; modified to include NICE CG181

Secondary Prevention (including ACS)

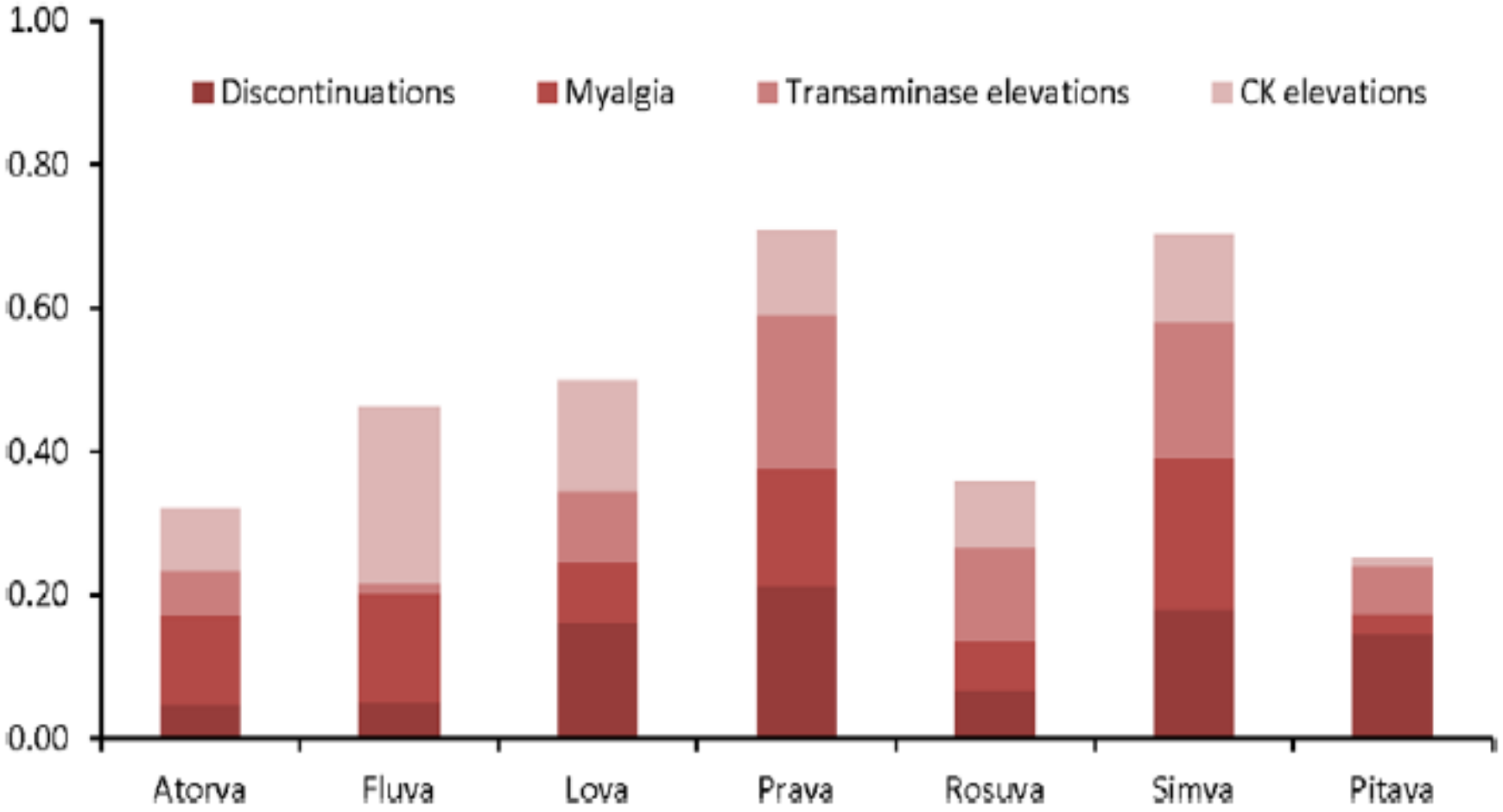
- Start statin treatment with atorvastatin 80 mg.
  - Use a lower dose of atorvastatin if any of the following apply:
    - potential drug interactions
    - high risk of adverse effects
    - patient preference
- Do not delay statin treatment in secondary prevention to manage modifiable risk factors
- If a person has acute coronary syndrome, do not delay statin treatment.
    - Take a lipid sample on admission and about 3 months after the start of treatment

Statin interventions

	Active treatment	Control	Relative risk	Absolute Effect (per thousand)
Statin vs placebo				
CVD mortality	2347/59459 (3.9%)	2882/59459 (4.8%)	0.81 (0.77-0.86)	**-9** (-7 to -11)
Non-fatal MI	1593/45915 (3.5%)	2318/45567 (5.1%)	0.69 (0.65-0.73)	**-16** (-14 to -18)
Stroke	1456/54602 (2.7%)	1867/54642 (3.4%)	0.78 (0.73-0.83)	**-8** (-6 to -9)
Statin : High intensity vs. moderate intensity				
CVD mortality	972/17730 (5.5%)	1026/17720 (7.0%)	0.95 (0.87-1.03)	-3 (-8 to +2)
Non-fatal MI	1058/17730 (6.0%)	41247/17720 (2.8%)	0.79 (0.67-0.93)	**-13** (-4 to -20)
Stroke	388/12735 (3.0%)	439/12714 (3.5%)	0.88 (0.77-1.01)	-4 (0 to -8)

Rabar S et al; BMJ 2014; 349 :g4356

Predicting the best statin to use



Trials =135; n=246955

Naci H et al; Circ CV Qual Outcome 2013; 6: 390

Primary Prevention

- Discuss the benefits of lifestyle modification and optimise the management of all other modifiable CVD risk factors if possible
- If lifestyle modification is ineffective or inappropriate offer statin treatment after repeating risk assessment
- Offer atorvastatin 20 mg to people who have a 10% or greater 10-year risk of developing CVD (QRisk2)
- For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction

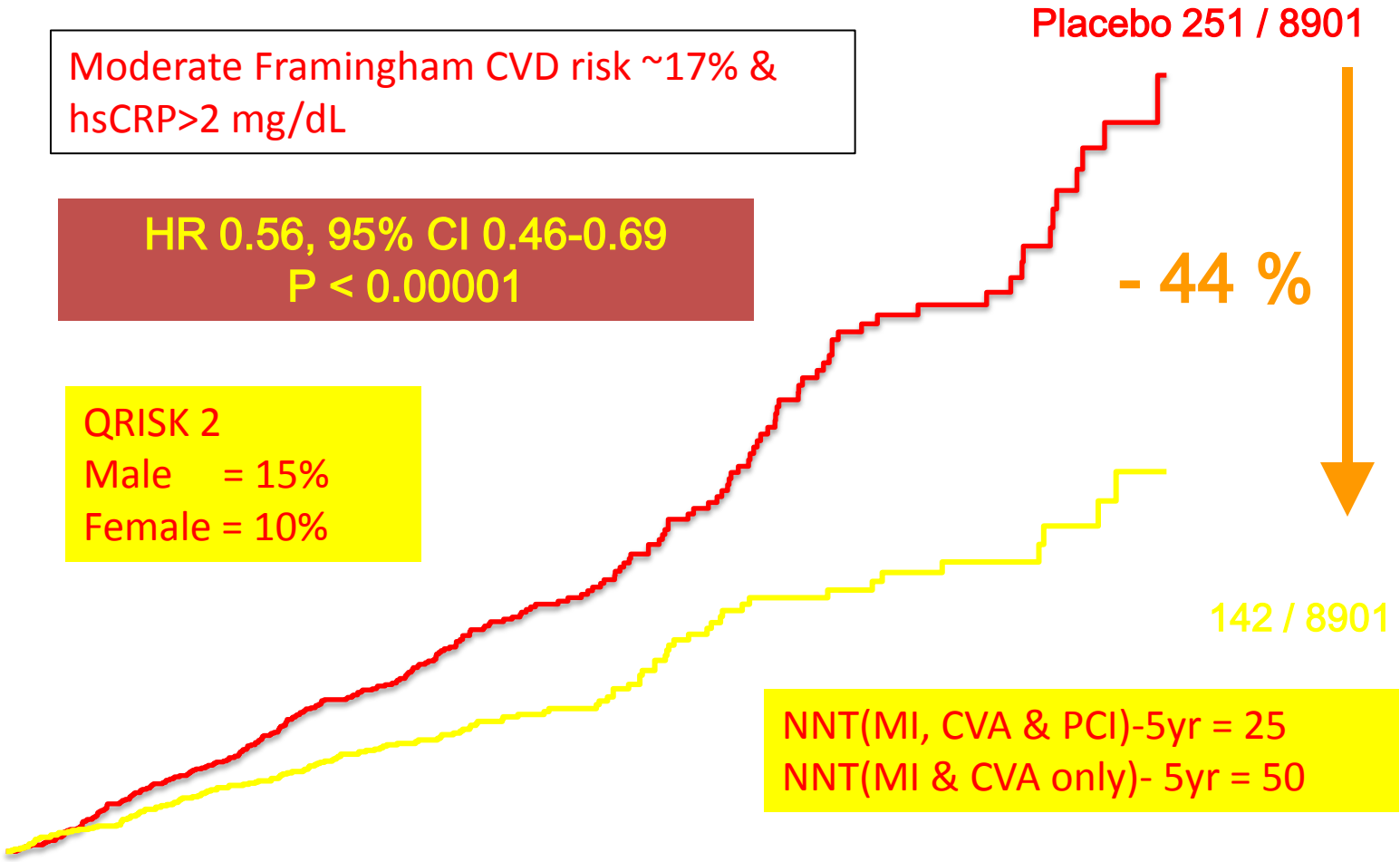
JUPITER
Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death

Ridker PM et al; NEJM 2008; 359; 2195

Moderate Framingham CVD risk ~17% & hsCRP>2 mg/dL

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

QRISK 2
Male = 15%
Female = 10%



NNT(MI, CVA & PCI)-5yr = 25
NNT(MI & CVA only)- 5yr = 50

N=17802

Type II diabetes

- Offer atorvastatin 20 mg for the primary prevention of CVD to people with type2 diabetes who have a 10% or greater 10-year risk of developing CVD
- Estimate the level of risk using the QRISK2 assessment tool.

Type 1 Diabetes

- Consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes
- Offer statin treatment for the primary prevention of CVD to adults with type 1 diabetes who:
  - are older than 40 years **or**
  - have had diabetes for more than 10 years **or**
  - have established nephropathy
- Start treatment for adults with type 1 diabetes with atorvastatin 20 mg

CKD

- Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD
- Increase the dose if
  - Multiple other CVD risk factors
  - <40% reduction in nonHDL-C is achieved and eGFR is >30 ml/min/1.73 m^2
- Agree the use of higher doses with a renal specialist if eGFR is <30 ml/min/1.73 m^2

Monitoring and Dose Escalation

- Measure TC, HDL-C and nonHDL-C in all people who have been started on high-intensity statin treatment at 3 months
  - **aim for >40% reduction in nonHDL-C**

- If <40% reduction in nonHDL-C:
  - discuss adherence and timing of dose
  - optimise adherence to diet and lifestyle measures
  - consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of co-morbidities, risk score or clinical judgement

Advice to patients

- Benefits of therapy….
  - Need for chronic treatment
- When to take
  - Does not matter
- Common side effects and what to do about them
  - Muscle aches; liver enzymes
- Drug / food interactions
  - Grapefruit juice
- What monitoring to expect
  - Repeat blood tests

- Address any concerns they have about statins…. ‘The Daily Mail effect’

Lipid monitoring

- LFTs
  - Check transaminase after 3 months then yearly

- No need for CK unless symptomatic
  - Do not offer statin if CK >1000iu/L (5 x ULN)
- Check glucose if new on statin and high risk for DM. Do not stop statin therapy if glucose increases.

- Check adherence etc if non-HDL-C response <40%

- Statin intolerance
  - Any dose statin reduces CVD
  - Reduce dose; switch intensity class; consult specialist

Muscle Pain with statins

- 87% people on statins complain of muscle pain …… BUT

- 85% of people not on statins complain of muscle pain

JAMA Intern Med. 2013;173(14):1318-1326

Creatine Kinase

- Before offering a statin,
  - ask the person if they have had persistent generalised unexplained muscle pain,
  - whether associated with previous lipid-lowering therapy
- If they have, measure CK levels.
  - If CK levels are more than 5 x ULN,
    - re-measure CK after 7 days.
    - If still 5 times the ULN, do not start statin treatment.
  - If CK levels are raised but < 5 X ULN start
    - start statin treatment at a lower dose

Intolerance

- If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose
- Tell the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins discuss the following possible strategies with them:
  - stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
  - reducing the dose within the same intensity group
  - changing the statin to a lower intensity group
- Seek specialist advice about options for treating people at high risk of CVD who are intolerant to 3 different statins

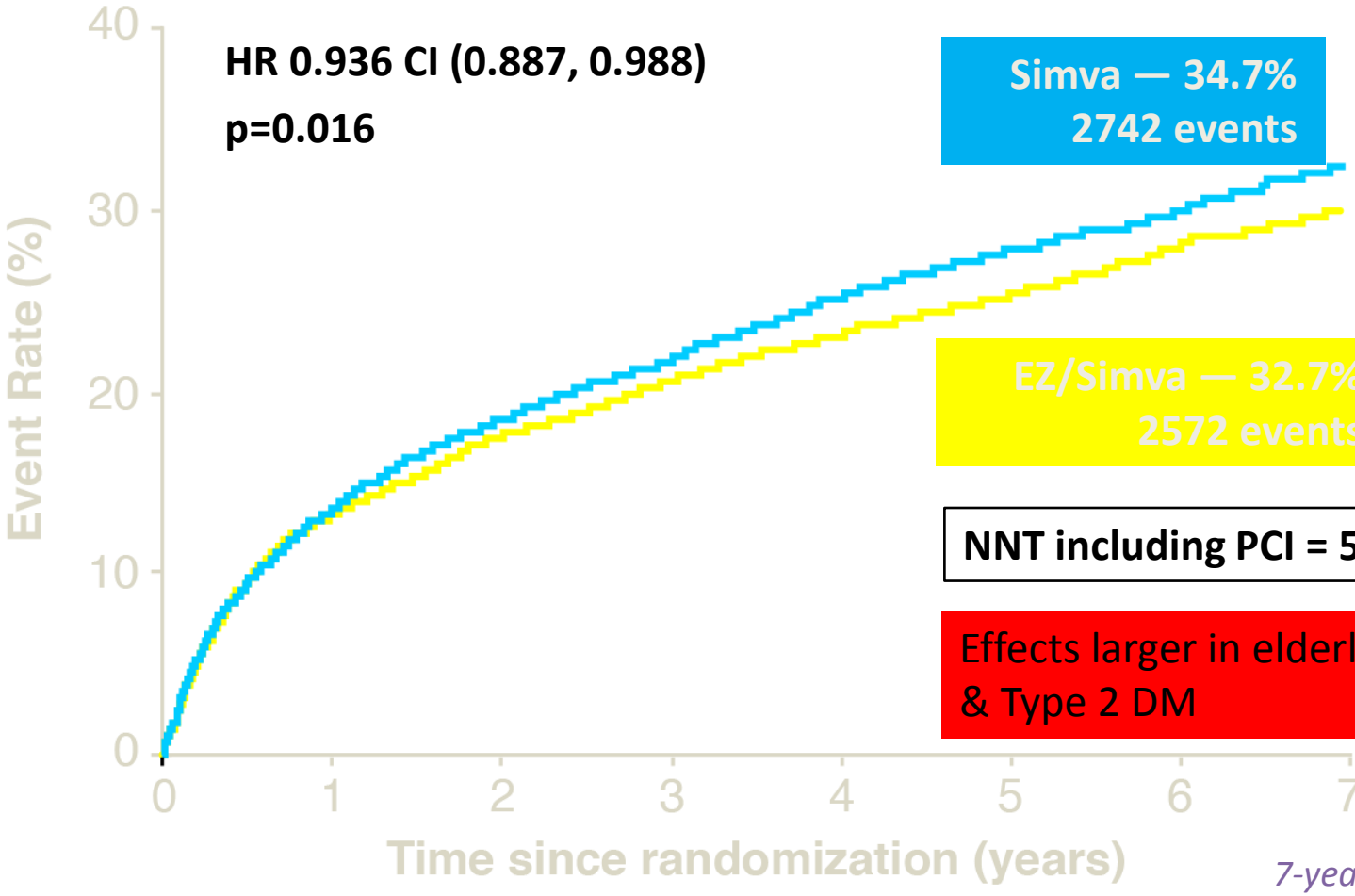
Secondary Drug Interventions

- Bile acid sequestrants
  - Weak monotherapy evidence on CVD
  - No combination evidence with statins
  - Do not use
- Fibrates
  - Meta-analysis: moderate monotherapy benefit
  - Meta-analysis: No combination therapy benefit
  - No routine use (i.e. $2^{nd}/3^{rd}$ line)
- Niacin
  - Weak monotherapy evidence
  - Meta-analysis: no combination therapy benefit
  - AE Meta-analysis: excess DM; myositis; infection
  - Do not use
- Omega-3 Fatty acids
  - Mixed diet and supplement trials. Multiple supplement trials used
  - Meta-analysis: no combination therapy benefit
  - Do not use

