Cardiovascular risk disease, prediction, prevention and management
Learning from cases

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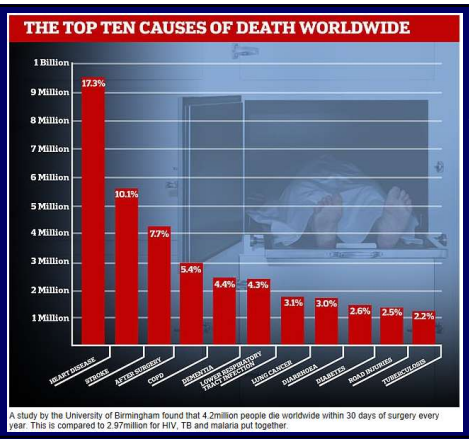

Daily Mail
February
2019

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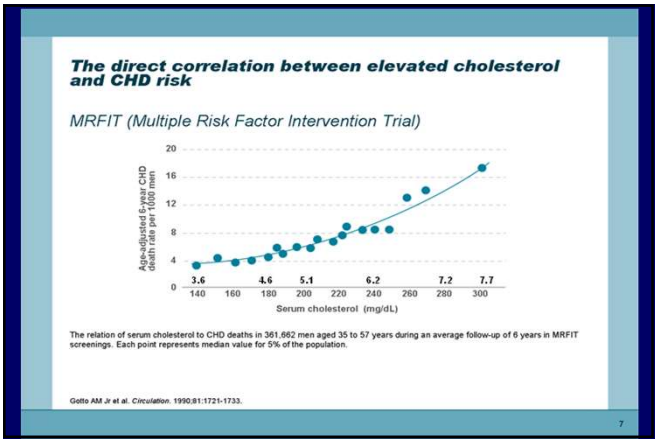

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Table 1 Modifiable risk factors for coronary heart disease and associated risk of myocardial infarction

Modifiable risk factors	OR (99% CI)	PAR (99% CI)*
Hyperlipidaemia	3.25 (2.81 to 3.76)	49.2% (43.8 to 54.5)
Smoking (current and former)	2.04 (1.86 to 2.25)	35.7% (32.5 to 39.1)
Hypertension	1.91 (1.74 to 2.10)	17.9% (15.7 to 20.4)
Abdominal obesity	1.62 (1.45 to 1.80)	20.1% (15.3 to 26.0)
Diabetes	2.37 (2.07 to 2.71)	9.9% (8.5 to 11.5)
Psychosocial factors (stress and depression)	2.67 (2.21 to 3.22)	32.5% (25.1 to 40.8)
Alcohol consumption†	0.91 (0.82 to 1.02)	6.7% (2.0 to 20.2)
Daily fruits and vegetables†	0.70 (0.62 to 0.79)	13.7% (9.9 to 18.6)
Physical activity (PA)†	0.86 (0.76 to 0.97)	12.2% (5.5 to 25.1)

Adapted from Yusuf *et al.*[2]
*Total PAR (population attributable risk) for all modifiable risk factors together: 90.4% (88.1–92.4).
†For alcohol consumption, daily fruits and vegetables and PA, PAR represents the risk in the individuals without these protective risk factors.

Varghese T, et al. Heart 2016;102:904–909

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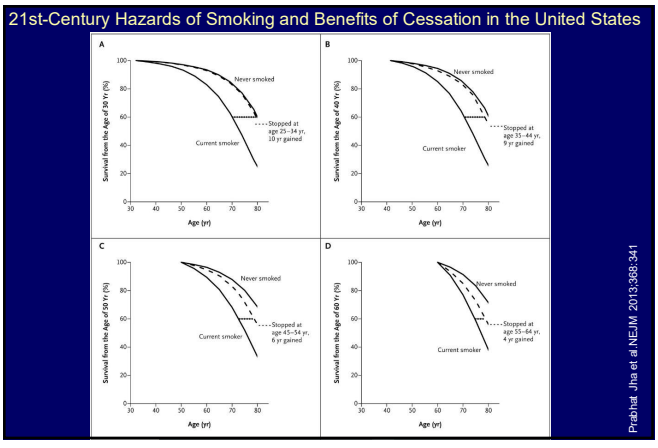

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Marital status and risk of cardiovascular diseases: a systematic review and meta-analysis

Chun Wai Wong,[1] Chun Shing Kwok,[1] Aditya Narain,[1] Martha Gulati,[2] Anastasia S Mihalidou,[3] Pensee Wu,[4,5] Mirvat Alasnag,[6] Phyo Kyaw Myint,[7] Mamas A Mamas[1]

Wong CW, et al. Heart 2018;104:1937–1948

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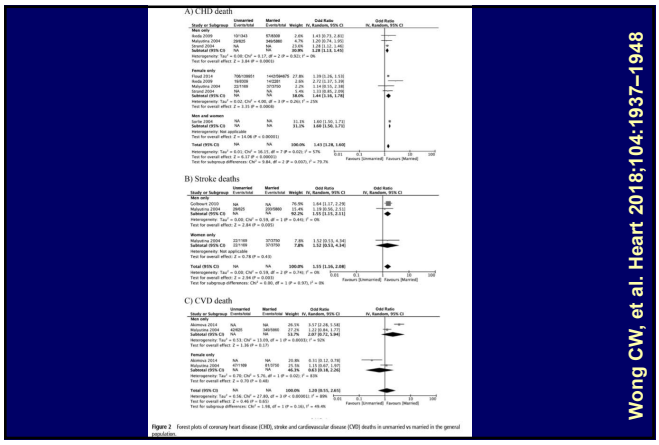
A) CHD death
B) Stroke deaths
C) CVD death
Wong CW, et al. Heart 2018;104:1937–1948

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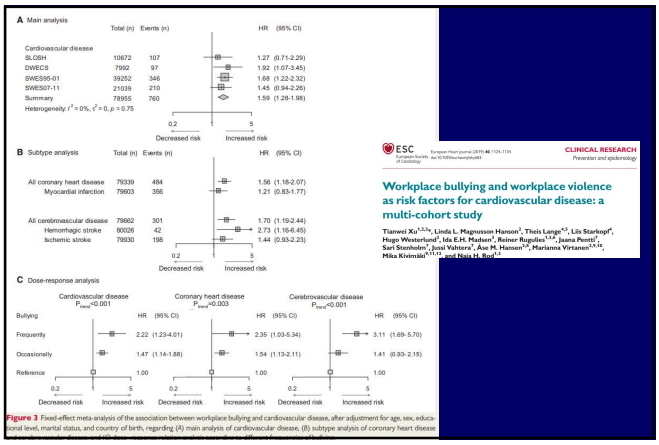
A Main analysis
B Subtype analysis
C Dose-response analysis
Decreased risk
Increased risk
CLINICAL RESEARCH
Workplace bullying and workplace violence as risk factors for cardiovascular disease: a multi-cohort study

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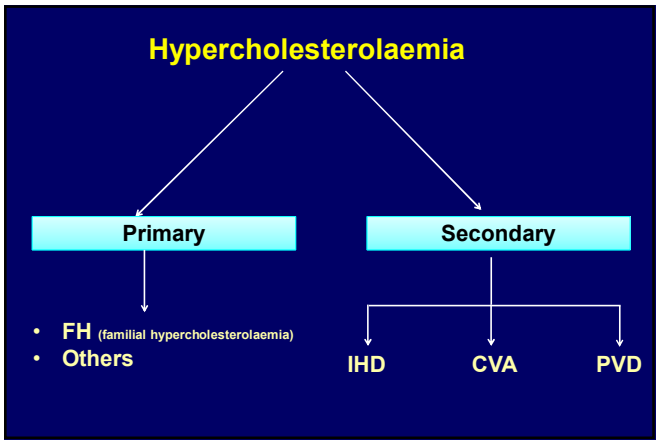
Hypercholesterolaemia
Primary
Secondary
FH (familial hypercholesterolaemia)
Others
IHD
CVA
PVD

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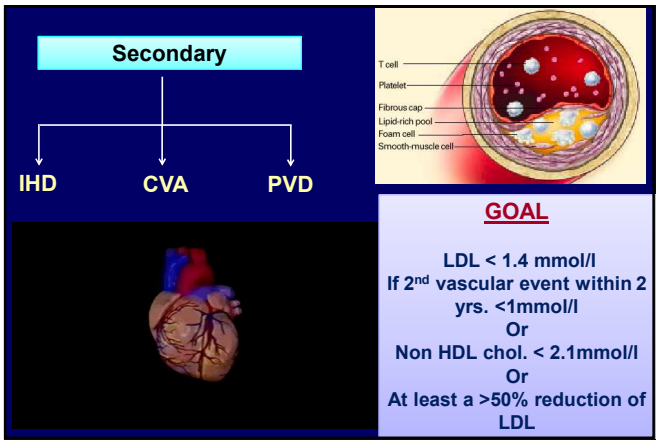
Secondary
IHD
CVA
PVD
T cell
Platelet
Fibrous cap
Lipid-rich pool
Foam cell
Smooth-muscle cell
GOAL
LDL < 1.4 mmol/l
If 2nd vascular event within 2 yrs. <1mmol/l
Or
Non HDL chol. < 2.1mmol/l
Or
At least a >50% reduction of LDL

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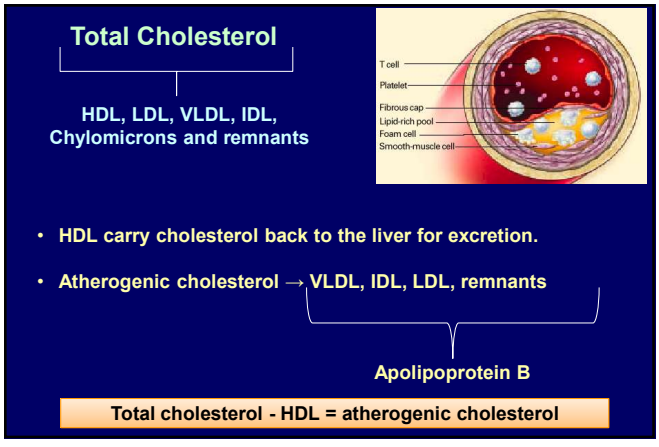
Total Cholesterol
HDL, LDL, VLDL, IDL,
Chylomicrons and remnants
T cell
Platelet
Fibrous cap
Lipid-rich pool
Foam cell
Smooth-muscle cell
HDL carry cholesterol back to the liver for excretion.
Atherogenic cholesterol → VLDL, IDL, LDL, remnants
Apolipoprotein B
Total cholesterol - HDL = atherogenic cholesterol

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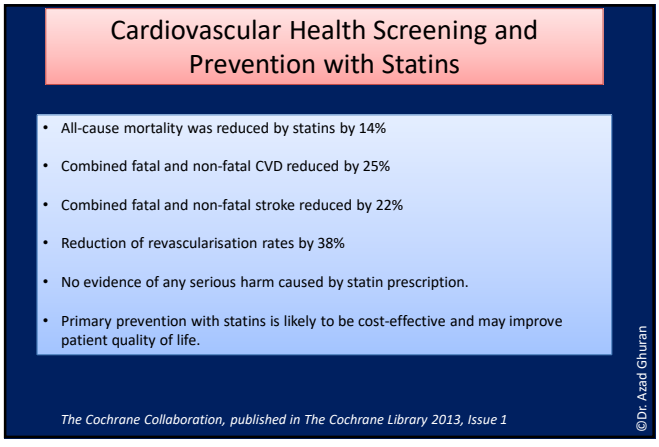
Cardiovascular Health Screening and Prevention with Statins
All-cause mortality was reduced by statins by 14%
Combined fatal and non-fatal CVD reduced by 25%
Combined fatal and non-fatal stroke reduced by 22%
Reduction of revascularisation rates by 38%
No evidence of any serious harm caused by statin prescription.
Primary prevention with statins is likely to be cost-effective and may improve patient quality of life.
The Cochrane Collaboration, published in The Cochrane Library 2013, Issue 1
©Dr. Azad Ghuran

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Primary Prevention

Risk Scores

- Framingham
- QRISK3
- JBS3
- ESC Heart Score
- Scottish ASSIGN

- FH (familial hypercholesterolaemia)
- Others

Q risk3 score	Goal
>20%	Very high risk, LDL < 1.4 mmol/l or at least a >50% reduction of LDL (non-HDl chol. < 2.1 mmol/l)
10-20%	High risk, LDL < 1.8 mmol/l (non-HDl chol < 2.5 mmol/l)
5-10%	Low-moderate risk, LDL < 2.5 mmo/L (non-HDl chol < 3 mmol/l)
1-5%	Low risk, LDL < 3 mol/L, (non-HDl chol < 3.5 mmol/l)
<1%	Very low risk

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1 Supplementary tables and figures

Supplementary Table 1 Total cardiovascular disease risk assessment systems

System	Risk	Variables	Reference
Framingham models	10-year risk of CHD events	Gender, age, TC, HDL-C, SBP, smoking status, diabetes, hypertensive treatment	1
Systematic Coronary Risk Estimation (SCORE)	10-year risk of CVD mortality	Gender, age, TC or TC/HDL-C ratio, SBP, smoking status	2
ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network)	10-year risk of first CVD event	Gender, age, TC, HDL-C, SBP, smoking (number of cigarettes), diabetes, area-based index of deprivation, family history	3
QRISK2	10-year risk of first CVD event	Gender, age, TC to HDL-C ratio, SBP, smoking status, diabetes, area-based index of deprivation, family history, BMI, antihypertensive treatment, ethnicity, rheumatoid arthritis, CKD stages 4–5, AF	4
Prospective Cardiovascular Munster Study (PROCAM)	Two separate scores calculate 10-year risk of major coronary events and cerebral ischaemic events	Age, gender, LDL-C, HDL-C, diabetes, smoking, SBP	5
Reynolds Risk Score	10-year risk of incident myocardial infarction, stroke, coronary revascularization, or CV death	Gender, age, SBP, smoking, high-sensitivity C-reactive protein, TC, HDL-C, family history of premature MI (parent aged <60 years), HbA1c if diabetic	6,7
CUORE	10-year risk of first CVD event	Age, gender, TC, HDL-C, diabetes, smoking, SBP, hypertensive treatment	8
Pooled Cohort equations	10-year risk of CVD event	Age, gender, TC, HDL-C, diabetes, smoking, SBP, hypertensive treatment, race	9
Globorisk	10-year risk of CVD mortality	Age, gender, smoking, SBP, diabetes, TC	10

AF = atrial fibrillation; BMI = body mass index; CHD = coronary heart disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction, SBP = systolic blood pressure; TC = total cholesterol.

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Table 4 Cardiovascular risk categories

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.

ESC European Heart Journal (2020) 41, 111–188 doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

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NICE. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. July 2014

- 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.
- 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.
- Measurement of total cholesterol, high-density lipoprotein (HDL) cholesterol, and non-HDL cholesterol. A fasting sample is not needed.

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NICE. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. July 2014

- Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD.
- Start statin treatment in people with CVD with atorvastatin 80 mg. Use a lower dose of atorvastatin if potential drug interactions or high risk of adverse effects
- Measure at 3 months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol.

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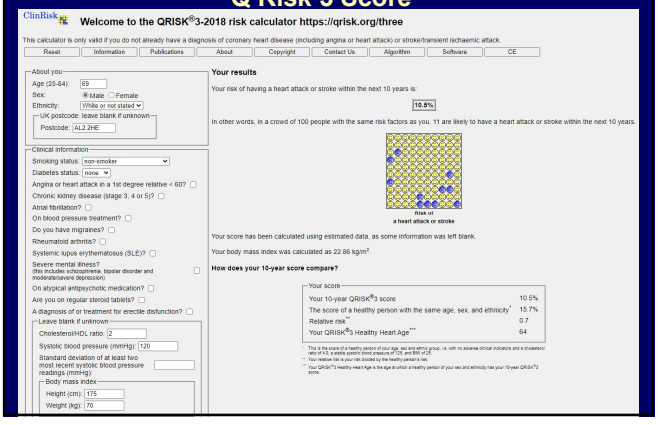
Q Risk 3 Score



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Daily Express Friday July 18 2014 7

Give statins to 17m, says NHS watchdog

By Jo Willey Health Editor

STATINS could soon be taken by as many as 17 million adults under new NHS guidelines to prevent heart problems.

The pills are currently offered to people who have a 20 per cent risk of developing cardiovascular disease within 10 years.

But updated guidance from the National Institute for Health and Care Excellence says the NHS should lower this threshold to include people with just a 10 per cent risk.

This could see an additional 4.5 million patients offered the drugs, bringing the total of all eligible people to 12 million – around 40 per cent of the adult population of England.

If everyone eligible took the drugs, Nice estimates that between 20,000 and 50,000 deaths could be prevented every year.

Professor Mark Baker, director of the Centre for Clinical Practice at Nice, said: "Everyone dies from something. The point is we don't stop people dying, we stop people dying before their time and stop them being ill and spending their last years of life recovering from stroke or as cardiac cripples. We prolong the period of life that is healthy.

"Statins are a safe and effective way of preventing heart attacks and strokes. We are not telling people they have to be on statins, but the guideline means they can be and that they will benefit."

The pills cost just a few pence a day per patient. But some doctors have expressed concern that the new rules will mean they are given needlessly to healthy people. There have been suggestions that statins can cause worrying side effects.

However, Prof Baker said: "It is ludicrous to suggest that we are overmedicalising the population when the whole point of using modern safe and effective drugs in an economic way is to prevent bad things happening in the future.

Tragedy

"There is a risk that the noise distorts the message to the point where people whose lives are going to be saved by statins come off them because they don't understand the confusion created by a tiny minority of doctors who write letters to the press or to the Secretary of State or to us. I think that is a potential tragedy."

The new measure is expected to cost the NHS around £52million.

As part of the guideline review, experts looked at the average blood pressure and cholesterol levels of English adults and found that the average man over the age of 60 and the average woman over the age of 65 would now qualify to take the preventative medications.

The new guideline recommends that people should first be encouraged to make changes such as stopping smoking and exercising regularly.

However if people are still seen to be at risk, they should then be offered statins.

The pills work by reducing cholesterol in the blood. They are the most commonly prescribed NHS drugs.

Data from the Health and Social Care Information Centre shows that last year 66.8 million doses of statins and other cholesterol-lowering drugs were dispensed in England – almost treble the 2003 figure of 25.7 million.

Health experts welcomed the decision. Jules Payne of athlete line Heart UK, said: "Statins have been thoroughly researched and shown to be safe."

But the British Medical Association said it was concerned about the workload for doctors asked to prescribe the pills. Dr Chaand Nagpaul, chair of its General Practitioners Committee, said: "Nice have failed to take into account the further impact this will have on already over-stretched GPs."

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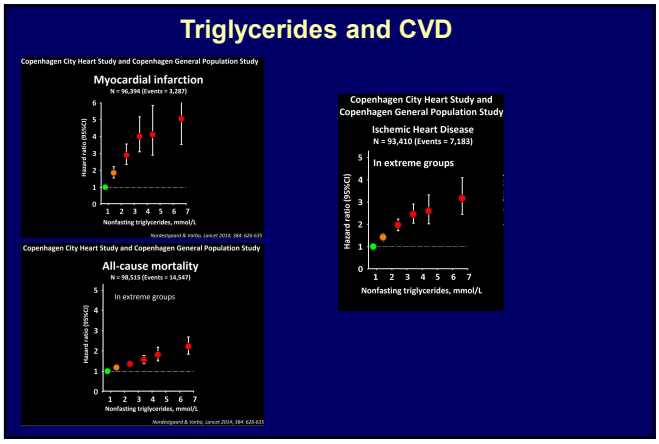

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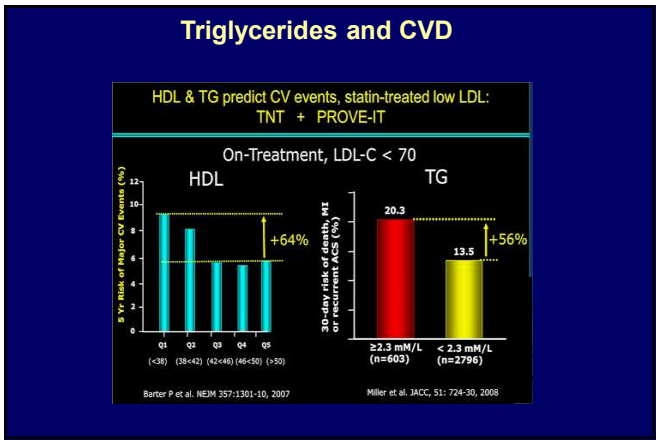

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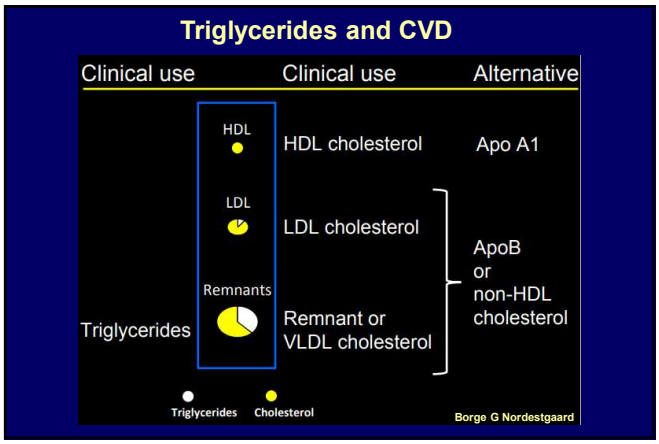

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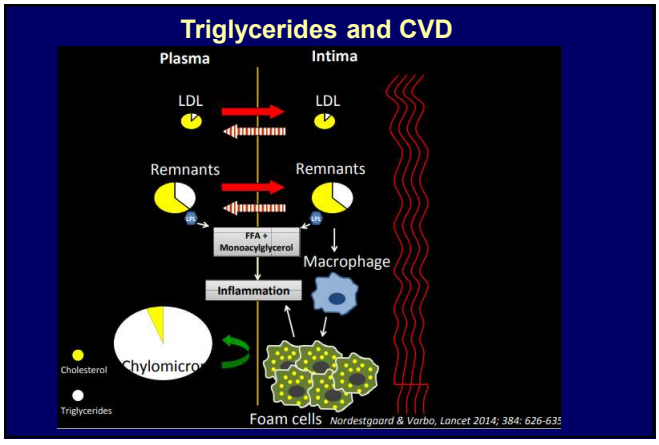

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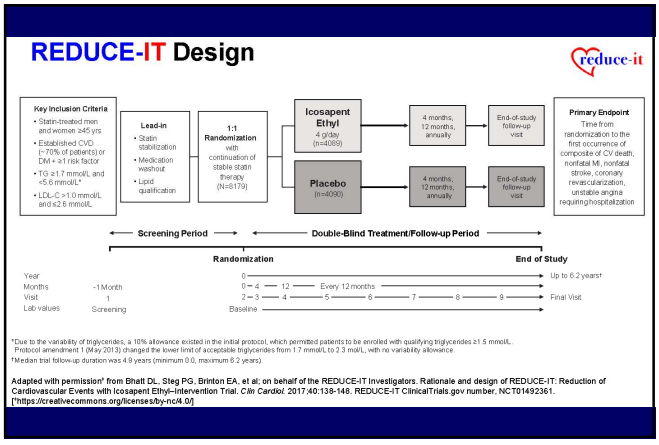

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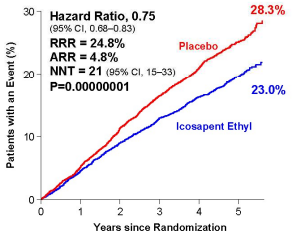
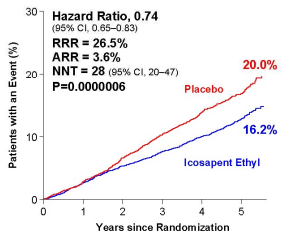
Primary and Key Secondary Composite Endpoints

reduce-it

Primary Composite Endpoint:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Key Secondary Composite Endpoint:
CV Death, MI, Stroke



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

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Cases

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Case 6

- 57 year old male
- Total Cholesterol = 4.2 mmo/l, HDL 1.01 mmol/l, LDL 2.7, TGL = 1.9 mmol/l, TC/HDL = 4.2
- BP 112/79
- Weight 97 kg
- Height 183 cms. BMI = 29
- Risk factors: hypertension, smoker >20/day, > 20yrs.
- PMH: renal calculi-lithotripsy, hypercalciuria*, hyperuricuria*, cholecystectomy, BPH
- Medication: candesartan 16mg od. *Dietary advice

26

Case 6

•57 year old male
•Total Chol. = 4.2 mmo/l, HDL 1.01 mmol/l, LDL 2.7, TGL = 1.9 mmol/l, TC/HDL = 4.2
•BP 112/79 Weight 97 kg Height 183 cms. BMI = 29
•Risk factors: hypertension, smoker >20/day, > 20yrs.