Ezetimibe

- People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with NICE TA 132 : Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia

IMPROVE-IT: Ezetimibe in ACS
Primary Endpoint — ITT



7-year event rates

CVD death, MI, UAS, CVA & PCI (≥30 days)

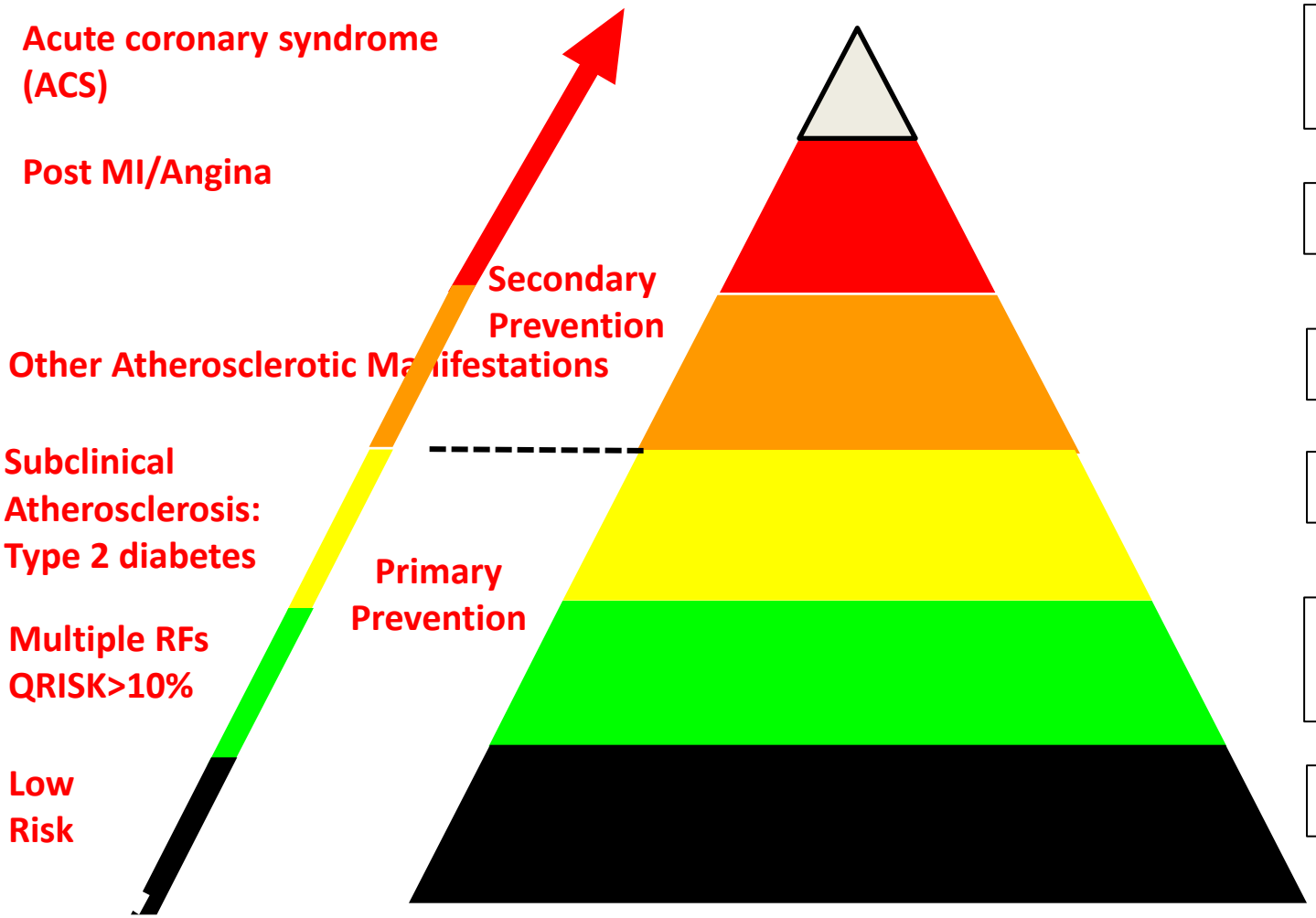
Cannon CP et al; NEJM 2015; 372 : 2387

New Guidelines

AHA-ACC (2013)	NICE (2014)
• Lipid measurements – as now – LDL-C retained • Secondary prevention – Atorvastatin >40mg • Primary Prevention & DM – Atorvastatin 20mg • No targets • Monitoring reduced • New risk calculator – ASCVD : 7.5% CVD risk	• Lipid measurements – Non-fasting – Use of non-HDL-C • Secondary prevention – Atorvastatin 80mg • Primary Prevention & DM – Atorvastatin 20mg • No targets • Monitoring reduced • New risk calculator – QRISK2: 10% risk

Stone NJ et al; Circ 2014; 129: S1-45
Rabar S et al; BMJ 2014; 349: g4356

NICE –CG 181 Continuum of CVD Risk and its treatment



Atorva 80mg (+ Eze 10mg)

Atorva 80mg

Atorva 80mg

Atorva 20+ mg

Lifestyle then Atorva 20mg

Lifestyle

Courtesy of CD Furberg.; modified to include NICE CG181

Conclusions

- Updated risk calculation systems
  - QRISK2 better than Framingham in UK
- Fixed doses vs. targets
  - Any statin at any dose better than placebo
  - No role for targets
  - Maximum high efficacy in CVD(+) e.g. atorvastatin 80mg
  - Moderate high efficacy in CVD(-), DM or CKD e.g atorvastatin 20mg
- Role of secondary risk modifiers
  - No evidence for HDL-C or TG modification as yet
- Role of secondary drugs
  - Minimal role for fibrates
  - No role for niacin, resins
  - ?Ezetimibe- IMPROVE-IT (11/14) & rpt NICE TA132

South London Algorithm for Lipid Management for the Primary and Secondary Prevention of CVD

(Adapted from NICE CG181: Lipid Modifaction July 2014)

Primary CVD prevention including people with type II diabetes

All patients with a CV risk ≥ 10% without known CVD, or familial hypercholesterolemia

Calculate CV risk using the QRisk2 risk calculator (for all < 85 years*, including those with type II diabetes)

If QRisk2 < 10% over the next 10 years

Give lifestyle advice; Ensure regular review of CVD risk in line with local guidance

If QRisk2 ≥ 10%** over next 10 years

Reassess CV risk after a trial of lifestyle modification and if QRisk2 remains ≥10% over 10 years **OFFER atorvastatin 20mg daily****

If there are potential drug interactions or atorvastatin 20mg is contraindicated or not tolerated, consider a lower dose of atorvastatin (or alternative generic agents, such as pravastatin)

➢**Reinforce lifestyle issues and check adherence to medication**

➢There are no specific lipid treatment targets for primary prevention, but if patient is considered higher risk due to the presence of multiple cardiovascular risk factors, consider increasing statin dose if necessary to reduce non-HDL cholesterol by 40% from baseline

People with type 1 diabetes

who:

- Are over 40 years old or
- have had type 1 diabetes for more than 10 years or
- have evidence of kidney disease or other CV risk factors

People with chronic kidney disease (CKD)

(eGFR < 60ml/kg/min)

Acute coronary syndromes and secondary prevention of CVD

All patients with established CVD or atherosclerotic vascular disease

Note: This guidance applies to new patients and may also be taken into consideration for those already on statins at their annual review. Patients stable on simvastatin do not need to be switched to atorvastatin

Identify and address all modifiable risk factors: smoking, diet, obesity, alcohol intake, physical activity, blood pressure and blood glucose / HbA1c**

Initiate atorvastatin 20mg daily***

(If potential drug interactions or atorvastatin 20mg is contraindicated or not tolerated, consider a lower dose of atorvastatin or consider an alternative generic agent)

Initiate atorvastatin 80mg daily***

(If potential drug interactions or atorvastatin 80mg is contraindicated or not tolerated, consider a lower dose of atorvastatin or consider an alternative agent)

➢**Once statin therapy has been initiated - repeat lipid profile at 3 months**

➢**Reinforce lifestyle issues** and check adherence to medication

➢**Aim to reduce non-HDL cholesterol by 40% from baseline**

- If baseline cholesterol is unknown, as a minimum, patients should be treated to achieve *at least* a total cholesterol ≤ 5mmol/L and non-HDL cholesterol ≤ 3.8mmol/L
- Increase statin dose if not achieving adequate reductions in cholesterol (and not already on maximum dose) – seek advice in renal disease

➢**Consider referral for specialist advice if** patients not achieving a 40% fall in non-HDL cholesterol on maximum tolerated dose of statin

➢Routine safety and efficacy monitoring should be undertaken

➢Patients should be reviewed annually, with lipid monitoring, to check efficacy and on-going adherence to therapy. Lifestyle issues should be revisited regularly

If statin therapy is contraindicated or not tolerated or not effective, do not offer a fibrate, nicotinic acid or bile acid binder or omega-3 fatty acids to lower CV disease risk.

People with primary hypercholesterolaemia may be considered for treatment with ezetimibe in line with NICE TA 132

*People ≥ 85years are at high CV risk due to age alone, but consider other CV risk factors, co-morbidities and patient preferences before initiating therapy. ** QRisk2 threshold of 20% applies for the introduction of antihypertensive therapies in people with hypertension. *** If initial statin dose not tolerated – reduce to maximum tolerated dose

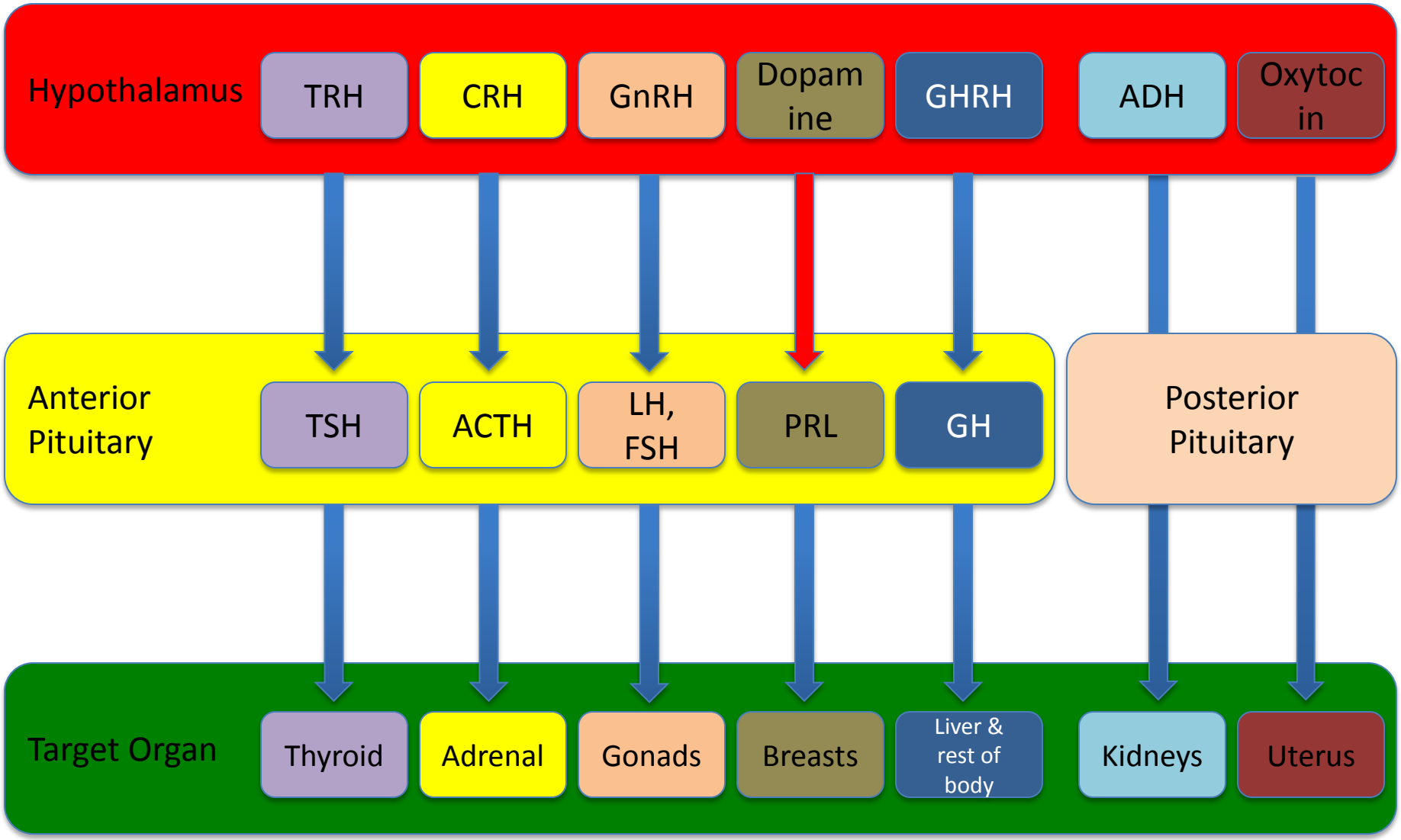
Pituitary disease for GPs

Dr Tricia Tan

Metabolic Medicine and Endocrinology

Hypothalamo-pituitary-endocrine organ axis

- Interface between brain and endocrine organs
- Amplification from
  - Releasing factor concentrations (10^{-15} M) to
  - Pituitary releasing hormone concentrations (10^{-12} M) to
  - Hormone concentrations (10^{-9} M)
- Pulsatility (amplitude/frequency) is important
- Diurnal rhythms
- Negative feedback


Hypothalamus
TRH
CRH
GnRH
Dopamine
GHRH
ADH
Oxytocin
Anterior Pituitary
TSH
ACTH
LH, FSH
PRL
GH
Posterior Pituitary
Target Organ
Thyroid
Adrenal
Gonads
Breasts
Liver & rest of body
Kidneys
Uterus

What can we measure?