	24th December 2013	2010	2009
Total Chol	4.2	4.8	5.3
HDL	1.01	1.2	1.2
LDL	2.7	2.93	3.7
Chol/HDL	4.2	3.9	4.4
TGL	1.9	1.44	0.97

↑ Benecol

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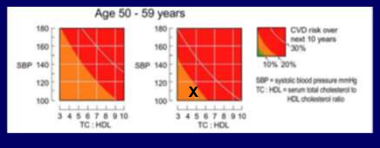
Case 6

10-year QRISK®2 score
Non smoker = 9%, 7% (QRISK3)
Smoker = 15.7% , 12.1 (QRISK3)

10-year Framingham score
= 16% (smoking)
= 8% (non smoking)



10-year JBS score
Non smoker = 12%, 11% (JBS3)
Smoker = 19%, 17 % (JBS3)

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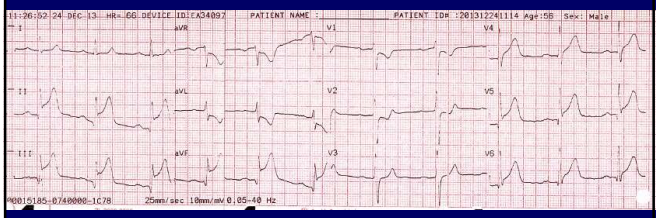
Case 6

This 57 year old gentleman was admitted with acute onset chest pain. He has a past history of hypertension for which he takes candesartan, cholecystectomy and renal calculi.

Christmas Eve 2013



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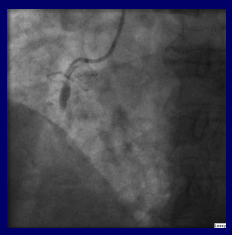
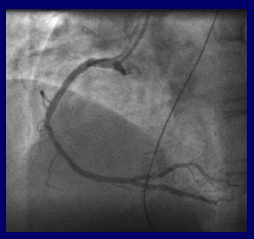
Case 6





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- 57 year old male
- Total Chol. = 4.2 mmo/l, HDL 1.01 mmol/l, LDL 2.7, TGL = 1.9 mmol/l, TC/HDL = 4.2
- BP 112/79 Weight 97 kg Height 183 cms. BMI = 29
- Risk factors: hypertension, smoker >20/day, > 20yrs.

10-year QRISK®3 score
Non smoker = 7.5%
Smoker = 13%
heart age 67

On average, expect
to survive to age 72
without a heart attack or stroke

60 65 70 75 80 85 90 95 100

expected life without a heart attack or stroke

Your risk of a heart attack or stroke
in the next 10 years is
17%

assuming you don't die of anything else

Heart age 72 yrs.

Interventions

Future smoking category: 20+/day

Systolic Blood Pressure: 112 → 112

Total Cholesterol: 4.2 → 4.2

HDL Cholesterol: 1.0 → 1.0

NonHDL Cholesterol: 3.2

BMI: 29.0

Reset

31

- 57 year old male
- Total Chol. = 4.2 mmo/l, HDL 1.01 mmol/l, LDL 2.7, TGL = 1.9 mmol/l, TC/HDL = 4.2
- BP 112/79 Weight 97 kg Height 183 cms. BMI = 29
- Risk factors: hypertension, smoker >20/day, > 20yrs.

Heart age 65 yrs.

On average, expect
to survive to age 78
without a heart attack or stroke
gaining 5.1 years through interventions

60 65 70 75 80 85 90 95 100

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: 112 → 112

Total Cholesterol: 4.2 → 4.2

HDL Cholesterol: 1.0 → 1.0

NonHDL Cholesterol: 3.2

BMI: 29.0

Reset

10-year QRISK®3 score
Non smoker = 7.5%,

32

- 57 year old male
- Total Chol. = 4.2 mmo/l, HDL 1.01 mmol/l, LDL 2.7, TGL = 1.9 mmol/l, TC/HDL = 4.2
- BP 112/79 Weight 97 kg Height 183 cms. BMI = 29
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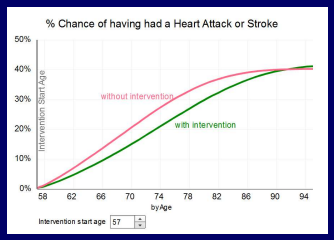

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Case WH

Thank you very much for referring this pleasant 66-year-old gentleman for a cardiology opinion. He has no history of chest pain/tightness or palpitations. He has a large hiatus hernia with the majority of his stomach within the left lower chest. This is causing volume loss and compressive atelectasis of the left lower lobe. He feels short of breath after getting up following a prolonged period of sitting, which improves after walking around. He goes to the gym twice a week and has no significant limitations. He monitors his blood pressure at home which is high, with readings between 148-155/88-95 mmHg. He has a high body mass index (35.8).

His cholesterol in the past was elevated at 6.5 mmol/l and when checked recently was 8 mmol/l. This has since been rechecked and his most recent blood test from 20th May 2016 measured a cholesterol of 5.7 mmol/l with a triglycerides of 1.5 mmol/l. I wonder whether the 8 mmol/l was an aberrant reading? The full blood count, Us&Es, liver function test, calcium, uric acid, and glucose were all normal.

His past medical history includes glaucoma, diverticulitis and irritable bowel syndrome.

His current medication consist of Nexium 40 mg daily, Zimovane 7.5 mg at night (approximately four times a week), and Voltarol occasionally for back pain.

His father died at age 62 with a myocardial infarction and suffered with asthma. His mother died at age 95. He has three older brothers. Two of his brothers suffer with prostate cancer, hypercholesterolemia, and hypertension.

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Case WH

- 66 year old male
- Total Chol. = 5.7 mmo/l, HDL 1.2 mmol/l, TGL = 1.5 mmol/l, TC/HDL = 4.8
- BP 155/95 Weight 120 kg Height 183 cms. BMI = 35.8
- Risk factors: newly diagnosed hypertension

On average, expect
to survive to age 83
without a heart attack or stroke

70 75 80 85 90 95 100

expected life without a heart attack or stroke

Your risk of a heart attack or stroke
in the next 10 years is
18%

assuming you don't die of anything else

Interventions

Future smoking category: No

Systolic Blood Pressure: 155 → 155

Total Cholesterol: 5.7 → 5.7

HDL Cholesterol: 1.2 → 1.2

NonHDL Cholesterol: 4.5

BMI: 35.8

Reset

Your score

Your 10-year QRISK®2 score	22.9%
The score of a healthy person with the same age, sex, and ethnicity*	14.3%
Relative risk**	1.6
Your QRISK® Healthy Heart Age***	74

* This is the score of a healthy person of your age, sex and ethnic group, i.e. with no adverse clinical indications and a cholesterol ratio of 4.0, systolic blood pressure of 125 and BMI of 25.

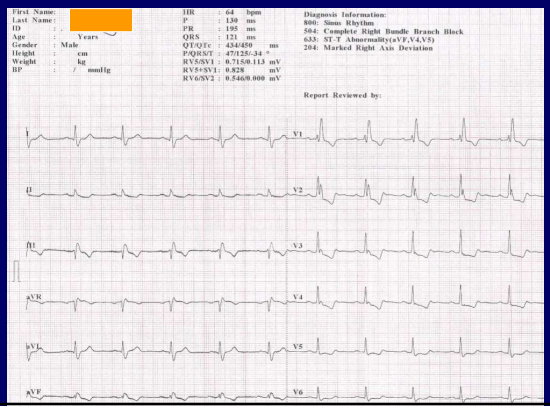
** Your relative risk is your risk divided by the healthy person's risk.

*** Your QRISK® Healthy Heart Age is the age at which a healthy person of your sex and ethnicity has your 10-year QRISK®2 score.

Commenced on aspirin 75 mg, atorvastatin 40 mg, Ramipril 2.5 mg

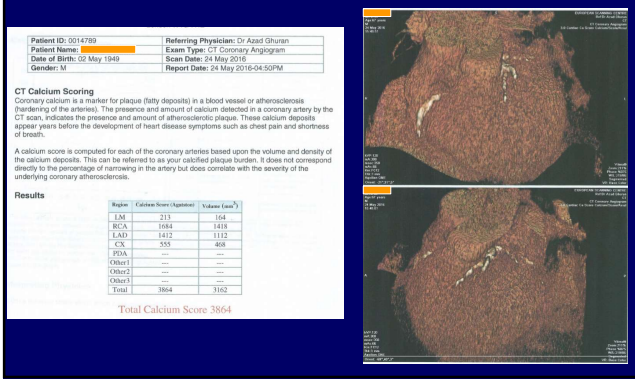
35

Case WH



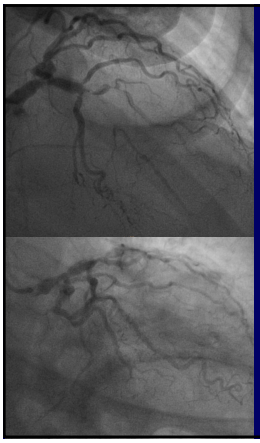
36

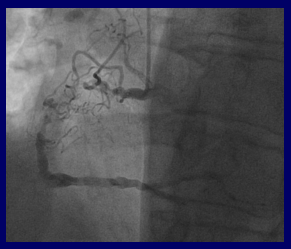
Case WH



37

Case WH





Quadruple CABG 13 days later

38

•35 year old male •Atypical chest pain – "like fire" with pain/paresthesiae in L hand •Total Chol. = 5.7 mmo/l, HDL 1.2 mmol/l, LDL 3.6, TGL = 1.9 mmol/l, TC/HDL = 4.8. Non HDL Chol = 4.5mmol/l •BP 125/80 •Weight 67 kg •Height 160 cms. •BMI = 26 •RF: Father CABG 40's	•61 year old female •Atypical chest pain. Dull radiating to neck. Occurs anytime. •Total Chol. = 5.7 mmol/l, HDL 2.16 mmol/l, LDL of 3.13 mmol/l, TGL = 0.9mmol/l, TC/HDL 2.6. Non HDL Chol = 3.54 •BP = 144/79 •Weight = 67kg •Height= 160 cms •BMI = 26.2 •RF= Mother CVS 53, Father MI 78
Triple vessel disease	Normal coronary arteries on coronary angiography
10-yr JBS3 Risk = 2.1% 10-yr. Qrisk 2 = 2% Lifetime risk (80yrs.) = 59.1	10-yr JBS3 Risk = 9.3 % 10-yr. Qrisk 2 = 8.2 % Lifetime risk (80yrs.) = 20.3

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Learning Point

- JBS 3 or QRISK 2/3 score is useful in predicting cardiovascular risk – general population
- Caution in interpreting 10-year cardiovascular risk sores using the JBS3 or QRISK 2 models in young patients (?<45-50)
- Better to use lifetime risk scores and family history
- Cardiac CT can further improve CHD risk stratification on an individual basis

40

Case 7

- 58 year old male
- Total Cholesterol = 5.6 mmo/l, HDL 1.4 mmol/l, LDL 3.54, TGL = 1.45 mmol/l, TC/HDL = 4
- BP 156/91
- Weight 82 kg
- Height 178 cms. BMI = 25.9
- Risk factors: FH IHD (mother CABG- 60yrs), ex-smoker 13 yrs.
- PMH: nil
- Medication: nil

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Case 7

•58 year old male
•Total Chol. = 5.6 mmo/l, HDL 1.4 mmol/l, LDL 3.54, TGL = 1.45 mmol/l, TC/HDL = 4
•BP 156/91 Weight 82 kg Height 178 cms. BMI = 25.9
•Risk factors: FH, ex-smoker 13 yrs.

	Score	
	QR2	QR3
10-year CVD risk QRISK®2 score	13.5%	17.3%
The score of a typical person with the same age, sex, and ethnicity*	9.7%	7.3%
Relative risk**	1.4	2.4
QRISK® Heart Age***	61	71

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Past Medical History:
1. Ex-smoker
2. Hyperlipidaemia

Medication: Omeprazole 20 mg od and GTN spray.

Blood Results: HbA1c 36, cholesterol 5.6, HDL 1.40, triglycerides 1.45, LDL 3.54, glucose 5.6, Hb 144, LFT's normal, sodium 137, potassium 4.8, urea 4.6, creatinine 77.

[redacted] was referred back in February however has delayed his appointment as he was away until [redacted] March. A month to six weeks ago whilst riding his pushbike he noticed central chest discomfort that lasted 5 minutes. It did not radiate to his necks, arms and jaw. These symptoms were reproducible on several occasions whilst riding his bike, however he could carry on with the bike ride and his symptoms resolved as he warmed up. He has not had any symptoms at rest. He was commenced on Omeprazole and since then, the symptoms had completely resolved. In fact he went to Switzerland and completed a cross country ski marathon and was completely asymptomatic throughout this challenge.

Family History: His mother had a CABG in her 60's but nil significant other.

Examination: Blood pressure 168/96 mmHg. Heart sounds are normal.
ECG is normal sinus rhythm with rate of 53 beats per minute with T-wave inversion in III and aVF and a Q-wave in lead III and aVF.

His Duke score showed a probability of coronary disease as 73% (male, hypertension and ECG changes). I have discussed Mr Mason's symptoms and ECG changes with Dr Azad Ghuran, Dr Ghuran believes Mr Mason has been investigated with a coronary angiogram quoting a 1 in 1000 risk of death, MI, stroke and major bleeding.

I have explained to Mr Mason even though he is now asymptomatic since the commencement of Omeprazole because of the ECG changes and risk factors we need to completely exclude there is no cardiovascular reason for his symptoms. He is happy to go ahead with his angiogram. I have made no changes to his current medication regime at the moment. Dr Ghuran will review this at the time of his angiogram. I have also requested an echocardiograph because of the ECG changes. I have made no appointment to see Mr Mason myself but he is followed up by Dr Ghuran.

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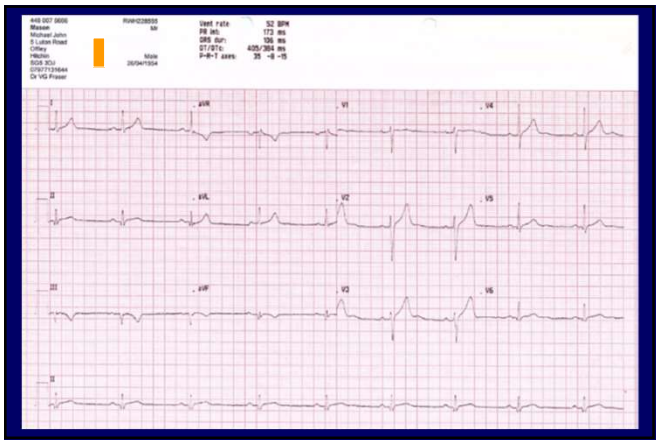

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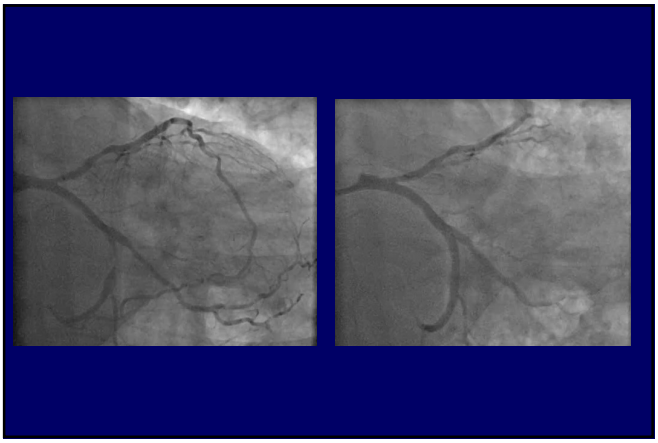

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Case 7

6 months later

Reviewed in Cardiology OPC 25th Sep. 2013

Asymptomatic. Stopped atorvastatin after 4 weeks – myalgia, muscle weakness and depressed

Referred to Dr. Viljoen

46

3 months later, 04/12/13

Diagnosis: Ischaemic heart disease – stented 2013
Intolerant to lipid lowering medication

Medication: Aspirin, Clopidogrel

Results: BP 150/76 Weight 83 kg Height 176 cm BMI 27

Creatinine 78, Cholesterol 5.4, Triglycerides 1.33, Fasting Glucose 6.0
Albumin 45, Haemoglobin 35

It had pleasure in reviewing this patient at the cardiovascular risk clinic on 4th December 2013. As you mention he has significant coronary disease, however, he has had a bad experience with Atorvastatin that led to severe muscle pains and also he felt depressed. His symptoms started approximately two weeks after he was on the treatment and subsequently there is a temporal relationship between his symptoms and taking the medication. I had quite a long discussion with him regarding the atherosclerosis time line and cardiovascular risk factors and the importance of lipid lowering especially in patient's who already have established cardiovascular disease. I discussed the rationale of treatment in the terms of our evidence of randomised controlled trials comparing statins to the placebos in patients who have established cardiovascular disease and the benefits of medication. In discussion with him, I started him on Rosuvastatin 5 mg to be taken on alternate days. We will see how he gets on in the first instance. I also warned him that if he plans to exercise a lot he can omit his statin dose on these occasions.

We see more statin related side effects in patients who exercise a lot and I understand that this may well be confounded but there seems to be an additional higher risk of intolerance. Providing he tolerates this well I would be grateful if you could continue this for him. He has also made substantial changes to his diet, he has cut down on butter and salt and also takes a lot of oily fish. All of these are healthy endeavours. I do not see a recent thyroid function test on him (I usual perform this prior to clinic appointments). I have provided him with a blood form to have his thyroid function test done. His TSH measures 2.02. I have also asked him to stop the medication in case he experiences any problems.

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~12 months later after PCI, 4th June 2014 — Case 7

Diagnosis: Ischaemic heart disease – stented 2013
Intolerant to lipid lowering medication - Atorvastatin 40mg and Rosuvastatin 5mg alternate days

Medication: Aspirin, Clopidogrel

Results: BP 130/82 Weight 85.6 kg

04/06/2014 Sodium 138, Potassium 4.8, Urea 4.8, Creatinine 102, Bilirubin 8, Alk phos 69, ALT 17, Albumin 45, CK 76, Cholesterol 5.9, HDL-cholesterol 1.21, Triglycerides 3.38, Glucose 5.2

It was a pleasure to review this patient at the cardiovascular risk clinic on 4th June 2014. Unfortunately he is unable to tolerate the Rosuvastatin 5 mg alternate days as this makes him feel really, in is own words, "rubbish". He definitely prefers some natural products and is now taking Lecithin for the last 6 months which he imports from Switzerland. He is not taking any salt or butter but does take Benecol. When I previously reviewed him in December 2013 his total cholesterol measured 5.4 mmol/l with LDL-cholesterol 3.33 mmol/l. I do not have any recent blood tests on him and have requested these today. The results are now available and are shown above for your information. I explained to him that we would aim for LDL-cholesterol of <2 and therefore recommend that we either try an alternative statin (this is a worthwhile endeavour) or something else such as Ezetimibe to get his cholesterol down.

I plan to review him again in clinic in approximately 6 months' time with prior follow-up investigations.

Follow up: 6/12

GP Action: Continuation of current medication.

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Case 7

- 58 year old male
- Total Chol. = 5.6 mmo/l, HDL 1.4 mmol/l, LDL 3.54, TGL = 1.45 mmol/l, TC/HDL = 4
- BP 156/91 Weight 82 kg Height 178 cms. BMI = 25.9
- Risk factors: FH, ex-smoker 13 yrs.

Life style and diet changes

	March 2013	October 2013	June 2014
Total Chol	5.6	5.4	5.9
HDL	1.4	1.47	1.21
LDL	3.54	3.3	(non fasting)
Chol/HDL	4	3.7	4.9
TGL	1.45	1.33	3.38

Atorvastatin 29th April 2013 Took ~4 wks

Rosuvastatin 5mg, 4th December 2013. Took ~ 3 wks

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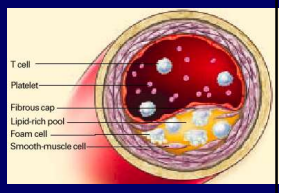
Case 7

24th September 2014 - Dr. Ghuran

- Not keen for a statin
- D/W Dr. Viljoen - Pravastatin 10mg



Future options:

- Fluvastatin
- Ezetimibe
- PCSK 9 inhibitors

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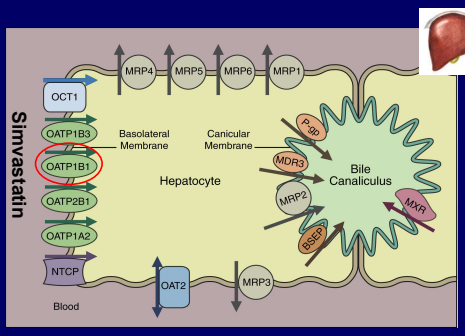
Multiple Membrane Transporters in Hepatocyte Work in Concert With Enzymes to Mediate Drug Elimination

Gene *SLCO1B1* encodes for OATP1B1



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Case 7

Effect of *SLCO1B1* genotypes on the systemic exposure of various statins

	Percentage increase in AUC for *SLCO1B1 CC* versus *SLCO1B1 TT*
Simvastatin	221%
Pitavastatin	162–191%
Atorvastatin	144%
Pravastatin	57–130%
Rosuvastatin	62–117%
Fluvastatin	19% (non-significant)

AUC = area under the plasma concentration-time curve

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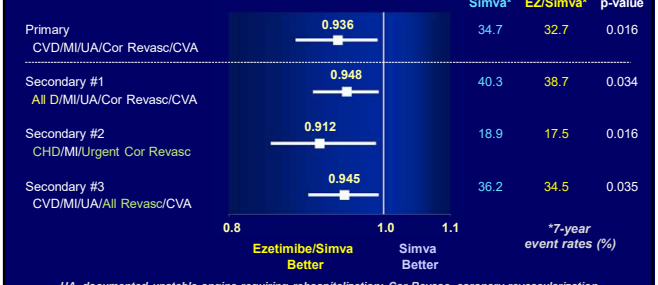
Primary and 3 Prespecified Secondary Endpoints — ITT



UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)

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Grouping of statins

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

- Low intensity; 20%-30%
- Medium intensity; 31%-40%
- High intensity; above 40%

* MHRA advice: there is an increased risk of myopathy associated with high-dose (80mg) simvastatin. The 80mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when benefits are expected to outweigh the potential risks.

Adapted from NICE clinical guidance 181, Appendix A: Grouping of statins. http://www.nice.org.uk/guidance/cg181/resources. Downloaded 29th September 2014

CARD-1131919-0000

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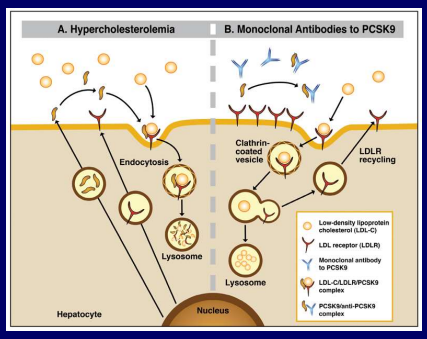
Proprotein convertase subtilisin/kexin type 9 (PCSK9)



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The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Table 2. Primary and Secondary End Points.