Pituitary hormones	End-organ hormones	End-organ effects
GH	IGF-I	Growth
TSH	FT4, FT3	Metabolism
LH, FSH	Oestradiol, testosterone	Gametes, 2° sexual features
ACTH	Cortisol	Metabolism, BP
PRL		Milk production
ADH (vasopressin)		Osmolality
Oxytocin		Uterine contractions

Case 1

- 46 yr old man
- Tiredness

- Free T4 8.0 pmol/L
- TSH 0.35 mU/L

What would you like to measure next?

a) Free T3

b) Cortisol

c) Gonadotropins

d) Glucose

e) Calcium

Secondary hypothyroidism

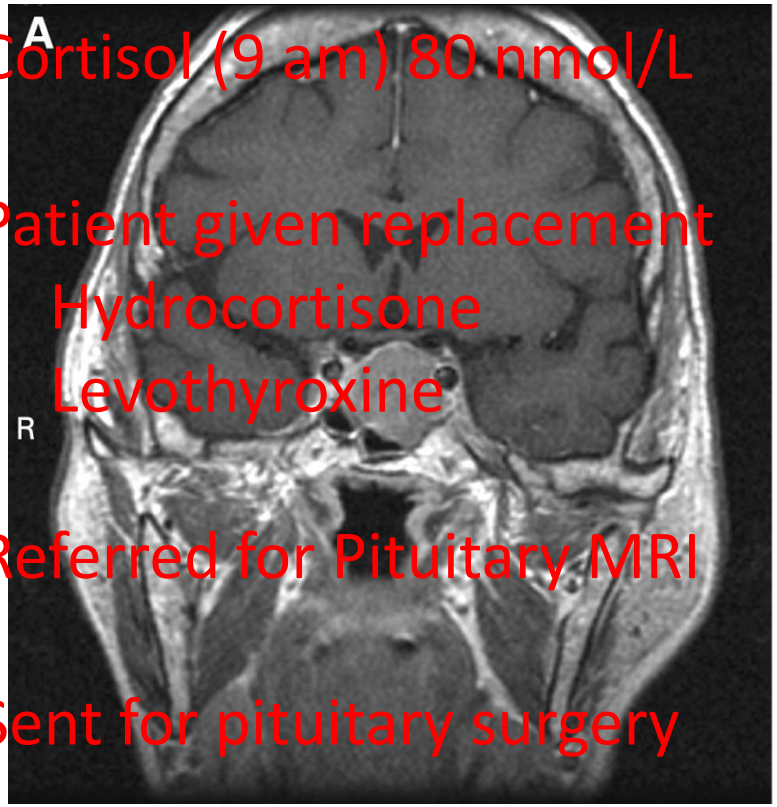
Cortisol (9 am) 80 nmol/L

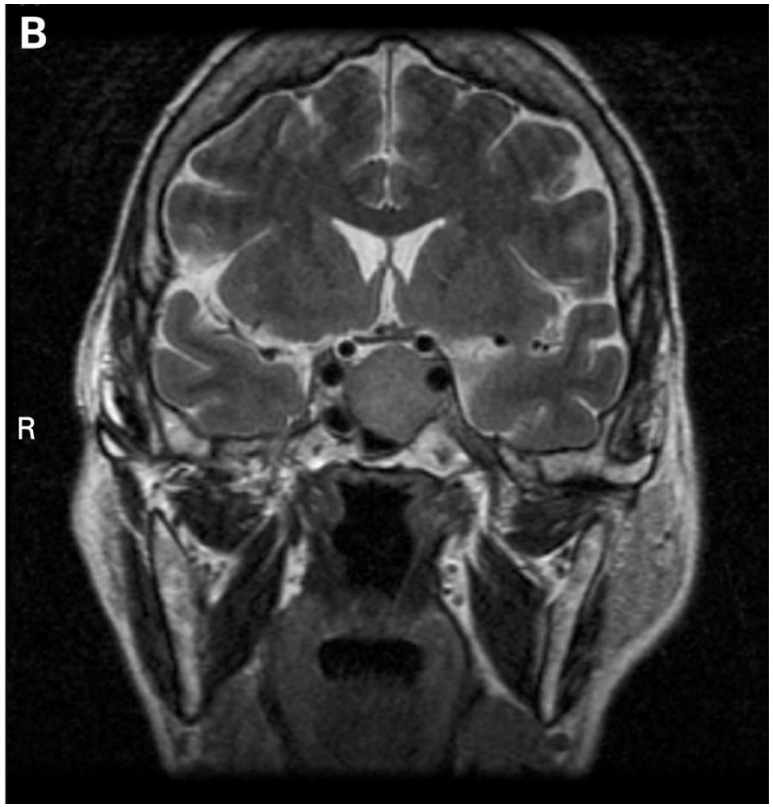
Patient given replacement

- Hydrocortisone
- Levothyroxine

Referred for Pituitary MRI

Sent for pituitary surgery





Secondary hypothyroidism and hypopituitarism

- Subnormal free T4 and T3
- Inappropriately normal TSH
  - less commonly low TSH
- Cortisol and thyroid hormones are essential hormones: MEASURE FIRST AND REPLACE
- Sex hormones, prolactin less important
- Sex hormones are most sensitive marker of hypopituitarism

Case 2

- 26 year old lady
- Secondary amenorrhoea for 6 months
- No medications

- PRL 1245 mU/L
- TFTs normal

What would be the test you would ask for next?

a) Cortisol
b) Gonadotropins
c) Oestradiol
d) IGF-I
e) PEG precipitation

Hyperprolactinaemia

- Prolactinoma
- Hypothyroidism (↑TRH releases prolactin)
- 'Disconnection' hyperprolactinaemia
  - Macroadenoma blocking dopamine flow to ant pituitary
- Drugs
  - Oestrogens, dopamine antagonists (antiemetics, antipsychotics), anti-depressants
- Stress (e.g. venepuncture)
- Macroprolactinaemia
- Pregnancy!

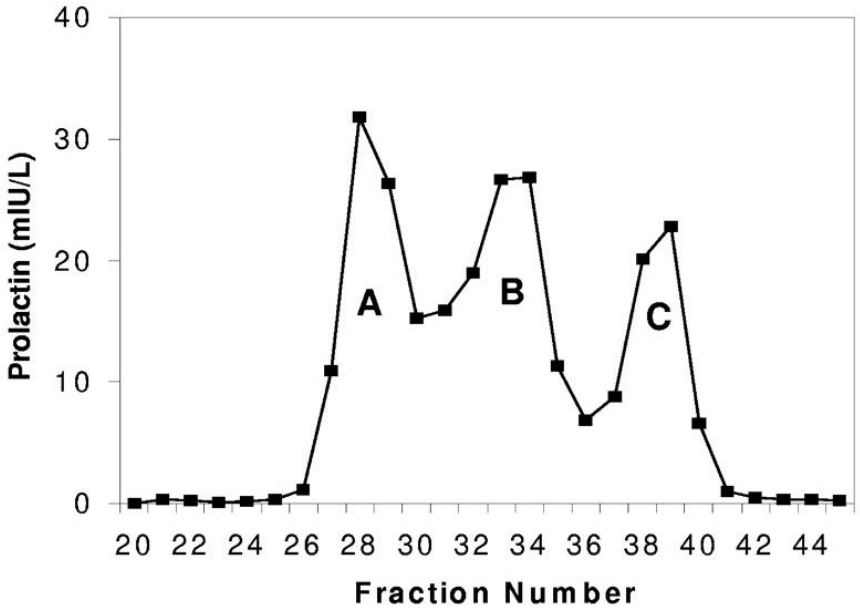
Macroprolactinaemia

A = monomeric prolactin (23 kD)
B = 'big' prolactin (60 kD)
C = macroprolactin (150 kD)
MacroPRL generally bio-inactive

Gold-standard technique is gel-filtration chromatography

Screening technique is PEG precipitation = re-measure PRL after PEG is used to remove macroPRL

b



Case 2

- Recovery after PEG precipitation = 230 mU/L

- Therefore macroprolactinaemia
- Other causes of amenorrhoea need to be excluded

Case 3

- 24 yr old lady, BMI 34 kg/m^2, amenorrhoea

- PRL 885 mU/L
- LH 17.4 U/L, FSH 8.6 U/L
- Oestradiol 342 pmol/L
- Testosterone 2.3 nmol/L
- SHBG 15 nmol/L

What is the most likely diagnosis?

a) Prolactinoma

b) Polycystic ovarian syndrome

c) Pituitary adenoma

d) Cushing's syndrome

e) Hyperthyroidism

Polycystic ovarian syndrome

- Hyperprolactinaemia is seen with PCOS in 1/6 cases
- Can be still be due to:
  - Exogenous oestrogen treatment (OCP etc.)
  - Co-existent pituitary microadenoma
  - Macroprolactinaemia
  - Drugs etc.
- So need to exclude these causes nevertheless = needs referral

Case 4

- 26 yr old lady
- Weight gain

- 9 am cortisol 1057 nmol/L
- Urine free cortisol normal

What medication could cause this problem?

a) Beclomethasone inhaler
b) Prednisolone
c) Combined oral contraceptive pill
d) Fluticasone
e) Fluoxetine

Oral contraceptive pill

- Cortisol is bound to proteins in circulation
  - Albumin
  - Cortisol binding globulin
- Oral oestrogens cause a rise in CBG
- This causes an increase in total cortisol levels but free cortisol remains normal
- Need to withdraw OCP for 6 weeks before re-measuring

Case 5

- 24 year old man
- Erectile dysfunction, poor libido

- LH 3.4
- FSH 2.7
- Testosterone (4 pm) 7.5 nmol/L

Diagnosis?

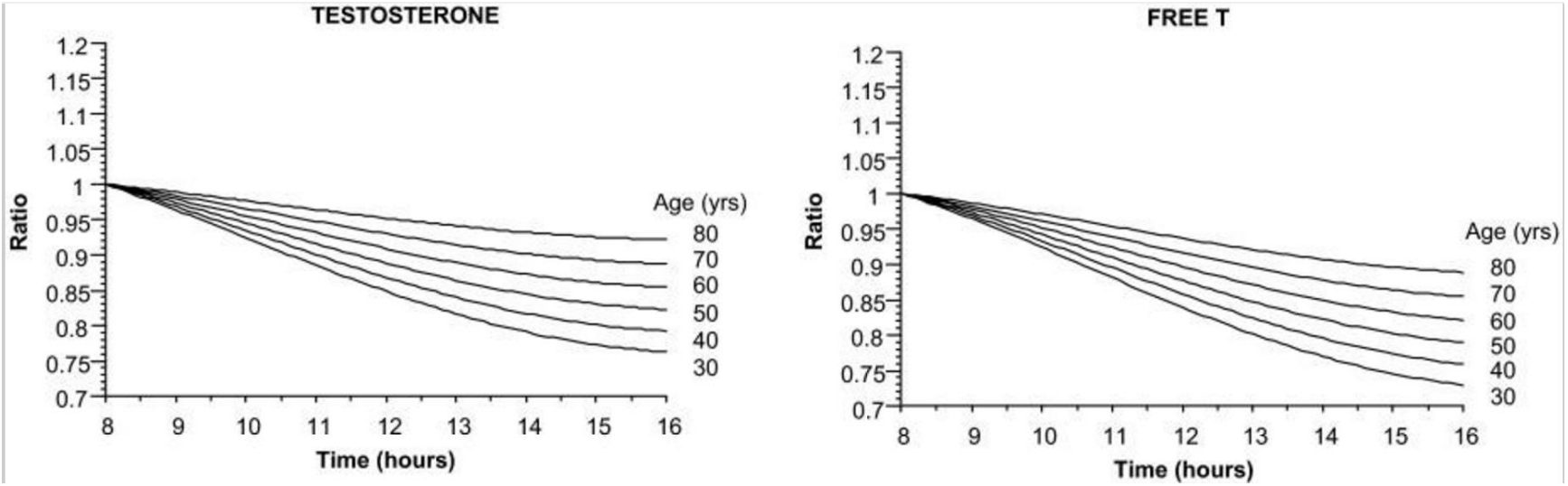
a) Primary hypogonadism

b) Secondary hypogonadism

c) Afternoon sample of blood

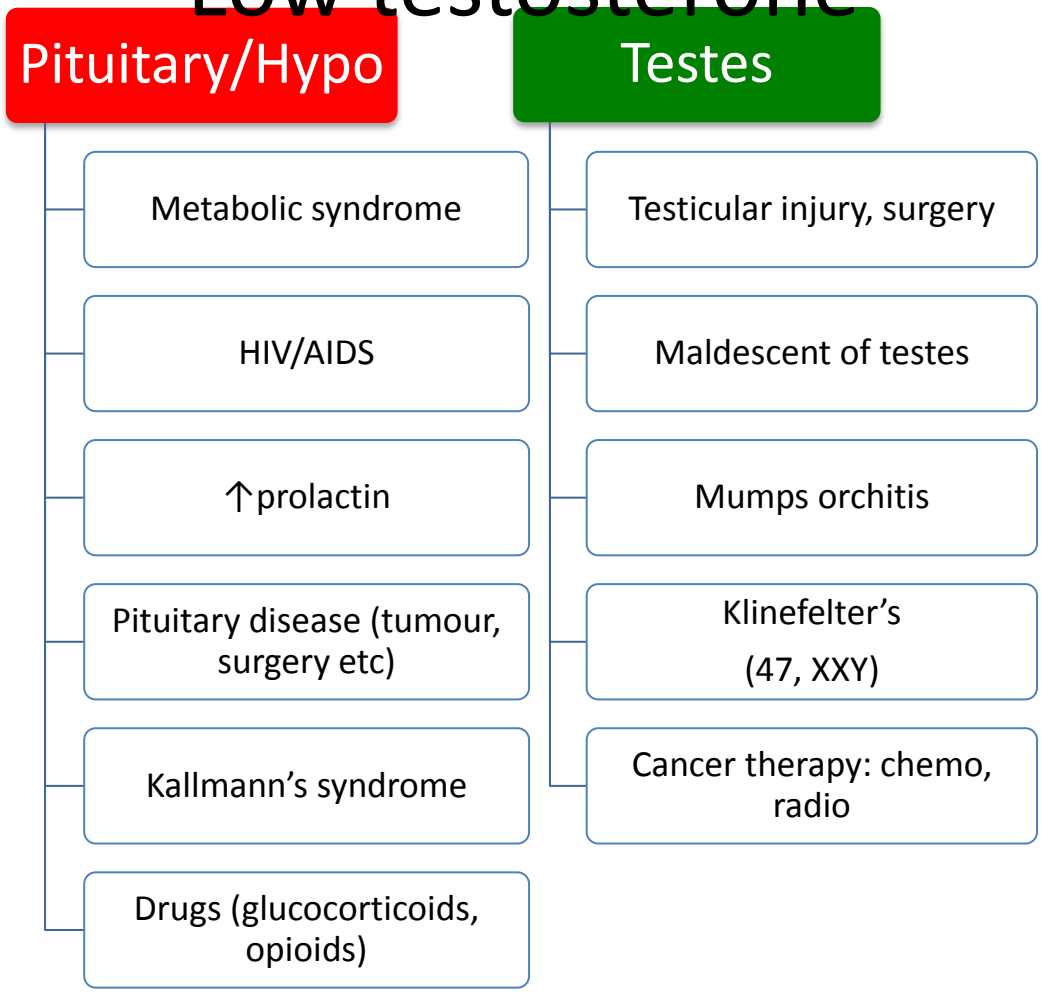
d) Assay interference

Diurnal variation in testosterone



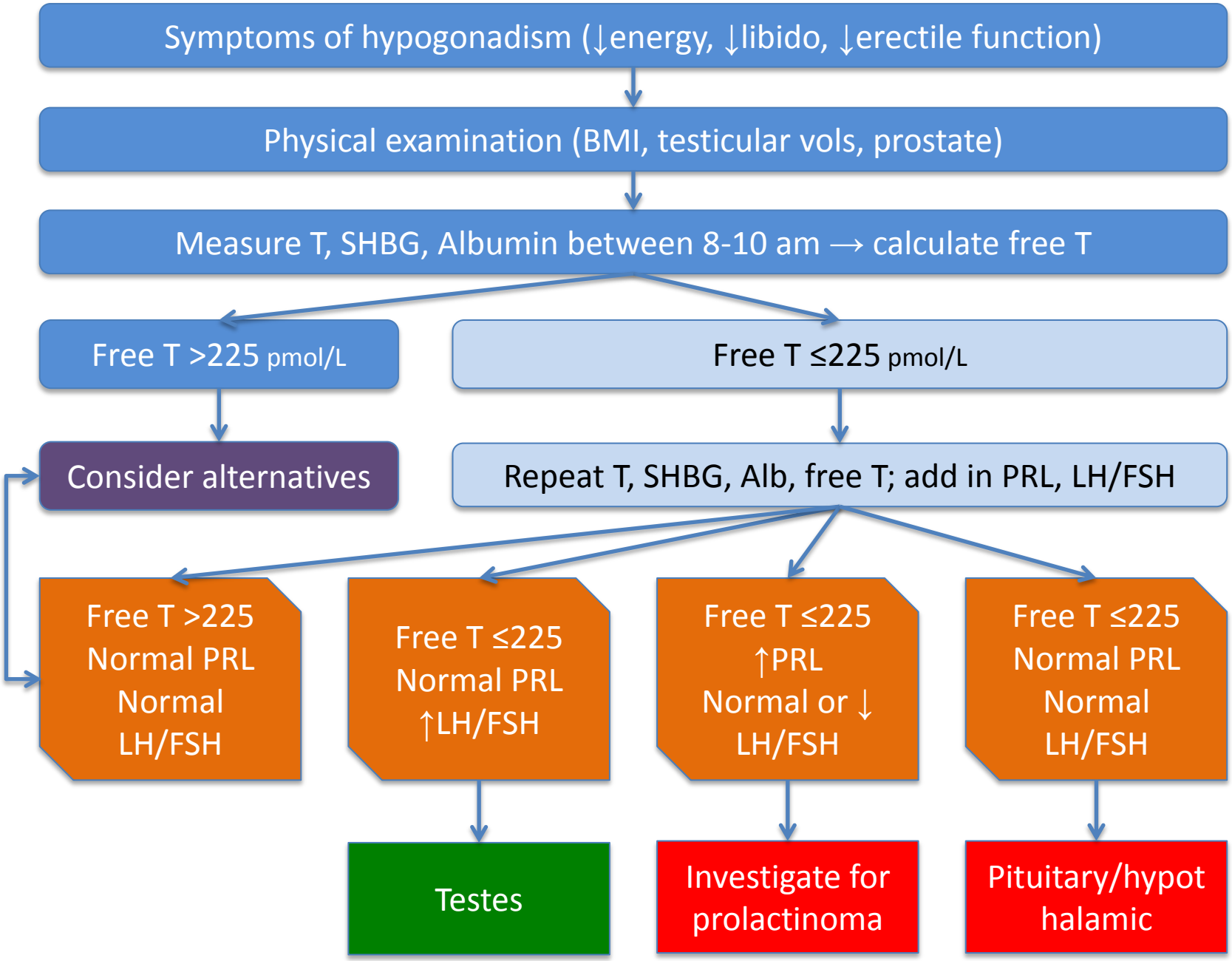
The diurnal variation is more marked in younger men than in older men
A low reading in an older man even in the afternoon may be sufficient

Low testosterone



Assessment of low testosterone

- 9 am blood tests
  - Testosterone
  - Sex hormone binding globulin
  - LH/FSH
- Calculate free testosterone
  - Vermeulen calculation – depends on empirically determined affinity constants of T for SHBG and Albumin
  - www.issam.ch/freetesto.htm


Symptoms of hypogonadism (↓energy, ↓libido, ↓erectile function)
Physical examination (BMI, testicular vols, prostate)
Measure T, SHBG, Albumin between 8-10 am → calculate free T
Free T >225 pmol/L
Free T ≤225 pmol/L
Consider alternatives
Repeat T, SHBG, Alb, free T; add in PRL, LH/FSH
Free T >225 Normal PRL Normal LH/FSH
Free T ≤225 Normal PRL ↑LH/FSH
Free T ≤225 ↑PRL Normal or ↓ LH/FSH
Free T ≤225 Normal PRL Normal LH/FSH
Testes
Investigate for prolactinoma
Pituitary/hypothalamic

Case 6

- 46 yr man
- Previous pituitary surgery
- Taking Levothyroxine 150 mcg OD

- TSH 0.1, FT4 16.4 pmol/L

What should you do to the Levothyroxine dose?

a) Increase

b) No change

c) Decrease

Replacement of thyroxine in pituitary disease

- TSH is not reliable in pituitary disease
- Aim for
  - FT4 between 14-19 pmol/L
  - FT3 in normal range

- Therefore no change in Levothyroxine dose required

Case 7

- 54 yr old
- Routine blood test screening

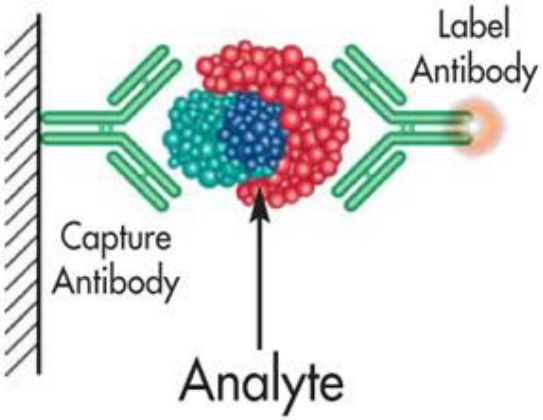
- TSH 5.76, FT4 28.9 pmol/L

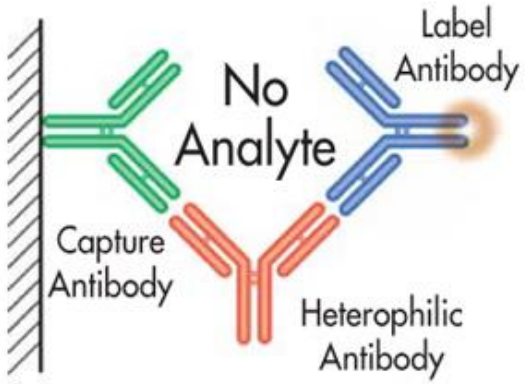
➢ Diagnosis?

High TSH, high FT4

a) Antibody interference with assay
b) Resistance to thyroid hormone syndrome
c) TSH-secreting pituitary tumour

Assay interference



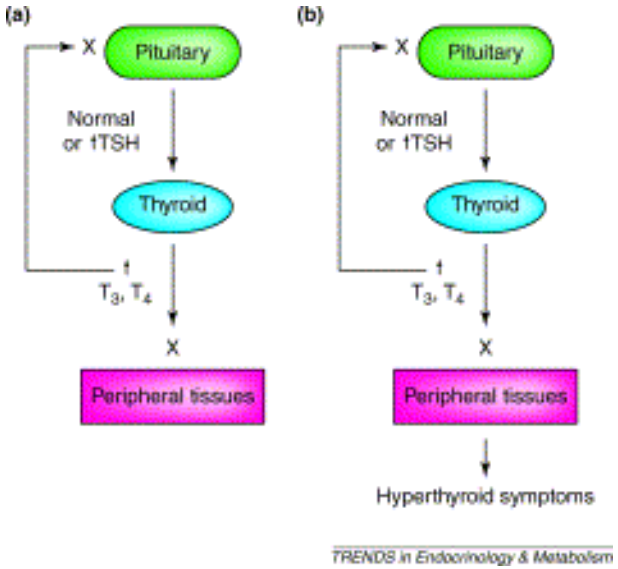


- Heterophile Abs = anti-animal Abs that bind both to the capture and label Ab
- Leads to falsely elevated levels.
- Can eliminate possibility by:
  - Running on different assay
  - Heterophile blocking tubes

Resistance to thyroid hormone

Mutations in thyroid hormone receptor
Leads to resistance to thyroid hormone
High T4, normal TSH

- Generalised resistance = no hyperthyroid symptoms
- Pituitary resistance = hyperthyroid symptoms (peripheral tissues still sensitive to high T4)



‘TSH’oma

- A TSH producing pituitary tumour – rare
- Leads to hyperthyroidism by overproduction of TSH
- Usually associated with ↑alpha-subunit relative to TSH

Case 7

- Sent blood tests to different assay:
  - Free T4 15.67
  - TSH 2.98
- Heterophile Ab interference
- No treatment is required, patient is euthyroid

Case 8

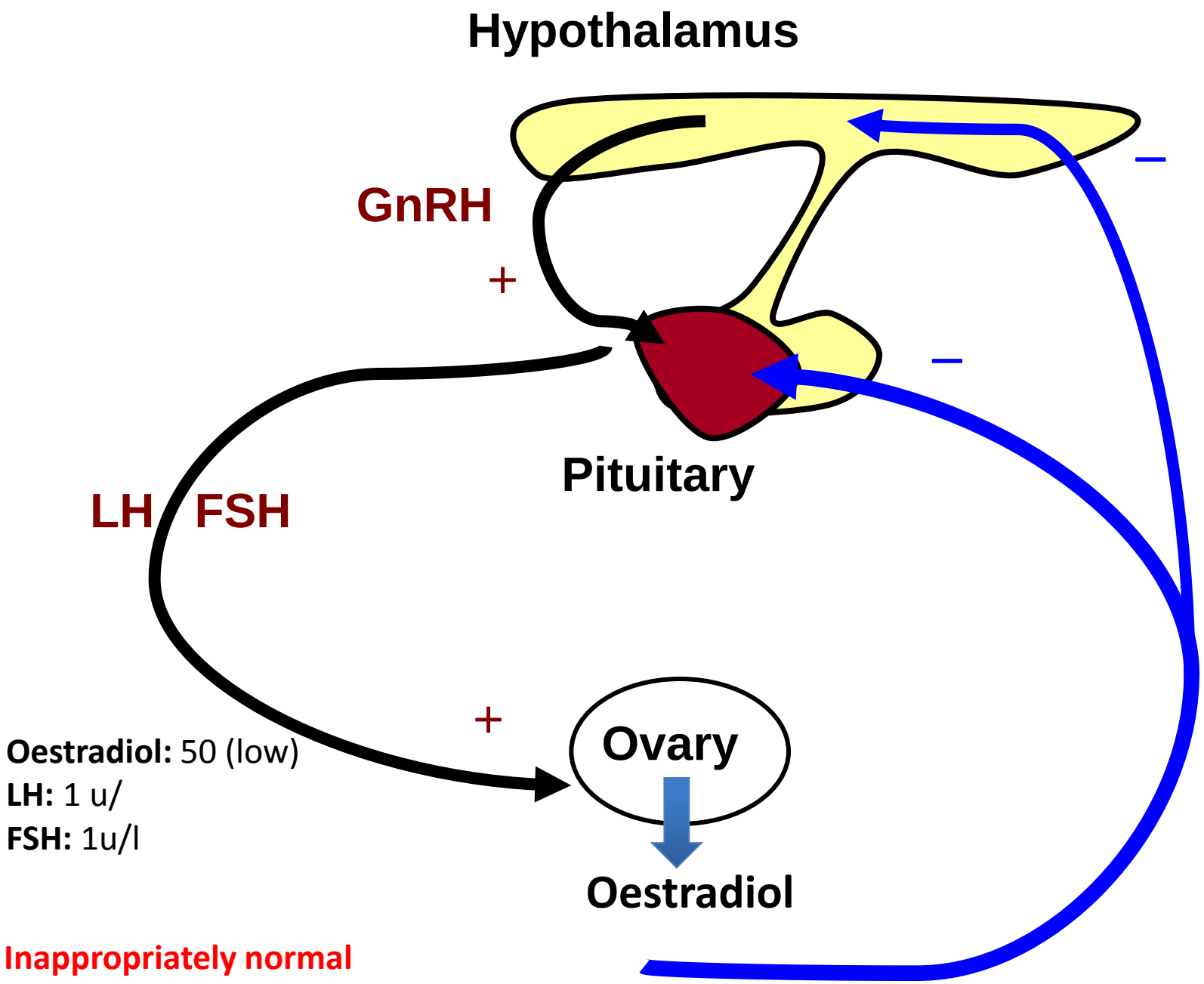
- 20-year-old woman
- Headache & vomiting
- ↓ libido, no periods

- PR: 60, BP: 110/80, BMI: 18
- CVS, Resp & GI exams: normal
- VF: normal to confrontation

Tests….

- Prolactin: 300 mu/l
- IGF-1: 90 (127-424 ng/l), GH: 12 (<8 µg/l)
- Free T4: 8 pmol/l, TSH: 1.5 mu/l
- LH: 1 u/l, FSH: 1u/l, oestradiol: 50 pmol/l
- Cortisol: 1200 (150-650 nmol/l)

- DHEA-S: 0.8 (1.8-10.3 µmol/L)
- OGTT: fails to suppress (nadir GH: 4 µg/l)


Hypothalamus
GnRH
+
–
–
Pituitary
LH FSH
+
Ovary
Oestradiol
Oestradiol: 50 (low)
LH: 1 u/
FSH: 1u/l
Inappropriately normal

What test would you do next?