Outcome	Evolocumab (N=13,784)	Placebo (N=13,780)	Hazard Ratio (95% CI)	P Value*
	no. of patients (%)			
Primary end point: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
Key secondary end point: cardiovascular death, myocardial infarction, or stroke	816 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
Other end points				
Cardiovascular death	251 (1.8)	240 (1.7)	1.05 (0.88–1.25)	0.62
Due to acute myocardial infarction	25 (0.18)	30 (0.22)	0.84 (0.49–1.42)	
Due to stroke	31 (0.22)	33 (0.24)	0.94 (0.58–1.54)	
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 (0.90–1.35)	
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54
Myocardial infarction	468 (3.4)	639 (4.6)	0.73 (0.65–0.82)	<0.001
Hospitalization for unstable angina	236 (1.7)	239 (1.7)	0.99 (0.82–1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71–0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64–0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73–0.95)	
Cardiovascular death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 (0.86–1.13)	0.82
Ischemic stroke or transient ischemic attack	229 (1.7)	295 (2.1)	0.77 (0.65–0.92)	0.003
CTTC composite end point†	1271 (9.2)	1512 (11.0)	0.83 (0.77–0.90)	<0.001

* Given the hierarchical nature of the statistical testing, the P values for the primary and key secondary end points should be considered significant, whereas all other P values should be considered exploratory.
† The Cholesterol Treatment Trialists Collaboration (CTTC) composite end point consists of coronary heart death, nonfatal myocardial infarction, stroke, or coronary revascularization.

N Engl J Med 2017;376:1713-22

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Case 7

Learning Point

- 10-year cardiovascular risk sores using the JBS3 or QRISK 2 models useful
- Because of differences in statin metabolism, "one statin does not fit all", and therefore try at least 3-4 different statins if side effects develop
- Ezetimibe and PCSK-9 inhibitors can be useful

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Case 11

Past Medical History:
1. Current smoker
2. Previous hernia repair

7th February 2014

Family History: Mother had a heart attack at 66 and passed away.

Medication Taken: Nil.

Blood Results: Hb 152, glucose 6.3, cholesterol 4.1, alk phos 131, creatinine 77, potassium 3.9, sodium 140, urea 4.6, TFTs normal.

Thank you for referring this 61-year-old gentleman to Rapid Access Chest Pain Clinic. Over the last month he has experienced episodes of chest discomfort lasting around 30 to 60 minutes. This has occurred only 5-6 times and he describes it as a dull ache which does not radiate to the neck, arm or jaw. He gets this mainly at rest and the most pronounced episode he noticed while he was at an auction. The pain was present for six hours with this gradual heaviness coming over him. He does not partake in regular exercise but is active and has never experienced any symptoms at all on exertion. He also mentioned unintentionally he has lost about a stone and half over the last year and gets mildly breathless on exertion.

On examination: blood pressure 150/76 mmHg. Heart sounds are normal. ECG is normal sinus rhythm, rate of 54 beats per minute. His Duke's score is 40%.

I have had a discussion with Dr Ghuran, Consultant Cardiologist who agrees this gentleman has got non-cardiac sounding chest discomfort however he does have some risk factors and feels he should be investigated further. We will offer him a CT coronary angiogram and will be written to with the results and if any further treatment is required. I have made no additions to medications. This CT scan will also give us some assessment on his lung status, I am a little concerned being a heavy smoker he has lost weight unintentionally. He will be written to with the results of the CT scan.

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Case 11

Typed: 07/03/2014

Further to this gentleman's recent clinic review in the Rapid Access Chest Pain Clinic, he has now had his CT coronary angiogram. This showed non significant calcific plaque his left mainstem with moderate disease in the proximal LAD. His calcium score was elevated at 264. I will appreciate if you can commence him on aspirin and atorvastatin 20 mg daily.

I note when he attended the Chest Pain Clinic his pulse rate was 54 beats per minute with a blood pressure of 150/76. I will appreciate if you can check his blood pressure and if it is more than 140/90 I will appreciate if you can commence him on amlodipine 5 mg daily. I will also arrange for him to have a coronary angiogram to assess his coronary anatomy in more detail. Should you have any queries, please do not hesitate to contact me.

Yours sincerely,

Q risk 2 score 18.1%

Dr Azad Ghuran MB ChB, MRCP, MD
Consultant Cardiologist

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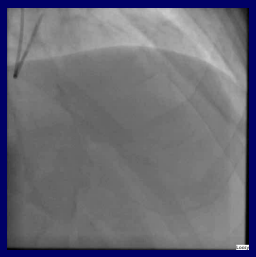
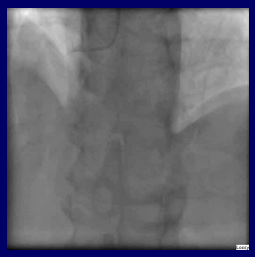
Case 11





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Case 11

Coronary Angiography: 21/03/2014
Typed: 22/03/2014

Further to this gentleman's review in the Rapid Access Chest Pain Clinic with atypical chest pain and CT coronary angiogram showing a calcium score of 264, calcific plaque in the left mainstem and proximal LAD, he was electively admitted today for coronary angiography. The procedure was carried out using a right transradial approach. The left mainstem was unobstructed. There was mild plaque disease in the proximal LAD with mild-to-moderate disease in the mid course. There was a large intermediate artery which was unobstructed. The AV circumflex artery had some mild plaque disease in the distal course. The right coronary artery was a large dominant vessel with mild plaque disease in the distal course. He has good LV systolic function with no gradient across the aortic valve.

This gentleman has no more than mild-to-moderate atherosclerotic plaque disease and I would suggest he continues aspirin and atorvastatin. I have also commenced him on lansoprazole 30 mg daily to see if this helps with his atypical symptoms. I have not arranged any further follow-up appointments but I will of course be happy to review him again in the clinic should the need arise. He should also stop smoking.

Yours sincerely,

Dr Azad Ghuran MB ChB, MRCP, MD

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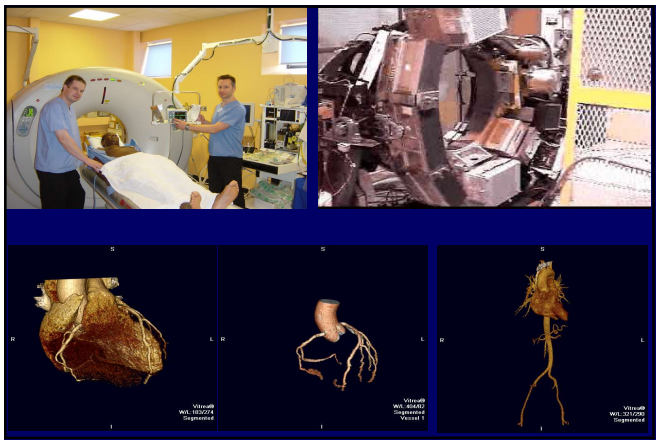

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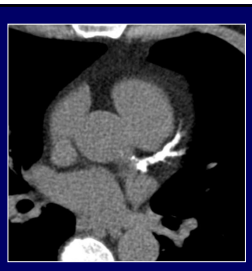

- Calcium in coronary arteries represents atherosclerosis
- Degree of Calcium correlates with atheroma burden

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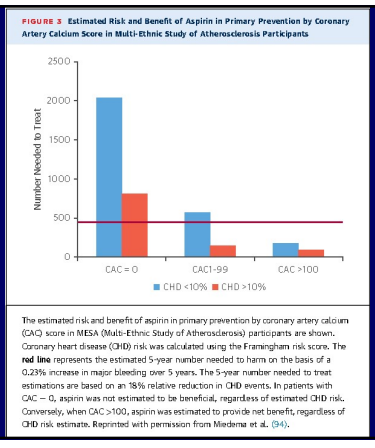
Coronary calcification in Asymptomatic

MESA (Multiethnic Study of Atherosclerosis)
NIH sponsored prospective study
6,814 Asymptomatic pts: 3.5 year follow-up

	Major Coronary Event		
CAC score	**No. at risk**	**Hazard Ratio (95% CI)**	**P-value**
0	8/3409	1.0	
1-100	25/1728	3.89 (2.72-8.79	<0.001
101-300	24/752	7.08 (3.05-16.47	<0.001
>300	32/833	6.84 (2.39-15.99)	<0.001

Detrano RC et al. N Engl J Med 2008;358:1336-5.

64



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Comparative Effective Dose of Radiological Investigations

- PA/Lateral CXR 0.04-0.06 mSv
- Head CT 1-2 mSv
- Chest CT 5-7 mSv
- Abd/Pelvis CT 8-11 mSv
- Diagnostic Cor Angiogram 1-5 mSv
- MSCT angiography 0.6-4 mSv

Life time cancer risk
1mSv = 1:20,000 additional risk
10mSv = 1:2000 additional risk
20mSv = 1:1000 additional risk

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Table 3. Estimated Risks of Fatal Malignancy or Death Resulting From Radiation Exposure and the Lifetime Odds of Dying as a Result of Selected Activities of Everyday Life

Exposure	Estimated Risk of Fatal Malignancy or Lifetime Odds of Dying (per 1000 Individuals)
Effective radiation dose	
1 mSv (calcium score/lung screen)	0.05
10 mSv (coronary CTA/abdomen CT, invasive coronary angiography, radionuclide myocardial perfusion study)[32]	0.5
50 mSv (yearly radiation worker allowance)	2.5
100 mSv (definition of low exposure)	5
Natural fatal cancer[39]	212
Passive smoking[33]	
Low exposure	4
High exposure, married to a smoker	10
Radon in home[34]	
US average	3
High exposure (1% to 3%)	21

AHA Science Advisory

Ionizing Radiation in Cardiac Imaging

A Science Advisory From the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention

Arsenic in drinking water[35,36]	
2.5 μg/L (US estimated average)	1
50 μg/L (acceptable limit before 2006)	13
Motor vehicle accident[37]	11.9
Pedestrian accident[37]	1.6
Drowning[37]	0.9
Bicycling[37]	0.2
Lightning strike[37]	0.013

CTA indicates CT angiogram.

National Safety Council estimates are based on data from National Center for Health Statistics and US Census Bureau. Deaths are classified on the basis of the Tenth Revision of the World Health Organization's *International Classification of Diseases*. Lifetime odds are approximated by dividing the 1-year odds by the life expectancy of a person born in 2005 (77.8 years).

TC Gerber et al. *Circulation.* 2009;119:1056-1965

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Learning Point

Case 11

- **It is not about cholesterol (LDL, HDL) but about overall risk cardiovascular risk which determines the magnitude of benefit of statin treatment**
- **Calcium scoring can be useful in selected patients in determining coronary artery disease risk.**
- **At present there is no class I evidence to suggest coronary artery disease risk reduction by commencing a statin – on going studies**

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Case 5A

46-year old lady

Diagnoses:
1. ?Exertional angina
2. Cardiac risk factors possible family history and lipid status unknown
3. Good LV systolic function with no regional wall motion abnormalities and no significant valvular abnormalities
4. Awaiting surgery to remove small polyp from the cervix

Medications: Aspirin 75 mg, Bisoprolol 2.5 mg and GTN spray prn.

I today had the pleasure to review this 45-year-old lady who for a while now has been noticing shortness of breath and chest tightness on exertion. When she stops exercising this does settle. You had started her on Ranitidine and this in a way has slightly eased part of her symptoms but she is not completely symptom free. As far as her cardiac risk factors are concerned she is not entirely sure, but her grandmother may have suffered from significant coronary artery disease and as far as she is aware she has not had her cholesterol levels tested. Her ECG is uneventful and an echocardiogram was reassuring without any significant changes. Her symptoms however could be an angina equivalent and today we have discussed various options to further investigate this. Out of these options the patient decided to go for a slightly less invasive test and we would therefore arrange for her to have a CT coronary angiogram. We will be in touch with the results of the test and we will review her at least one more time in clinic in three months' time.

We are aware that the patient is awaiting minor surgery to her cervix (polypectomy).

Yours sincerely,

Dictated and verified by Doctor but not signed

Chol 6 mmol/l
HDL 2.23 mmol/l
Chol/HDL 2.7
TGL 0.75 mmol/l

Weight = 60 kg
Height 162 cms.

BMI = 23

No FH of IHD

BP (S)125/71 mmHg

Conclusion:
1. Calcium Score: 0 (< 25 percentile)
2. Significant disease in the right coronay artery

10-yr JBS3 Risk = 1.3%
10-yr. Qrisk 2 = 1.2% (Q3 = 1%)
Lifetime risk (80yrs.) = 13%

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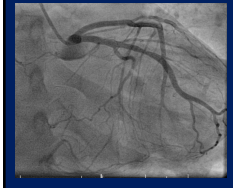
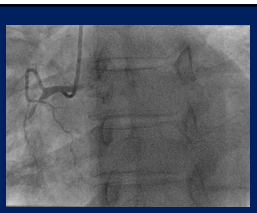
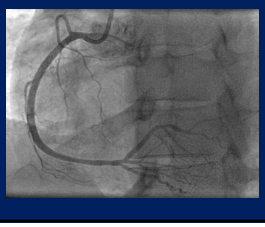
Case 5A







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Learning Point

Case 5A

- **Although high HDL cholesterol levels may be reassuring and lead to a favourable TC:HDL ratio, it can be dysfunctional resulting in CAD**
- **Be weary of a calcium score of 0 in young patients**
- **Never do a calcium score alone without a CT coronary angiography.**

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Clinical Case 2

56 year old lady. Asymptomatic.
Full medical: TC 7 mmol/l, HDL 2 mmol/l, LDL 4 mmol/l, triglycerides 2.2 mmol/l and a TC:HDL ratio of 3.5.

FHx: ischaemic heart disease. Her father is alive and had a stroke 59 yrs. Her mother died at age 60 but had three previous MI and CABG prior to her death. Her younger sister died of ovarian cancer at age 35. Maternal uncle died at age 56 with an MI. Maternal grandmother died of an MI at age 36 and her maternal great uncle died at age 63 with an MI.

PMH: bilateral oophorectomy for ovarian cysts, no diabetes, hypertension, non-smoker.

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Thank you very much for referring this lovely 56 year old lady who recently had a full medical and was noted to have a cholesterol of 7 mmol/l, HDL 2 mmol/l, LDL 4 mmol/l, triglycerides 2.2 mmol/l and a total cholesterol to HDL ratio of 3.5. She is currently asymptomatic from a cardiac point of view.

In terms of her other risk factors, there is a significant family history of ischaemic heart disease. Her father is alive at age 84 but had a stroke about 25 years ago. Her mother died at age 60 but had three previous myocardial infarctions and coronary artery bypass surgery prior to her death. Her younger sister died of ovarian cancer at age 35. Her maternal uncle died at age 56 with a myocardial infarction, her maternal grandmother died of a heart attack at age 36 and her maternal great uncle died at age 63 with a myocardial infarction.

In terms of her past medical history, she has previously suffered with shingles of her lower back, bilateral oophorectomy for ovarian cysts, bilateral bunion surgery.

Her current medication consists of Premarin. She drinks up to six units of alcohol a week and does not smoke. She gets regular exercise, goes to the gym and practices yoga.

Examination: pulse 70 beats per minute, regular. JVP not elevated. Blood pressure 140/80. Heart sounds S1 plus S2. She had good peripheral pulses. There is no peripheral stigma of hyperlipidaemia.

During her full medical she had normal full blood count, Us&Es, liver function test, calcium, phosphate, fasting glucose, iron indices, thyroid function test, high sensitive CRP with a level of 0.9 (0 to 5). There was normal vitamin D, spirometry and an unremarkable urine analysis. She had an MRI of her brain, heart and colon which was normal. Carotid Dopplers were normal. Ultrasound of her abdomen and pelvis were also normal. A copy of her ECG was in

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her medical file and it was completely normal. She underwent an exercise tolerance test where she exercised for 11 minutes 12 seconds on the Bruce protocol reaching Stage IV and 100% of her maximum predicted heart rate with a workload of 13.40 Mets. The test was discontinued because she reached her maximum predicted heart rate. There were no significant ST or T wave changes. She already has a very good diet as she works as a chef. Using the European Society of Cardiology Heart Score, she scores 2% of having a significant cardiovascular event at ten years.

Given her significant family history despite a normal high sensitive CRP and carotid Dopplers my opinion would be to commence a statin agent. Her relative risk is double that of a person of her age without hypercholesterolaemia (European Society of Cardiology 2011 guidelines on the management of hyperlipidemia). Despite having a long discussion about whether to commence a statin agent or not, Fiona would like to observe her cholesterol for the time being and have it rechecked in approximately three months' time. If it is still high then she may consider commencing lifelong statin treatment. We also discussed the options of obtaining a calcium score/CT coronary angiogram. If this is abnormal then she will definitely need a statin agent. We can also measure her Apolipoprotein B, Apolipoprotein A1 and lipoprotein A levels which may be more predictive for cardiovascular events. Given her family history and her relatively young age, even if these investigations are negative, I will still opt for commencing a statin agent and therefore I would prefer not to arrange these investigations.

I also discussed with her the concept of total cholesterol burden and exposure levels to high cholesterol over a period of time. Assuming she has a calcium score and it is 0 at this point in time, it may not be truly reflective of future risks over the next few decade. Fiona would like to have a think about what we discussed today and we will review the situation in three months' time with an up to date fasting lipid profile.

Lastly, the other issue is that of hormone replacement therapy (HRT), which we did not discuss today. There is an increased the risk of coronary heart disease in women who start combined HRT more than ten years after the menopause. She is currently on Premarin which is an estrogen only HRT and I am therefore happy for her to continue with this for the time being.

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Five months later

[redacted]

Diagnoses:

1. **Hyperlipidaemia with a strong family history of ischaemic heart disease**
2. **Bilateral oophorectomy for ovarian cysts**
3. **Previous shingles**
4. **Chronic hip pain**

I reviewed Fiona today in clinic. She remains asymptomatic from a cardiac point of view. Her fasting lipid profile showed a total cholesterol of 6.8 mmol/L, triglycerides 1.48 mmol/L, HDL cholesterol 2.25 mmol/L, LDL cholesterol 3.95 mmol/L and a total cholesterol to HDL ratio of 3.02. Her Apolipoprotein A1 was 2.16 (1.08 to 2.25 g/L), Apolipoprotein B 1.01 (0.60 to 1.17 g/L) and Lipoprotein (a) 119 (<300 mg/L). Although her cholesterol is elevated, all her other high risk lipid profiles were normal.

I again had a long discussion about commencing a statin agent and Fiona is adamant that she does not want to commence one unless absolutely necessary. I can understand her point of view and consequently I have arranged for her to have a CT coronary angiogram and calcium score. If this is completely normal then there would be a rationale not to commence a statin agent.

Yours sincerely

Dictated and verified by Doctor but not signed
Dr Azad Ghuran MB ChB, MRCP, MD
Consultant Cardiologist

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Diagnoses:

1. **Hyperlipidaemia with a strong family history of ischaemic heart disease**
2. **Bilateral oophorectomy for ovarian cysts**
3. **Previous shingles**
4. **Chronic hip pain**

Further to this lady's recent clinic review, she has now had her CT coronary angiogram and calcium score. This showed a calcium score of 0 with normal coronary arteries. She now has had normal carotid Dopplers, normal high sensitivity CRP and normal Lipoprotein B, Apolipoprotein A1 and Lipoprotein A. With all these normal investigations it is hard to justify commencing a statin agent and I have reassured Fiona. I would suggest she has a carotid Doppler ultrasound scan, a repeat calcium score and CT coronary angiogram in about five years' time.

I have not arranged any further follow up appointments but I will of course be happy to review her should the need arise.

Yours sincerely

Dictated and verified by Doctor but not signed

Dr Azad Ghuran MB ChB, MRCP, MD
Consultant Cardiologist

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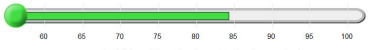
- **56 year old female**
- **Total Chol. = 7 mmol/l, HDL 2 mmol/l, LDL 4 mmol/l, TGL = 2.2 mmol/l, TC/HDL = 3.5**
- **BP 140/80 Weight 65 kg Height 173 cms. BMI = 21.7**
- **Risk factors: FHx.**

Heart age 62 yrs.

On average, expect
to survive to age 84
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
5.9%
assuming you don't die of anything else

10-year QRISK®2 score 5.6
Heart age 58 yrs

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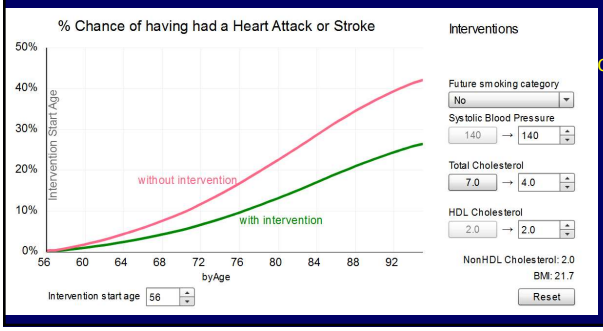
•56 year old female
•Total Chol. = 7 mmo/l, HDL 2 mmol/l, LDL 4 mmol/l, TGL = 2.2 mmol/l, TC/HDL = 3.5
•BP 140/80 Weight 65 kg Height 173 cms. BMI = 21.7
•Risk factors: FHx.



Case 2

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Learning Point

Case 2

- Not everyone with a high risk score or a high cholesterol is predisposed to developing coronary artery or stroke disease
- Sometimes useful to investigate patients who develop side effects from statins or are reluctant to take statins and need reassurance
- On the contrary, it can be useful to demonstrate early atherosclerosis disease which may serve as the basis to commence statin treatment

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Case VC – DOB 29th July 1968
Lipid profile 1997 (29 years) – 2018 (49 years)

Strong FHx IHD. Father is alive at 76 years with coronary stents and previous myocardial infarctions at 58 years and 75 years. Cholesterol was not high. Mother is alive at 75 years, having had a myocardial infarction at 70 years, and has a high cholesterol. Older brother died at 48 years, suddenly and unexpectedly, and a postmortem revealed a myocardial infarction. Paternal grandfather died in his mid-50s with a myocardial infarction. Maternal grandfather had a myocardial infarction in his late 60s.