A. LDDST

B. no further tests

C. refer for pituitary surgery

D. repeat OGTT

E. TRH test

Anorexia nervosa

- **GH resistance:** ↑ GH, ↓ IGF-1, False-positive OGTT
- ↓ LH & FSH & oestradiol (↓ leptin/GnRH)
- ↓ Free T4, normal TSH
- ↑ Cortisol (activation of HPA axis)

Other Endocrine manifestations

- **↓ADH**
  - Central DI
- **Adrenals**
  - ↓ adrenal androgens (↓ libido)
  - ↑ metanephrines
- **Bones**
  - ↑ cortisol & ↓ androgens & IGF-1: **osteoporosis**

Case 9

- 56 yr old man
- Weight gain, striae

- Could this be Cushing's syndrome?
  - 9 am Cortisol 495 nmol/L

What is the next best test?

a) Urine collection for cortisol
b) Overnight dexamethasone suppression (1 mg)
c) Low dose dexamethasone suppression
d) CRF test

Urine collection for cortisol

- Cheap
- Non invasive
- A good rule-out test

- Needs patient cooperation to collect a complete collection

Low-dose dexamethasone test

- Involves two blood samples at baseline and at T=48 h
- Patients take dexamethasone 0.5 mg q6h (0900h, 1500h, 2100h, 0300h) x 8 doses
- Definitive diagnostic test (normal: 48h <50 nmol/L)
  - Specificity 70%, sensitivity 96%

➢ Cumbersome for primary care

➢ Involves two blood tests

➢ Certain drugs cause increased breakdown of dexamethasone and therefore false positive results

Overnight dexamethasone suppression

- Patients instructed to take 1 mg dexamethasone at 2300h
- Take blood test at 9 am
- Normal cut-off is <50 nmol/L

➢ Performs comparably to LDDST

- Specificity 80%, Sensitivity >95%

➢ Practically easier than LDDST

What is the next best test?

- Would probably select overnight dexamethasone suppression test
  - Simple to do
  - Good performance

Imperial College Healthcare NHS
NHS Trust

Faecal Occult Blood testing

Mrs Sophie Barnes FRCPath
Consultant Clinical Scientist

Learning objectives

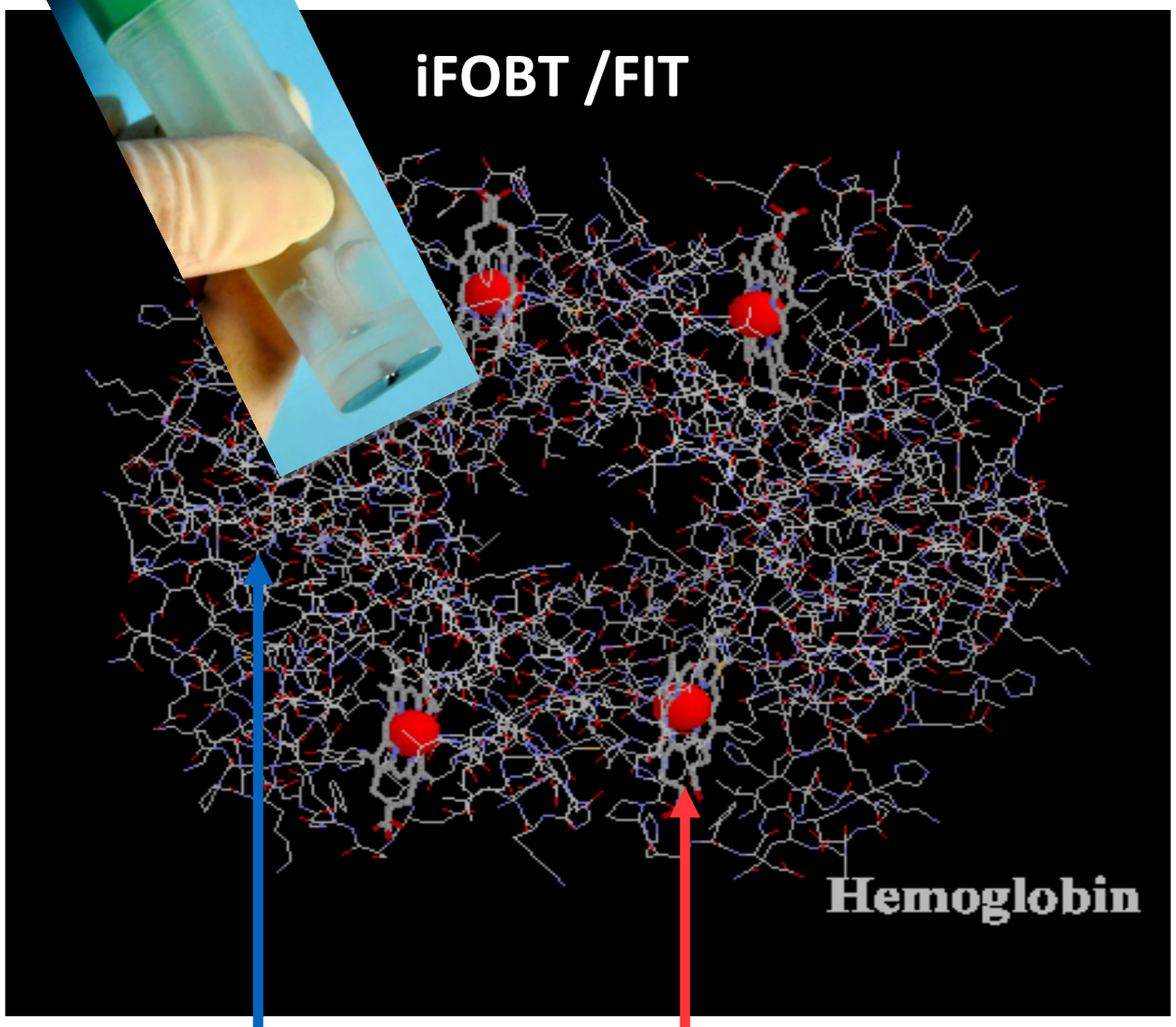
- Different tests available for Faecal Occult Blood (FOBt)
- Current requesting practice at Imperial from audit data
- Current guidelines and recent changes
- The risks of guaic FOBt
- Future developments in this field

Colorectal cancer

- 3rd most common cancer
- 2nd most common cause of death in Europe
- 1st cause of cancer death in non-smoking males

Faecal occult blood

- Blood in faeces invisible to naked eye
- Surrogate marker for bowel cancer



Haemoglobin – Haem

Haemoglobin - Globin

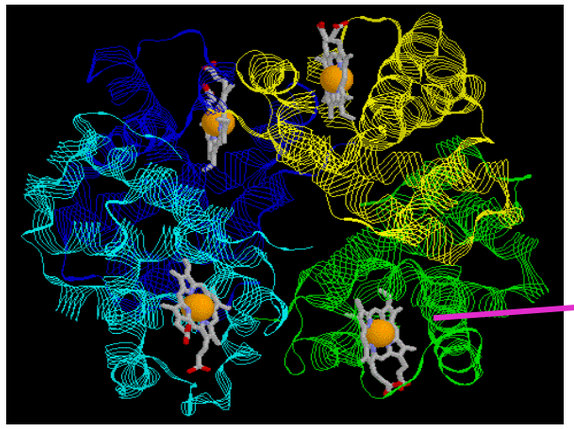
- Antibody recognition of the tertiary structure produced by the folding of the amino acid chain in the globin

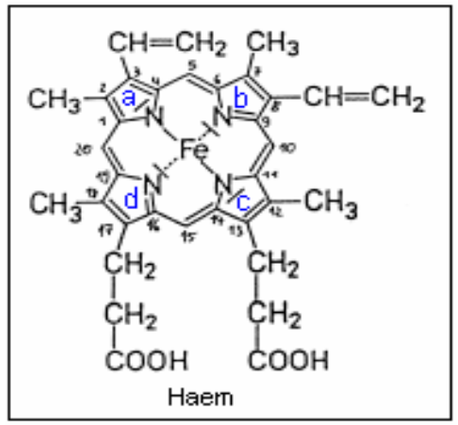
Haem

Globin

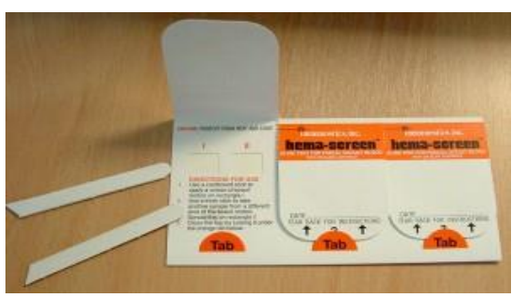
Faecal Occult Blood Test

Guaiacum officinale
- Lignum Vitae



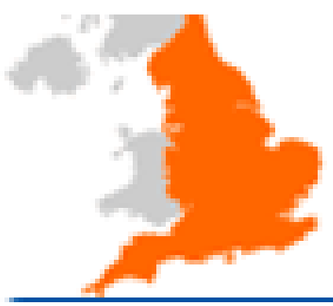


Guaiac Acid (Colourless) + H_2O_2 —(Haem, Peroxidase)→ Oxidised Guaiac (Blue)



NHS Bowel Cancer Screening

- 5 UK hubs since April 2006
- Biennial basis for 60-74 y olds
- On request > 75 y olds



NHS Bowel Cancer Screening Programme

NICE CG 27, 2005

Referral guidelines for suspected cancer

Urgent referral if symptomatic:

- > 40 y rectal bleeding, change bowel habit 6/52
- > 60 y rectal bleeding > 6/52 regardless
- > 60 y change habit > 6/52 without bleeding
- Any age R abdo mass consistent with large bowel
- Any age palpable rectal mass
- IDA and Hb < 110 g/L male, < 100 g/L post-men female

Indications for FOB

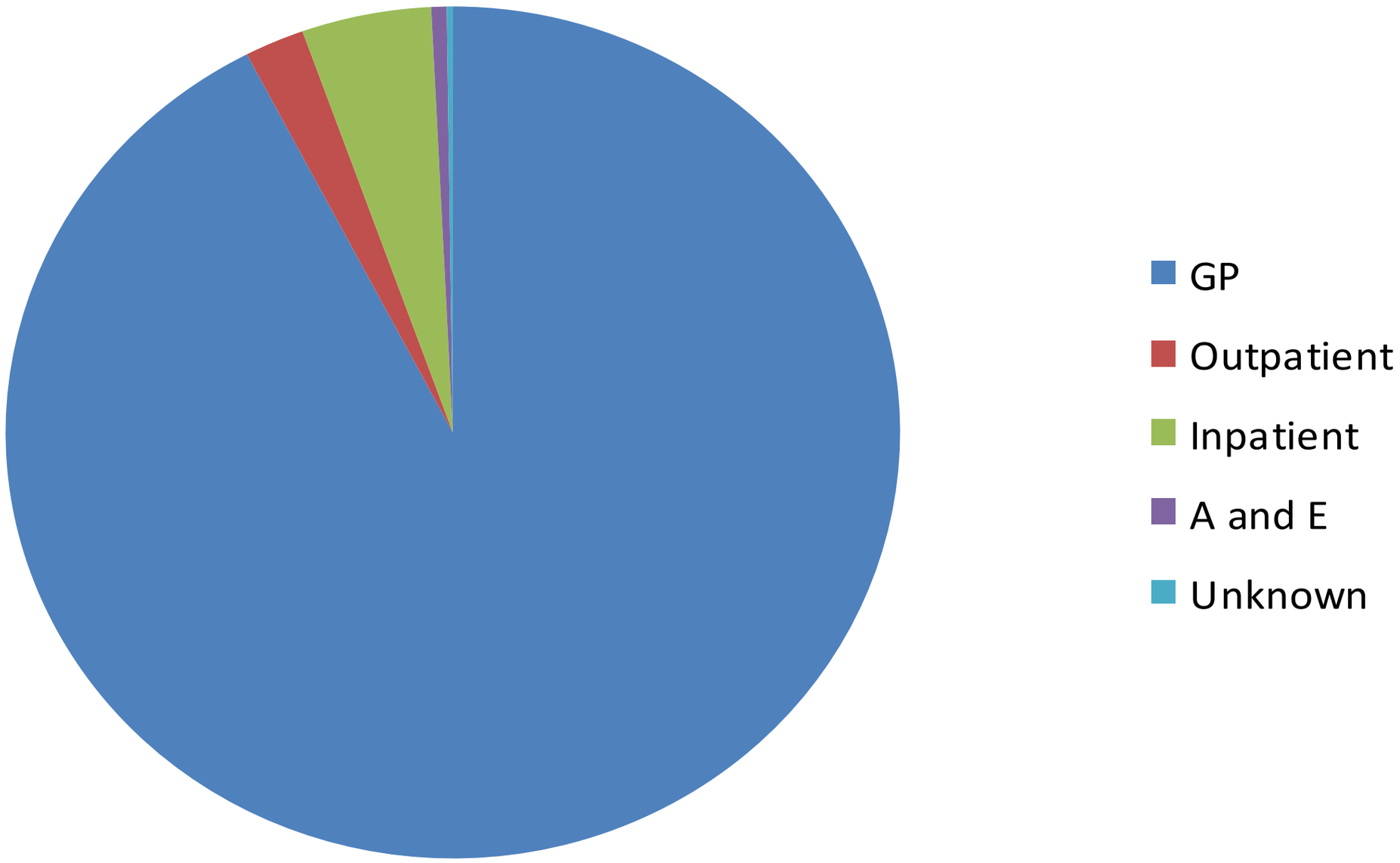
- Asymptomatic screening
- Paediatric patients
- Symptomatic but bowel visualisation difficult
- Follow up of established disease
- Ix familial CRC

Fraser CG, Problems with the investigation of a problem with faecal occult blood tests. Ann Clin Biochem 47: 391-2, 2010.

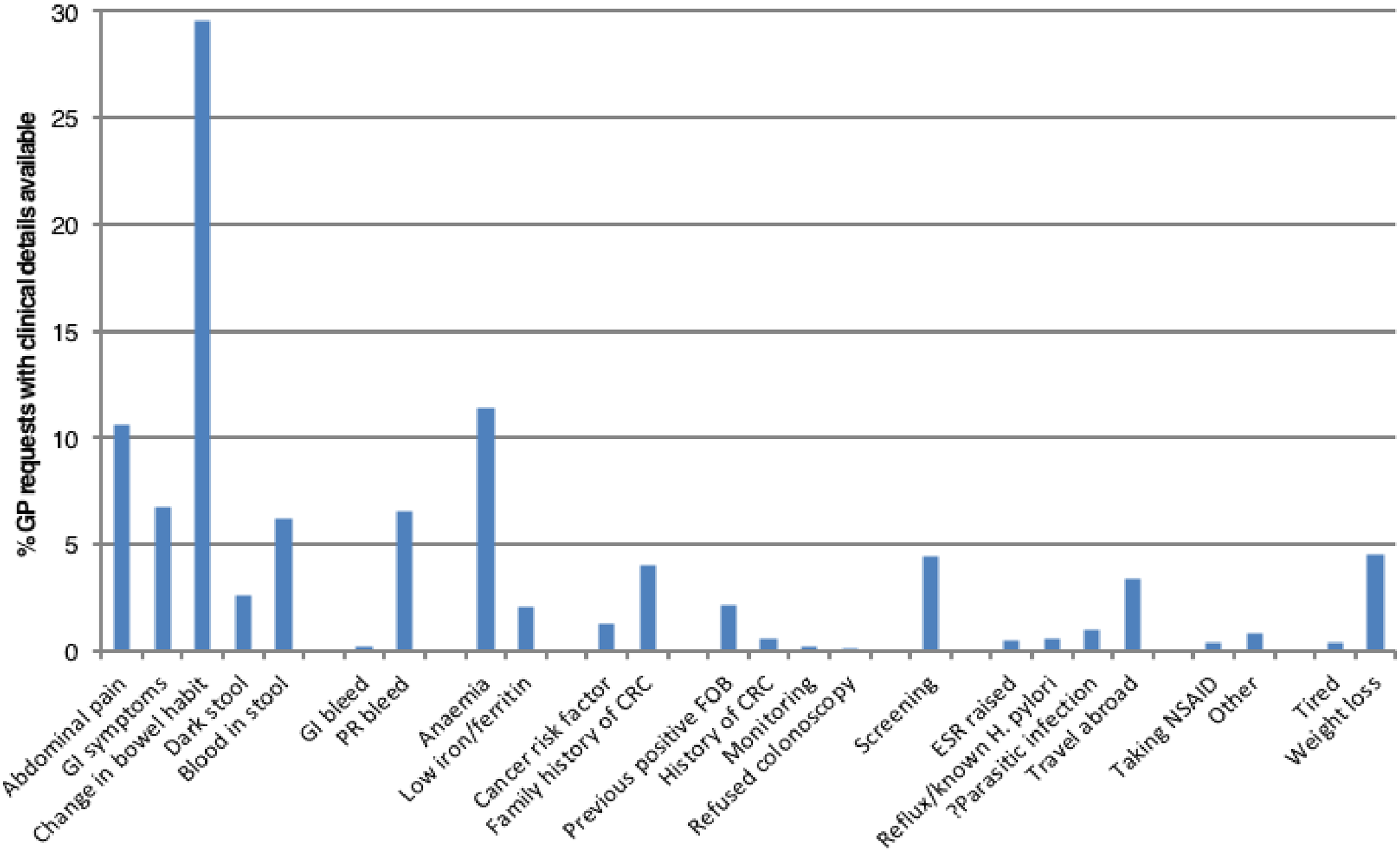
ICHNT Audit

- All FOB requests 2013/2014
- 3242 requests
- 2656 requesting events (grouped if within week)
- 2456 individual patients
- 270 pcm, 9 per day

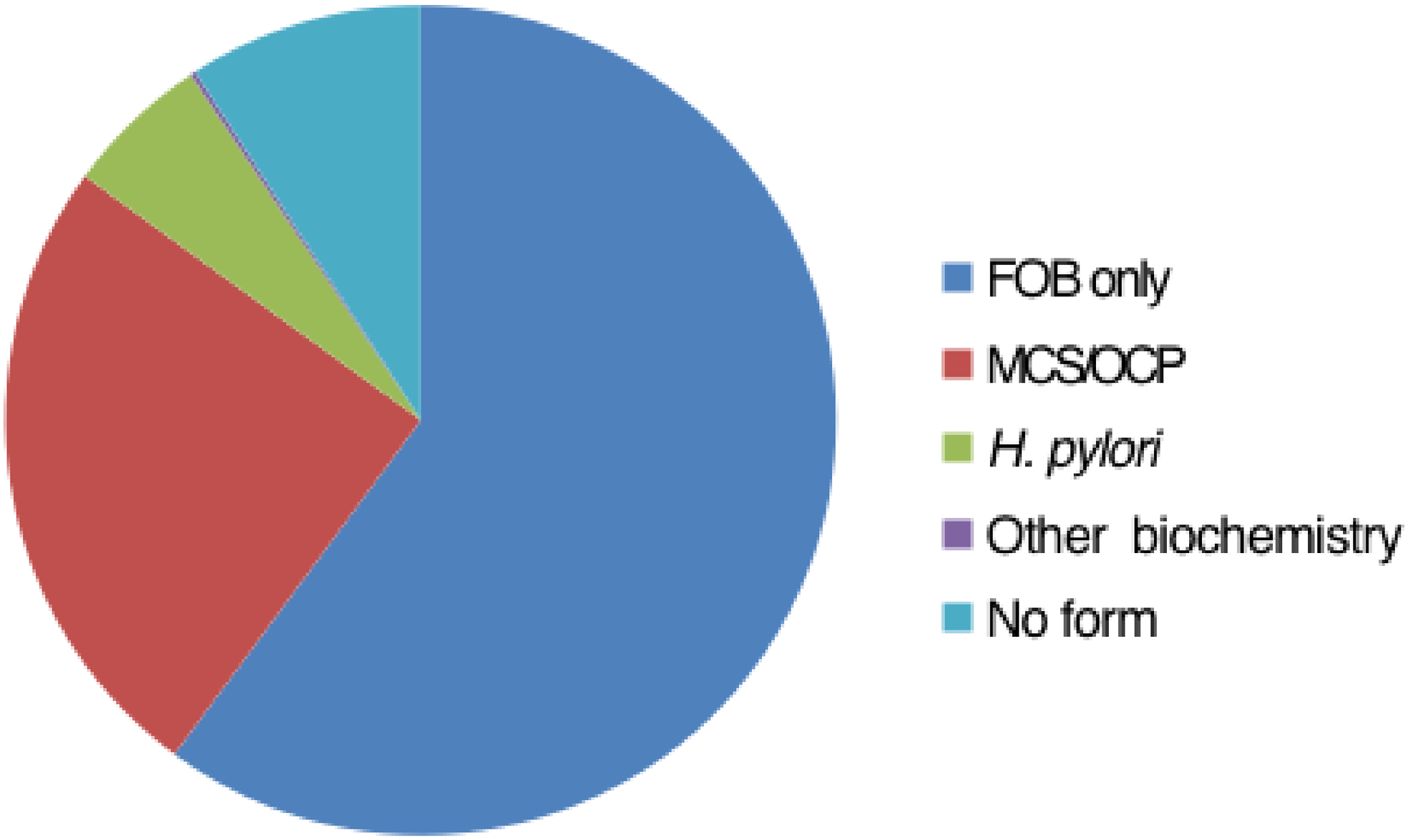
Source of requests



Clinical details



Simultaneous faecal requests



Urgent referral indicated?

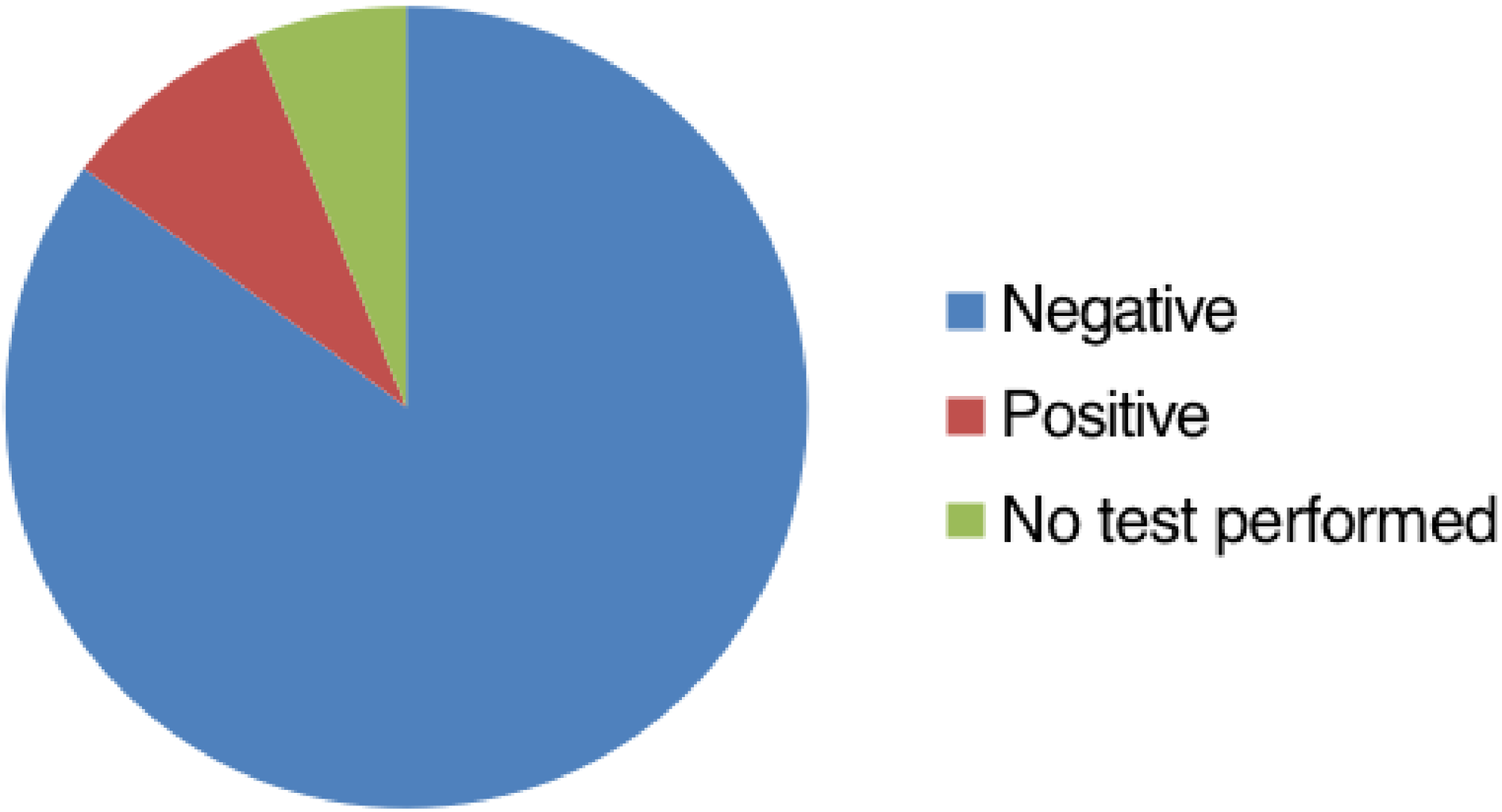
NCD	954	39.2%
No	1344	55.2%
Yes, GI Sx	10	0.4%
Possible, GI Sx time not given	47	1.9%
Yes, anaemia	41	1.7%
Possible, no recent Hb	17	0.7%
Sx suggest refer upper GI	22	0.9%
Total	2435	

Appropriate request*

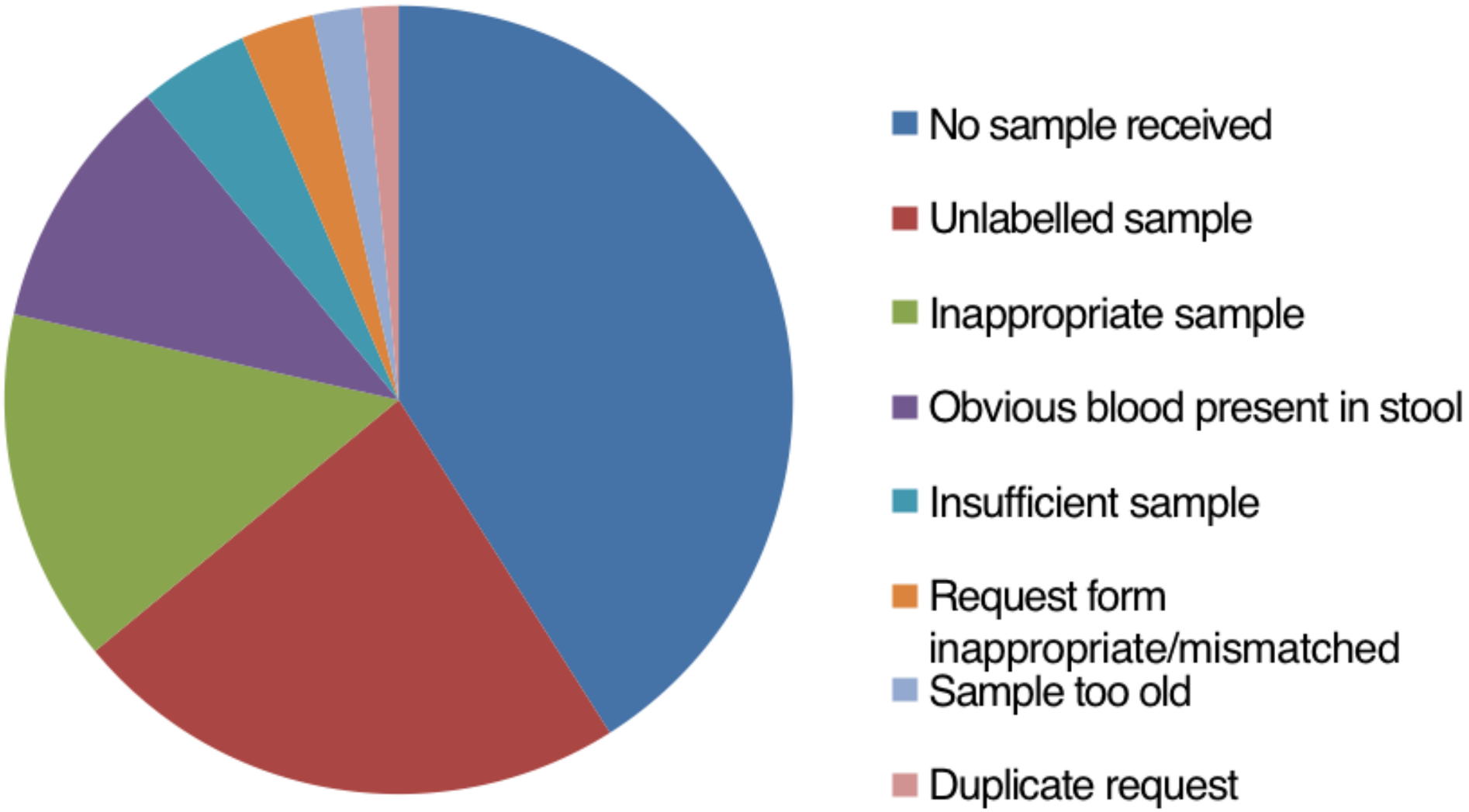
NCD	1173	39.2%
No	1567	52.3%
Yes, screening	82	2.7%
Yes, FHx	83	2.8%
Yes, monitoring	21	0.7%
Yes, paediatric	70	2.3%
Total	2996	

** Fraser CG, Problems with the investigation of a problem with faecal occult blood tests. Ann Clin Biochem 47: 391-2, 2010*

Outcome of testing



Reason not performed



No. Samples received per patient

No. Samples		
1	2297	86.5%
2	130	4.9%
3	224	8.4%
4	1	0.04%
6	1	0.04%
Duplicate	3	0.11%
Total	2656	

Conclusions from audit (1)

- Sample date and time should be recorded on request forms / samples by patients
- Samples should be sent to laboratory promptly
- 3 samples over 3 different days are not being received for most cases.
- Improve patient preparation?