PMx: probable anaphylaxis/cardiorespiratory arrest at 17 years following contrast administration during investigation of urinary tract

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Case VC – DOB 29th July 1968
Lipid profile 1997 (29 years) – 2018 (49 years)

	1997	2002	2005	2008	2010	2018
Age	29	34	37	40	42	49
TC	4.9	5.2	5	5.1	4.8	5.3
HDL	1.4	0.9	1.1	1.5	1.6	
LDL	3	3.9	3.5	3.1	2.7	
TGL	1.2	0.9	0.8	1.1	1	
UE	N	N		N	N	
LFT	n	N		N	N	
Glu	n	N		N	N	
BMI (kg/m2)	21.7	22	24	23	23	23.1
BP			112/68			
Q risk3	0.2		0.6		0.8	1.5
JBS3			0.96		1.3	4.2

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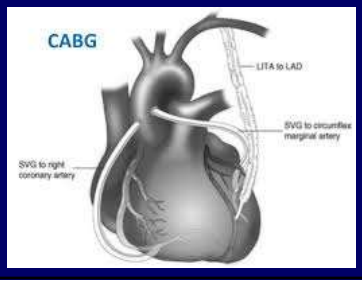
Case VC – DOB 29th July 1968

NSTEMI, May 2018. Significant disease in LAD and RCA and moderate disease in OM

Coronary artery bypass surgery - 25 May 2018
LIMA to LAD, *SVG to OM and SVG to PDA.*



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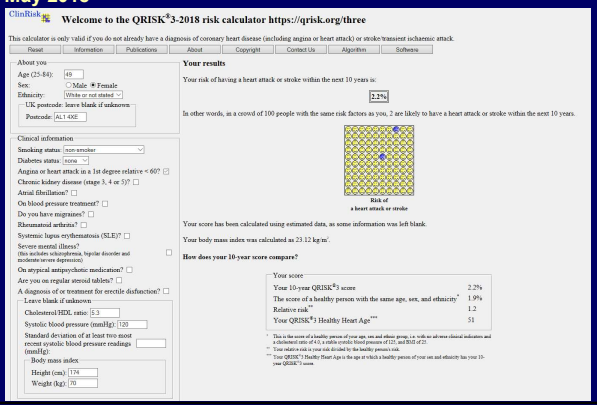
May 2018 Case VC – DOB 29th July 1968



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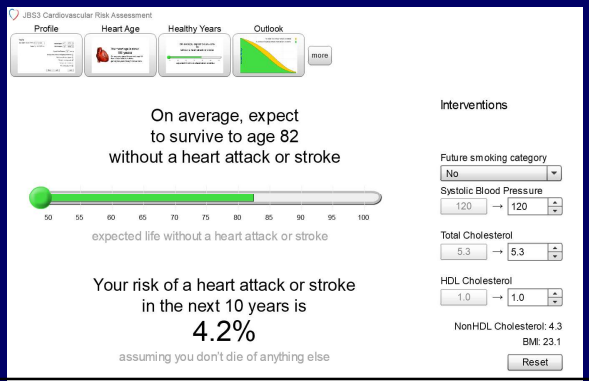
May 2018 Case VC – DOB 29th July 1968



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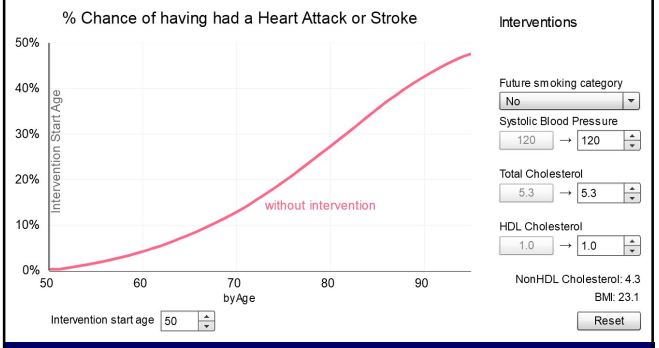
Case VC – DOB 29th July 1968



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Case VC – DOB 29th July 1968

FBC, U&E's, liver function test, and haemoglobin A1c are all normal.

29/06/18:

Total cholesterol 3.5 mmol/L
HDL 1.4 mmol/L
LDL 1.6 mmol/L
Triglycerides 1.1 mmol/L
Non-HDL 2.1 mmol/L.
Lipoprotein (a) 168 nmol/L (normal < 50 nmol/l).

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Conclusion

- **Hyperlipidaemia is associated with an increased risk of cardiovascular disease**
- **Intensive risk factor lowering in established CVD**
- **Not all patients with high cholesterol will have a cardiovascular event particularly those with high functional levels of HDL.**
- **Not all patients with a normal cholesterol level are protected from a cardiovascular event**
- **There is a continuum of risk throughout life and most CVD events occur in individuals with intermediate risk based on current risk models.**
- **Cardiovascular risk management of patients should be individualised after discussing all risks and benefits on/off drug therapy (aspirin/statins) using risk prediction models directed to the appropriate population. Targeted investigations.**

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Testosterone: a hormone preventing cardiovascular disease or a therapy increasing cardiovascular events?

European Heart Journal (2016) 37, 3569–3575

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Testosterone and cardiovascular disease

Decreasing testosterone levels - older men
- decrease by 1–2% per year

- **Low T**
- **Manopause**
- **Hypogonadism**
- **Andropause**

Some of the symptoms of androgen deficiency include:

- **breast development (gynaecomastia)**
- **reduced muscle mass and strength**
- **increased body fat, particularly around the abdomen**
- **weaker erections and orgasms**
- **reduced amount of ejaculate**
- **reduced bone mass, therefore increased risk of osteoporosis**
- **reduced sexual desire**
- **hot flushes and sweating**
- **lethargy and fatigue**
- **Depression**
- **loss of body hair**

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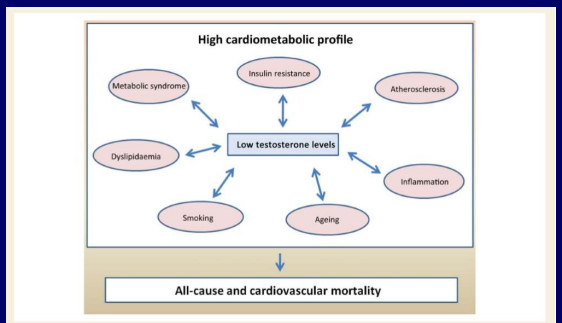

Figure 1 Association between low endogenous testosterone levels and cardiovascular risk factors, as well as with all-cause and cardiovascular mortality in men. The association between low testosterone levels (including total and free testosterone levels) and cardiovascular risk factors has been reported in several observational studies, especially in older men. Available evidence from meta-analyses suggest that low levels of testosterone are associated with an increased risk of mortality from all causes and cardiovascular disease. Only arrows between testosterone levels and other factors have been drawn. Figure inspired from reviews of Morgentaler *et al.*[20] Herring *et al.*,[11] and Oskui *et al.*[9]

European Heart Journal (2016) 37, 3569–3575

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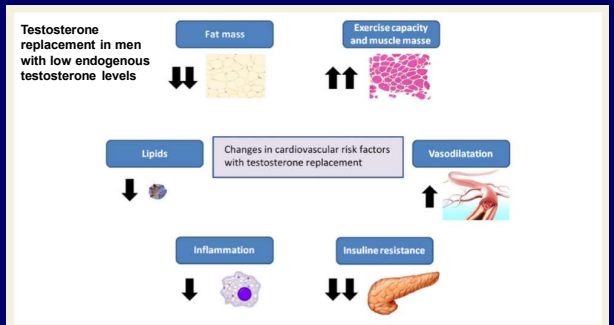

Figure 2 Changes in cardiovascular risk factors with testosterone replacement therapy in men with low endogenous testosterone levels. In men with low testosterone levels, testosterone therapy has been associated with a reduction in fat mass, total cholesterol, glucose concentration, serum concentrations of inflammatory markers and with an increase in time to onset of symptomatic angina with exercise (vasodilatation), muscle mass, and exercise capacity in men with symptomatic heart failure. Figure inspired from reviews of Morgentaler *et al.*[20] Herring *et al.*,[11] and Oskui *et al.*[9]

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Testosterone and cardiovascular disease

Table 3 Association between testosterone replacement therapy and cardiovascular outcomes

Years	Number of patients on testosterone	Country	Mean follow-up (years)	Mean age (years)	MACE	Results (users vs. non-users)
2010[17]	209	USA	0.5	74	MedRac cardiac events	OR 5.8 (95% CI 2.0–16.8)
2013[23]	1223	USA	2.3	60.6	Mortality, MI and Stroke	HR 1.29 (95% CI 1.04–1.58)
2013[24]	2994	Meta-analysis	NA	NA	CVD events (ICD classification)	OR 1.54 (95% CI 1.09–2.18)
2014[27]	55 593	USA	0.3	54.4	Non-fatal MI	RR 1.36 (95% CI 1.03–1.81)
2014[24]	6355	USA	NA	NA	MI	HR 0.84 (95% CI 0.69–1.02)

CI, confidence intervals; CVD, cardiovascular disease; HR, hazard ratios; ICD, international classification of disease; MACE, major adverse cardiovascular events; MI, myocardial infarction; NA, not available; OR, odds ratios; RR, relative risk; TRT, testosterone replacement therapy.

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Testosterone therapy

- **In men with androgen deficiency with a diagnosis of hypogonadism resulting from an established medical disease of the testes, pituitary, or the hypothalamus**
- **Symptomatic**
- **Documented low testosterone levels**
- **Screening for androgen deficiency in the general population is not recommended.**
- **In older men with low testosterone levels, testosterone placement should be based on an individualized approach discussing the risks and benefits, as well as the uncertainty surrounding this therapy.**
- **Systematic prescription of testosterone replacement therapy in all men with low testosterone is not recommended.**
- **Replacement of therapy in men with decompensated heart failure, with MI or a revascularization procedure in the preceding 6 months is not recommended**

European Heart Journal (2016) 37, 3569–3575

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Case 1

39 yr. old male admitted on the 20th July 2016 with a history of right-sided facial, arm and leg weakness, difficulties moving his lips and an expressive dysphasia. Two days earlier he complained of left-sided face and arm weakness that lasted 20 seconds. For the preceding three weeks he noticed that his vision was blurred.

An urgent CT – no significant findings.

ECG showed atrial fibrillation with a ventricular rate of 130 beats per minute.

He works as a personal trainer.
Previously lost 12-14 stone (76 -88 kg) over the preceding 3½ year period Using ephedrine, caffeine, anabolic androgenic steroids, thyroxine and caffeine.

PMx: nil.

FHx: mother died of a stroke at age 57 which may be related to a clot originating in her leg. He has a sister with three miscarriages.

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Case 1

Non smoker. Drinks alcohol occasionally and denies using any recreational drugs.

HB mildly elevated at 171 gm/L with a normal MCV, CRP, ferritin, TFT's, haemoglobin A1c, beta-2 microglobulin, ANA and anti-cardiolipin antibody. Although lupus anticoagulant screen was done it could not be interpreted given that he was on Apixaban. Creatinine was mildly elevated at 135 mmol/L, with sodium of 138 mmol/L, potassium 4.9 mmol/L and an eGFR of 51 ml/min, LDH was mildly elevated at 353 IU/L. He was negative for factor V Leiden.

His ventricular rate was adequately controlled on bisoprolol 10 mg daily. He was also commenced on Ramipril and the dose was slowly titrated up to 5 mg bd, and Apixaban 5mg BD

An inpatient echocardiogram demonstrated moderately dilated left ventricle (LVDD 6.5 cm, LVDS 4.97 cm) with significant LV systolic impairment. There was no significant valvular abnormalities. The right ventricular systolic pressure was 26 mmHg. Inferior vena-cava was dilated with poor inspiratory collapse.

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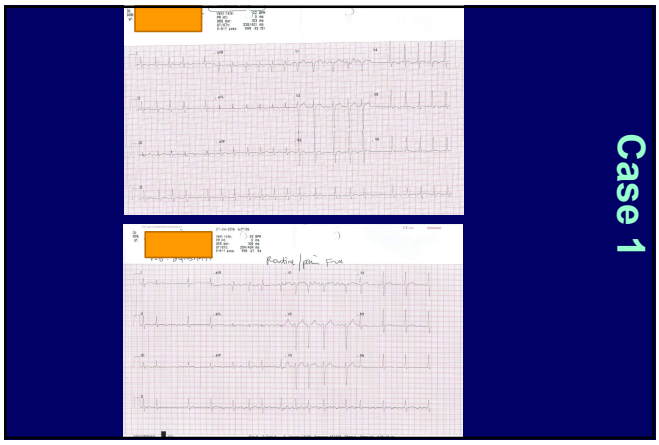

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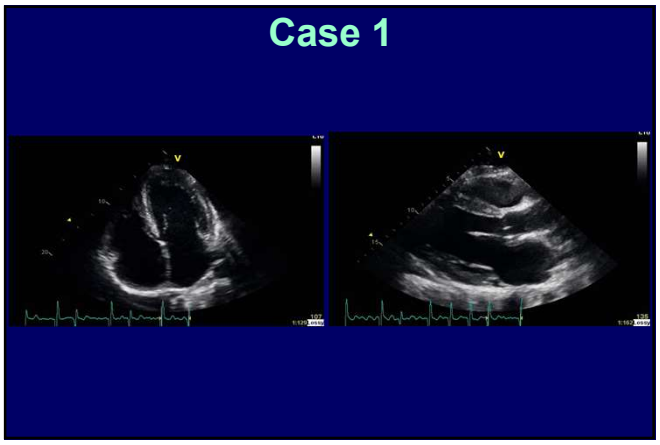