Conclusions from audit (2)

- Based on the clinical details provided, many requests are not appropriate
- In some cases urgent referral for suspected lower GI cancer is indicated.
- FOB should not be used for investigation of symptomatic patients
- Requests for urgent testing are not appropriate.

New guidelines NG12, 2015

- **1.3 Lower gastrointestinal tract cancers - Colorectal cancer**

- 1.3.1 Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if:

- they are aged 40 and over with unexplained weight loss and abdominal pain **or**

- they are aged 50 and over with unexplained rectal bleeding **or**

- they are aged 60 and over with:
- iron-deficiency anaemia **or**
- changes in their bowel habit, **or**
- tests show occult blood in their faeces (see recommendation 1.3.4 for who should be offered a test for occult blood in faeces). **[new 2015]**

New guidelines NG12, 2015

Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in

1.3.2 people with a rectal or abdominal mass. **[new 2015]**

1.3.3 adults aged under 50 with rectal bleeding **and** any of the following unexplained symptoms or findings:

- abdominal pain
- change in bowel habit
- weight loss
- iron-deficiency anaemia. **[new 2015]**

New guidelines NG12, 2015

1.3.4 Offer testing for occult blood in faeces to assess for colorectal cancer in adults without rectal bleeding who:

- are aged 50 and over with unexplained:
  - abdominal pain **or**
  - weight loss, **or**
- are aged under 60 with:
  - changes in their bowel habit **or**
  - iron-deficiency anaemia, **or**
- are aged 60 and over and have anaemia even in the absence of iron deficiency.
- **[new 2015]**

The risks of guaic FOBt

- Guaiac test
- crude chemical method, presence of a blue colour
- very poor diagnostic sensitivity and specificity for CRC
- False negatives - not all cancers and pre-cancers will bleed
- FN rate as high as 50%

Why recommend FOB in NG12?

- Positive results will be referred for colonoscopy; more cancers should be detected.
- Will negative result patients represent within one year?
  - ***Or*** are negative patients reassured; more likely to ignore any possible symptoms?

BMJ 2015;351:h4256 doi: 10.1136/bmj.h4256 (Published 11 August 2015)

LETTERS

SUSPECTED CANCER IN ADULTS

Use of faecal occult blood tests in symptomatic patients

Robert Steele *president*[1], Ian Forgacs *president*[2], Gwyn McCreanor *president*[3], Sally Benton *director*[4], Michael Machesney *chair*[5], Colin Rees *vice president (chair of endoscopy)*[2], Stephen P Halloran *member, bowel screening advisory committee*[6], Muti Abulafi *chair*[7], Deborah Alsina *chief executive*[8]

[1]Association of Coloproctology of Great Britain and Ireland, London WC2A 3PE, UK; [2]British Society of Gastroenterology, London, UK; [3]Association for Clinical Biochemistry and Laboratory Medicine, London; [4]NHS Bowel Cancer Screening Southern Programme Hub, Royal Surrey County Hospital, Surrey Research Park, Guildford, UK; [5]Colorectal Cancer Clinical Reference Group, NHS England, c/o Bowel Cancer UK (Secretariat), London; [6]Public Health England (Secretariat), London, UK; [7]Colorectal Cancer Pathway Group, London Cancer Alliance, London; [8]Bowel Cancer UK, London

MM is also colorectal pathway director, London Cancer; CR is chair of research, European Society of GI Endoscopy, Munich, Germany; SPH is former director of the NHS Bowel Cancer Screening Southern Programme Hub.

Despite serious reservations expressed during consultation, the National Institute for Health and Care Excellence (NICE) has recently issued referral guidance for suspected colorectal cancer in which faecal occult blood testing (FOBT) is recommended for certain low risk symptomatic patients.[1 2] We believe that this will lead to false reassurance and delayed investigations. We should like to point out that:

1. The guidance is particularly worrying for people under 60 with iron deficiency anaemia. Current NICE guidance on anaemia states that men and non-menstruating women of any age with unexplained iron deficiency anaemia should be referred urgently[3]

2. The guidelines do not specify which FOBT is recommended—the only one currently available in the UK is the guaiac test, which detects no more than 50% of colorectal cancers[4]

3. Guaiac FOBT based UK screening programmes require up to nine stool samples, and reliable interpretation is possible only in laboratories with dedicated staff and strict quality assurance. This test should be used only in this context and for population screening only

4. Anyone seeking advice about symptoms wishes reassurance that there is no serious disease. The guaiac test is not sufficiently sensitive for this purpose and because negative tests provide reassurance diagnosis is likely to be delayed

5. This comes at an unfortunate time—evidence is rapidly accumulating that quantitative faecal immunochemical testing (FIT), used at an appropriate cut-off concentration, can be useful for triaging symptomatic patients, including those who warrant urgent referral.[5] Currently, however, FIT is available only for research and in very few centres.

Until there is a firm evidence base for the use of FIT at an appropriate cut-off level and FIT analysers become widely available, GPs should not use FOBTs to help investigate symptomatic patients.

Competing interests: RS is also clinical director of the Scottish Bowel Screening Programme.

Full response at: www.bmj.com/content/350/bmj.h3044/rr-0.

1 Hamilton W, Hajioff S, Graham J, et al. Suspected cancer (part 2—adults): reference tables from updated NICE guidance. *BMJ* 2015;350:h3044. (23 June.)
2 National Institute for Health and Care Excellence. Suspected cancer: recognition and referral. (NG12.) 2015. www.nice.org.uk/guidance/ng12.
3 National Institute for Health and Care Excellence. Clinical knowledge summary. Anaemia—iron deficiency. Scenario: management. Referral or seeking specialist advice. 2013. http://cks.nice.org.uk/anaemia-iron-deficiency#!scenario:recommendation:5.
4 Young GP, Symonds EL, Allison JE, et al. Advances in fecal occult blood tests—the FIT revolution. *Dig Dis Sci* 2015;60:609-22.
5 McDonald PJ, Digby J, Innes C, et al. Low faecal haemoglobin concentration potentially rules out significant colorectal disease. *Colorect Dis* 2013;15:e151-9.

Cite this as: *BMJ* 2015;351:h4256

Why not?

- Letter from experts in the field of CRC
  - gastroenterologists, colorectal surgeons, clinical biochemists, bowel cancer charities

- Under 60 with IDA?
  NICE guidance on Anaemia should refer urgently

- Which FOBt?

- Guaiac FOBT based UK screening programmes
  up to nine stool samples
  best with dedicated staff for population screening

Future developments

- Faecal immunochemical Test (FIT)
- Increased sensitivity and specificity cf gFOBt
- Evidence base for its use in the symptomatic population is currently limited
- Should be available in a year…..
- Any volunteers?

Please call....

Duty Biochemist

020 3313 0348

Practical tips on interpreting semen analysis

Dr. Channa Jayasena PhD MRCP FRCPath

Clinical Lead & Consultant in Male Fertility / Andrology, Hammersmith Hospital

Clinical Senior Lecturer in Reproductive Endocrinology, Imperial College London

1 in 8 couples seek fertility treatment

30-50% cases due to male factor

Centres for Disease Control and Prevention/
National Centre of Health Statistics. 2006-10.

Jargon buster

Oligospermia = low sperm concentration

Aesthenospermia = low sperm motility

Oligoaesthenospermia = O + A

Teratospermia = low percentage of normal sperm (<4%)

Azoospermia = no sperm

Causes of male infertility

Impaired sperm production

- Obesity, smoking, alcohol
- Infection – chlamydia, gonorrhoea
- Chemotherapy
- Undescended testes
- Previous mumps or TB
- Kleinfelter's (XXY)
- Idiopathic

Obstruction – usually causes azoospermia

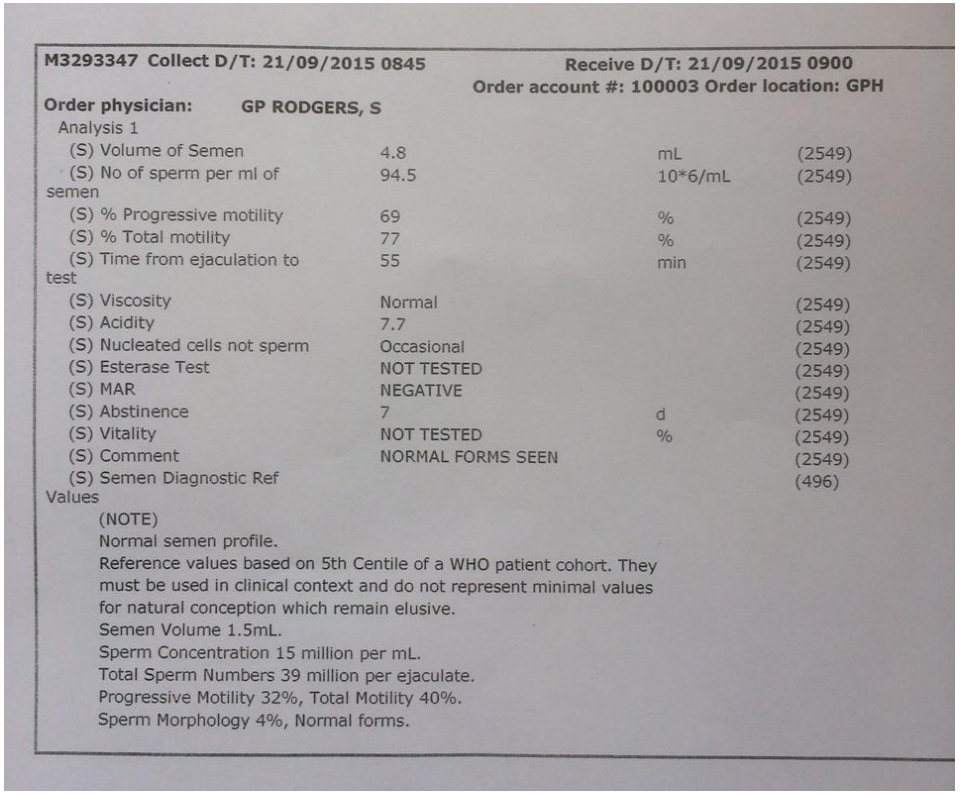
- Epididymal
- Seminal outflow

How does semen analysis help?

It helps you decide….

- 1) Is infertility due to male factor?
- 2) If male fertility present, how severe is it?
- 3) Does the couple require specialist referral?

Semen analysis



M3293347 Collect D/T: 21/09/2015 0845 **Receive D/T: 21/09/2015 0900**
Order account #: 100003 Order location: GPH

Order physician: **GP RODGERS, S**

Analysis 1

(S) Volume of Semen	4.8	mL	(2549)
(S) No of sperm per ml of semen	94.5	10*6/mL	(2549)
(S) % Progressive motility	69	%	(2549)
(S) % Total motility	77	%	(2549)
(S) Time from ejaculation to test	55	min	(2549)
(S) Viscosity	Normal		(2549)
(S) Acidity	7.7		(2549)
(S) Nucleated cells not sperm	Occasional		(2549)
(S) Esterase Test	NOT TESTED		(2549)
(S) MAR	NEGATIVE		(2549)
(S) Abstinence	7	d	(2549)
(S) Vitality	NOT TESTED	%	(2549)
(S) Comment	NORMAL FORMS SEEN		(2549)
(S) Semen Diagnostic Ref Values			(496)

(NOTE)
Normal semen profile.
Reference values based on 5th Centile of a WHO patient cohort. They must be used in clinical context and do not represent minimal values for natural conception which remain elusive.
Semen Volume 1.5mL.
Sperm Concentration 15 million per mL.
Total Sperm Numbers 39 million per ejaculate.
Progressive Motility 32%, Total Motility 40%.
Sperm Morphology 4%, Normal forms.

Looking at a semen sample under microscopy

- Incubate sample for 30min for liquefaction
- Test 100ul semen in Leja 20 chamber
- Multiply up to quantify sperm number / ml
- You cannot test the whole sample

What if you cannot see any sperm?

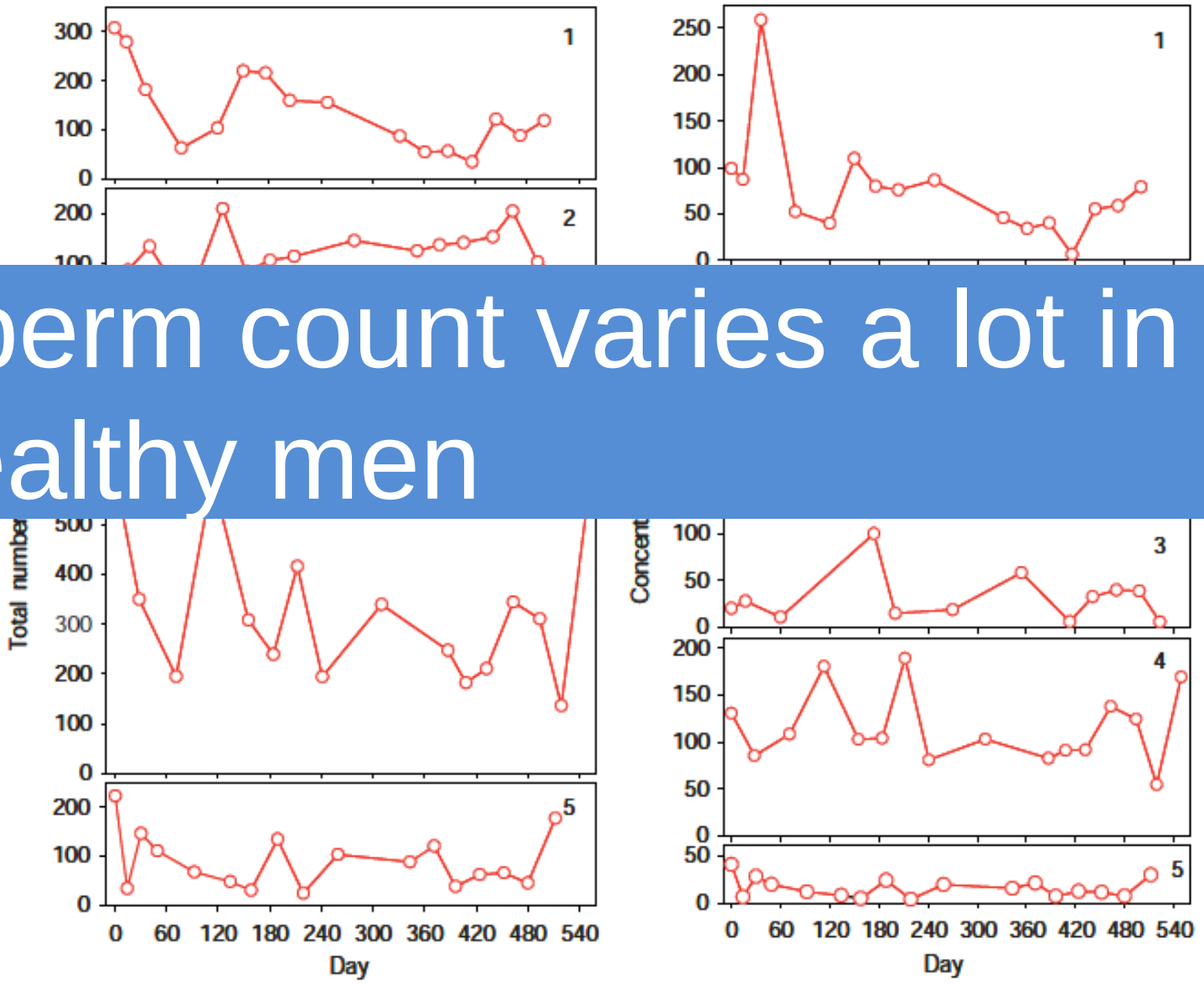
- Normal magnification (eg. Leja 20)
- Could be 0 - 50,000 sperm / ml
- Use higher magnification (eg. Leja 100)
- If you still see nothing, could be 0 - 5000 sperm / ml

It is difficult to quantify sperm at low concentrations

- This is why reports often say ‘occasional sperm seen’

Centres for Disease Control and Prevention/
National Centre of Health Statistics. 2006-10.

Sperm count varies a lot in healthy men



Limitations of semen analysis

- Big biological variation
- Sampling error, particularly at low concentrations
- Counting error – they move!!!!

Important request a confirmatory semen analysis in your patient

Computer Aided Semen Analysis (CASA)

- Good for high concentrations
- Not good at low concentrations
- (need to confirm with manual count)
- **WE HAVE DISCONTINIUED CASA**

Which numbers should we focus on?

- **Ejaculate volume** should be >2ml
  - <0.5 indicates seminal outflow
- **Sperm concentration** should be >20million
  - 5-20: possible to conceive naturally, but may take a bit longer
  - <5: difficult to conceive naturally
- **Total motility** should be >40%
  - <20-40: possible to conceive naturally, but may take a bit longer
  - < 20: difficult to conceive naturally

Total motile sperm count

=volume x concentration x (total motility/100)

- >39 million = WHO reference range (i.e. normal fertility / above 5th centile)
- <5 million = difficult to conceive naturally – suggest referral
- 5-39 million = possible to conceive naturally, but may take a bit longer – suggest referral

Which numbers should we focus on?

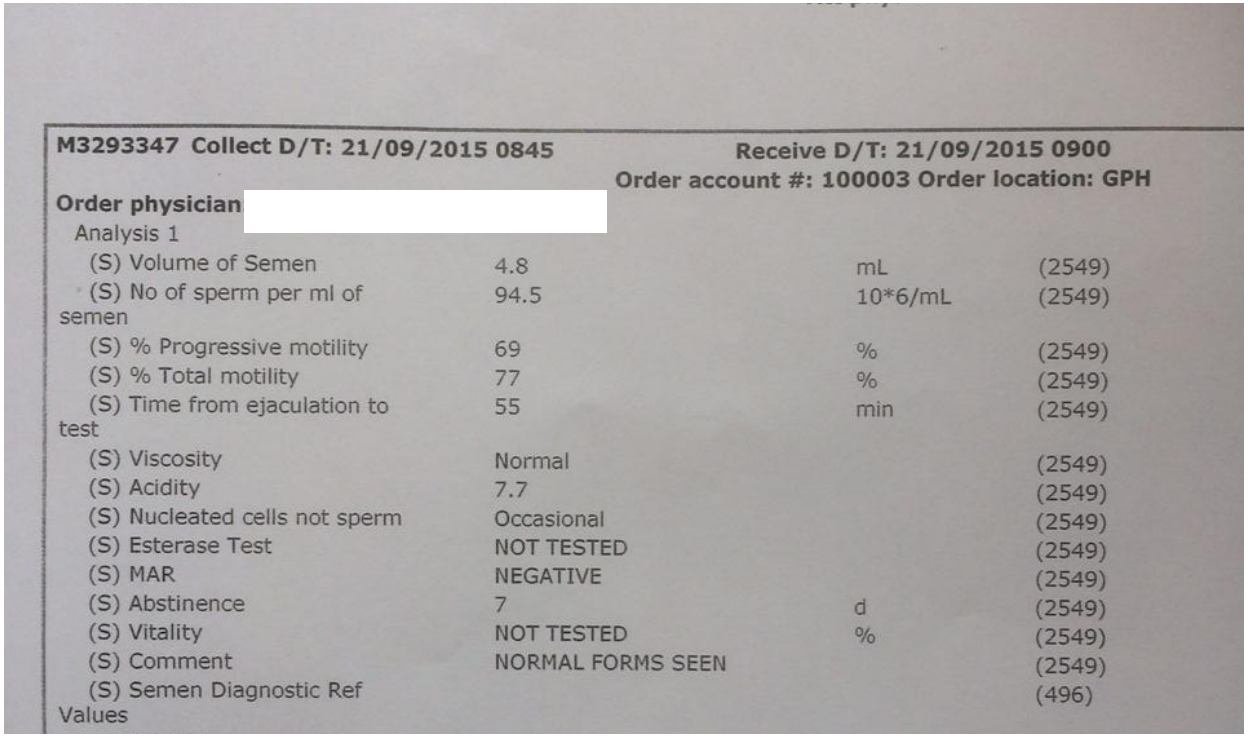
- **Evidence of white cells** may indicate infection:
  - Esterase high
  - Peroxidase high
  - Lots of ‘Nucleated cells not sperm (NCNS)’
  - Lots of ‘Round cells’

- Morphology (>4% is normal)
  - Poor repeatability, difficult to interpret
  - Unsure what this adds, except for the IVF setting

Worked examples

Centres for Disease Control and Prevention/
National Centre of Health Statistics. 2006-10.

Patient 1

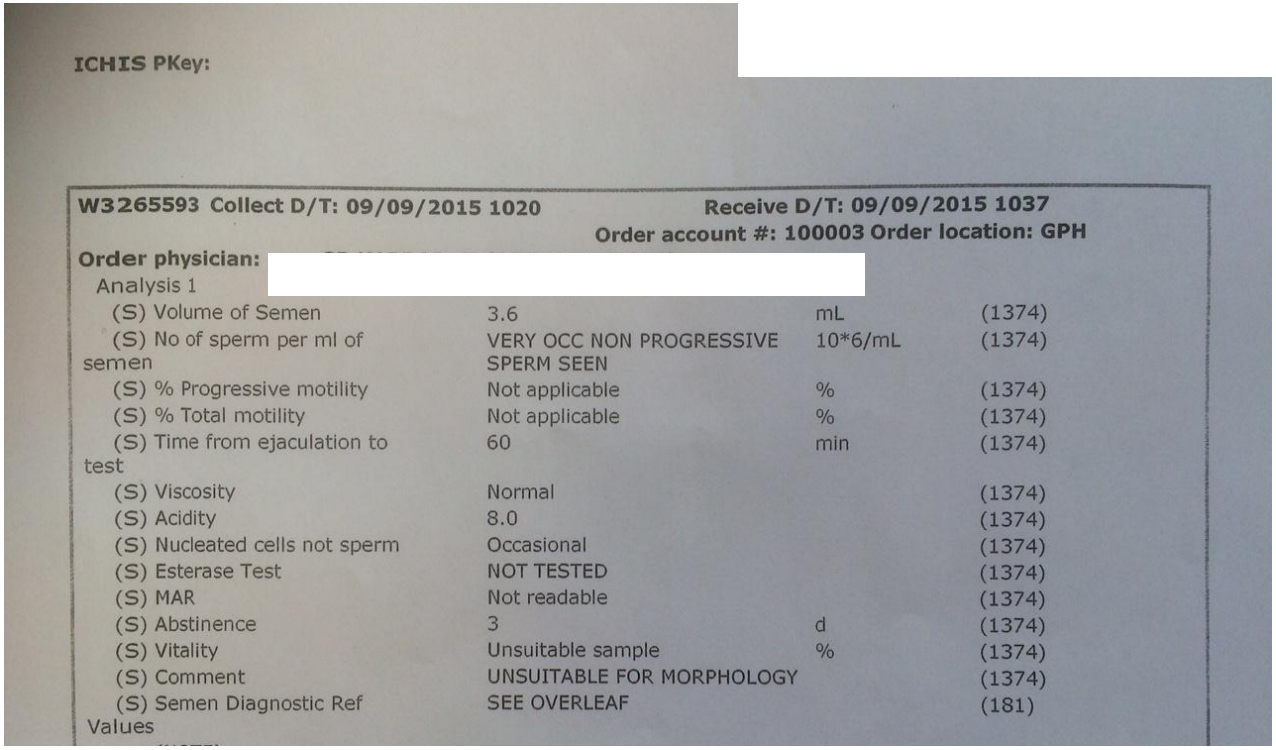


M3293347 Collect D/T: 21/09/2015 0845 **Receive D/T: 21/09/2015 0900**
Order account #: 100003 Order location: GPH

Order physician

Analysis 1			
(S) Volume of Semen	4.8	mL	(2549)
(S) No of sperm per ml of semen	94.5	10*6/mL	(2549)
(S) % Progressive motility	69	%	(2549)
(S) % Total motility	77	%	(2549)
(S) Time from ejaculation to test	55	min	(2549)
(S) Viscosity	Normal		(2549)
(S) Acidity	7.7		(2549)
(S) Nucleated cells not sperm	Occasional		(2549)
(S) Esterase Test	NOT TESTED		(2549)
(S) MAR	NEGATIVE		(2549)
(S) Abstinence	7	d	(2549)
(S) Vitality	NOT TESTED	%	(2549)
(S) Comment	NORMAL FORMS SEEN		(2549)
(S) Semen Diagnostic Ref Values			(496)

Patient 2



ICHIS PKey:

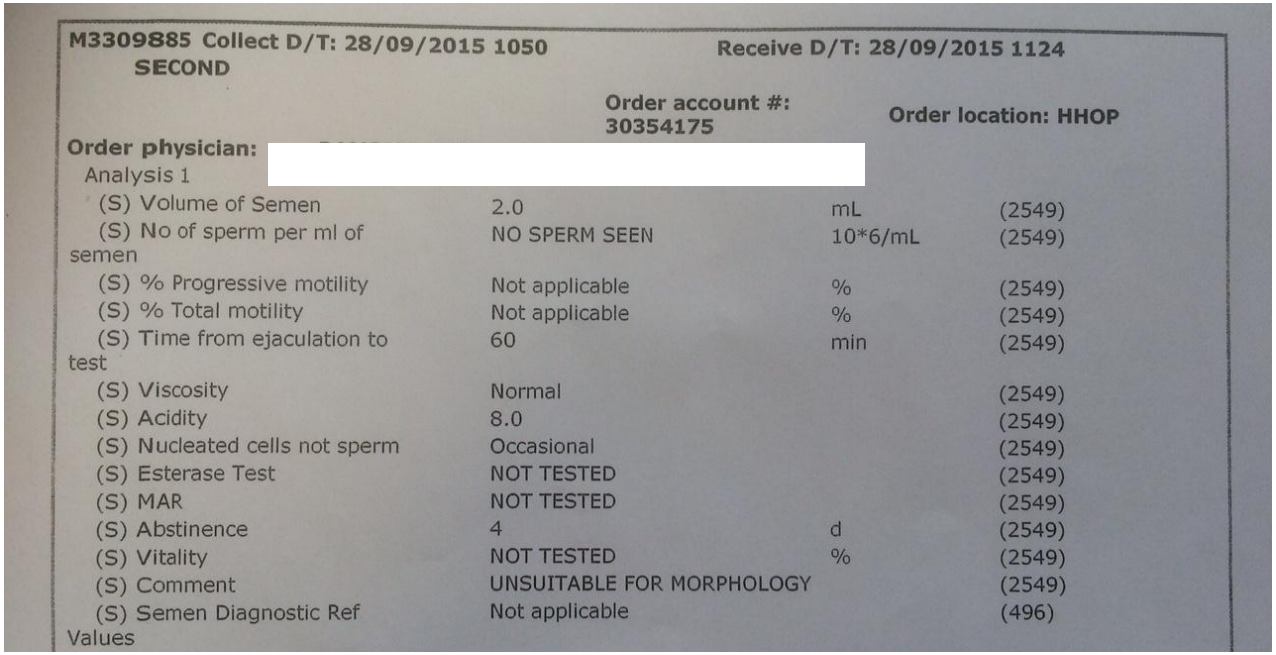
W3265593 Collect D/T: 09/09/2015 1020 **Receive D/T: 09/09/2015 1037**
Order account #: 100003 Order location: GPH

Order physician:

Analysis 1

(S) Volume of Semen	3.6	mL	(1374)
(S) No of sperm per ml of semen	VERY OCC NON PROGRESSIVE SPERM SEEN	10*6/mL	(1374)
(S) % Progressive motility	Not applicable	%	(1374)
(S) % Total motility	Not applicable	%	(1374)
(S) Time from ejaculation to test	60	min	(1374)
(S) Viscosity	Normal		(1374)
(S) Acidity	8.0		(1374)
(S) Nucleated cells not sperm	Occasional		(1374)
(S) Esterase Test	NOT TESTED		(1374)
(S) MAR	Not readable		(1374)
(S) Abstinence	3	d	(1374)
(S) Vitality	Unsuitable sample	%	(1374)
(S) Comment	UNSUITABLE FOR MORPHOLOGY		(1374)
(S) Semen Diagnostic Ref Values	SEE OVERLEAF		(181)

Patient 3



M3309885 Collect D/T: 28/09/2015 1050 Receive D/T: 28/09/2015 1124
SECOND

Order account #: 30354175 **Order location: HHOP**

Order physician: [redacted]

Analysis 1

(S) Volume of Semen	2.0	mL	(2549)
(S) No of sperm per ml of semen	NO SPERM SEEN	10*6/mL	(2549)
(S) % Progressive motility	Not applicable	%	(2549)
(S) % Total motility	Not applicable	%	(2549)
(S) Time from ejaculation to test	60	min	(2549)
(S) Viscosity	Normal		(2549)
(S) Acidity	8.0		(2549)
(S) Nucleated cells not sperm	Occasional		(2549)
(S) Esterase Test	NOT TESTED		(2549)
(S) MAR	NOT TESTED		(2549)
(S) Abstinence	4	d	(2549)
(S) Vitality	NOT TESTED	%	(2549)
(S) Comment	UNSUITABLE FOR MORPHOLOGY		(2549)
(S) Semen Diagnostic Ref Values	Not applicable		(496)

Summary

- **Ejaculate volume** should be >2ml
- **Sperm concentration** should be >20million / ml
- **Total motility** should be >40%
- **Total motile count (TMC)** should be >39 million / ejaculate

- **Morphology** is not a reliable test

- **Refer patients with abnormal tests early (best chance of preventing IVF)**

Please contact us

- Male fertility clinic – joint urology - endocrinology
- Testicular sperm retrieval (Mr. J. Ramsay)
- Diagnostic semen analysis
- Sperm cryopreservation

Dr. Channa Jayasena, Consultant

Department of Andrology, Hammersmith Hospital

c.jayasena@imperial.ac.uk

07799400094