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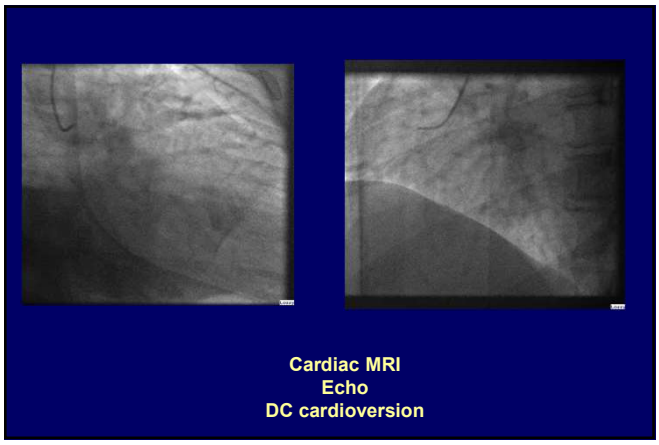

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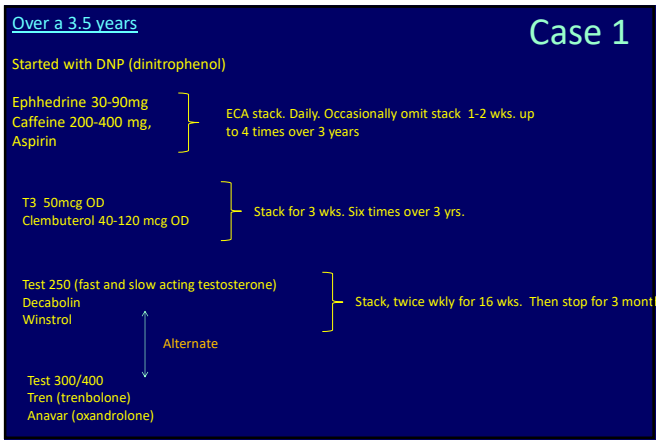

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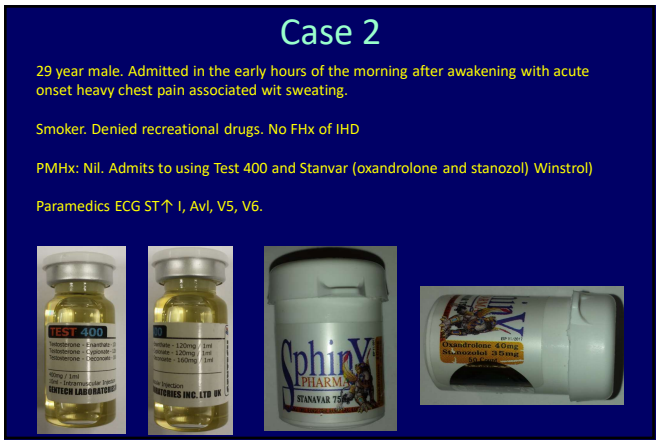

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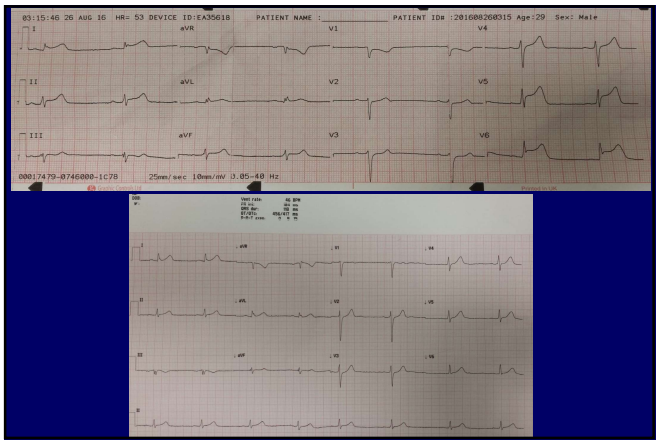

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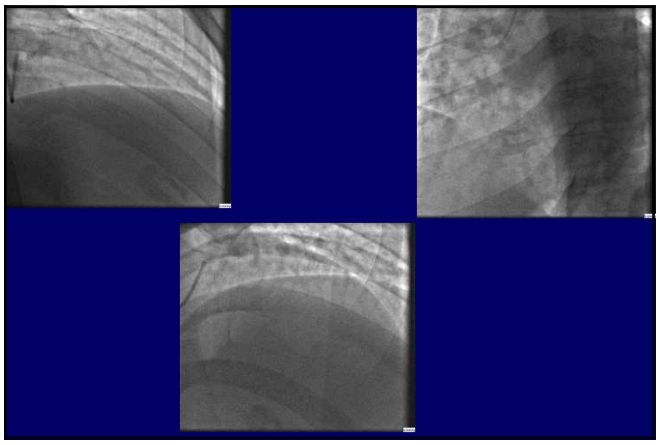

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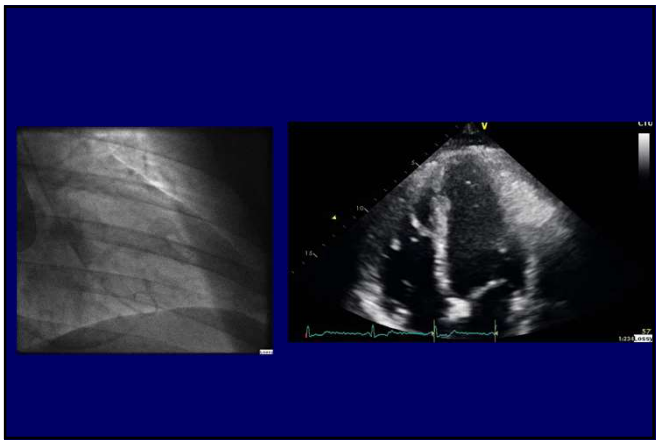

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Case 3

49 year male. Active. High intensity interval training 3-4x/week

RF: pre-diabetic 2 yrs. on metformin. Choleterol 5.4 mmol/l, LDL 3.5 mmol/l, HDL 1.2 mmol/l, TGL 1.5 mmol/l. Ex-smoker 25 years.. No FHx.

PMx: low testosterone on a general health check, vitilgo, lumbar disc herniation

DHx (before MI): metformin 500mg BD and testosterone enanthate 210mg once weekly. No recreational drugs.

21/4/17: burning chest pain. Anterior MI. 2 stents to LAD

Reviewed 3rd May 2017

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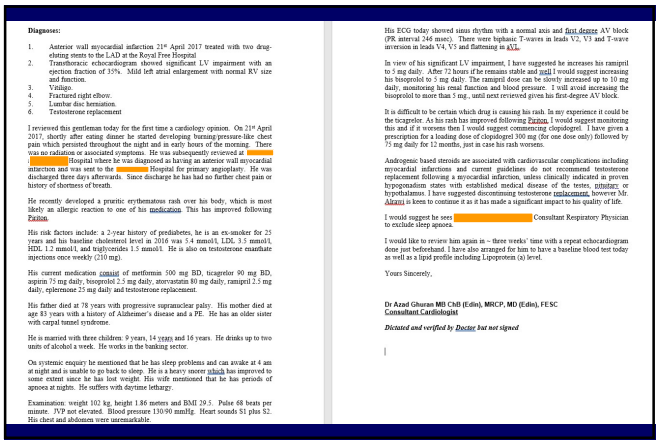

Diagnoses:

1. Anterior wall myocardial infarction 21st April 2017 treated with two drug-eluting stents to the LAD at the Royal Free Hospital
2. Transthoracic echocardiogram showed significant LV impairment with an ejection fraction of 35%. Mild left atrial enlargement with normal RV size and function.
3. Vitiligo.
4. Fractured right elbow.
5. Lumbar disc herniation.
6. Testosterone replacement

I reviewed this gentleman today for the first time a cardiology opinion. On 21st April 2017, shortly after eating dinner he started developing burning pressure-like chest pain which persisted throughout the night and in early hours of the morning. There was no radiation or associated symptoms. He was subsequently reviewed at [redacted] Hospital where he was diagnosed as having an anterior wall myocardial infarction and was sent to the [redacted] Hospital for primary angioplasty. He was discharged three days afterwards. Since discharge he has had no further chest pain or history of shortness of breath.

He recently developed a pruritic erythematous rash over his body, which is most likely an allergic reaction to one of his medication. This has improved following Fexino.

His risk factors include: a 2-year history of prediabetes, he is an ex-smoker for 25 years and his baseline cholesterol level in 2016 was 5.4 mmol/l, LDL 3.5 mmol/l, HDL 1.2 mmol/l, and triglycerides 1.5 mmol/l. He is also on testosterone enanthate injections once weekly (210 mg).

His current medication consist of metformin 500 mg BD, ticagrelor 90 mg BD, aspirin 75 mg daily, bisoprolol 2.5 mg daily, atorvastatin 80 mg daily, ramipril 2.5 mg daily, eplerenone 25 mg daily and testosterone replacement.

His father died at 78 years with progressive supranuclear palsy. His mother died at age 83 years with a history of Alzheimer's disease and a PE. He has an older sister with carpal tunnel syndrome.

He is married with three children: 9 years, 14 years and 16 years. He drinks up to two units of alcohol a week. He works in the banking sector.

On systemic enquiry he mentioned that he has sleep problems and can awake at 4 am at night and is unable to go back to sleep. He is a heavy snorer which has improved to some extent since he has lost weight. His wife mentioned that he has periods of apnoea at nights. He suffers with daytime lethargy.

Examination: weight 102 kg, height 1.86 meters and BMI 29.5. Pulse 68 beats per minute. JVP not elevated. Blood pressure 130/90 mmHg. Heart sounds S1 plus S2. His chest and abdomen were unremarkable.

His ECG today showed sinus rhythm with a normal axis and first degree AV block (PR interval 246 msec). There were biphasic T-waves in leads V2, V3 and T-wave inversion in leads V4, V5 and flattening in aVL.

In view of his significant LV impairment, I have suggested he increases his ramipril to 5 mg daily. After 72 hours if he remains stable and well I would suggest increasing his bisoprolol to 5 mg daily. The ramipril dose can be slowly increased up to 10 mg daily, monitoring his renal function and blood pressure. I will avoid increasing the bisoprolol to more than 5 mg., until next reviewed given his first-degree AV block.

It is difficult to be certain which drug is causing his rash. In my experience it could be the ticagrelor. As his rash has improved following Fexino, I would suggest monitoring this and if it worsens then I would suggest commencing clopidogrel. I have given a prescription for a loading dose of clopidogrel 300 mg (for one dose only) followed by 75 mg daily for 12 months, just in case his rash worsens.

Androgenic based steroids are associated with cardiovascular complications including myocardial infarctions and current guidelines do not recommend testosterone replacement following a myocardial infarction, unless clinically indicated in proven hypogonadism states with established medical disease of the testes, pituitary or hypothalamus. I have suggested discontinuing testosterone replacement, however Mr. Alagni is keen to continue it as it has made a significant impact to his quality of life.

I would suggest he sees [redacted] Consultant Respiratory Physician to exclude sleep apnoea.

I would like to review him again in ~ three weeks' time with a repeat echocardiogram done just beforehand. I have also arranged for him to have a baseline blood test today as well as a lipid profile including Lipoprotein (a) level.

Yours Sincerely,

Dr Azad Ghuran MB ChB (Edin), MRCP, MD (Edin), FESC
Consultant Cardiologist

Dictated and verified by Doctor but not signed

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Conclusion

- Intensive risk factor lowering in patients with established CVD
- Not all patients with high cholesterol will have a cardiovascular event particularly those with high functional levels of HDL.
- Not all patients with a normal cholesterol level are protected from a cardiovascular event
- There is a continuum of risk throughout life and most CVD events occur in individuals with intermediate risk based on current risk models.
- Cardiovascular risk management of patients should be individualised after discussing all risks and benefits on/off drug therapy (aspirin/statins) using risk prediction models directed to the appropriate population. Targeted investigations.
- Testosterone therapy: in men with androgen deficiency with a diagnosis of hypogonadism resulting from an established medical disease of the testes, pituitary, or the hypothalamus.

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