# Coronary Artery Disease Risk Prediction and Prevention

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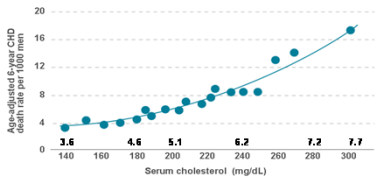
www. hertslondoncardiology.co.uk

## Hypercholesterolaemia

- **Primary**
  - FH (familial hypercholesterolaemia)
  - Others
- **Secondary**
  - IHD
  - CVA
  - PVD

## The direct correlation between elevated cholesterol and CHD risk

*MRFIT (Multiple Risk Factor Intervention Trial)*




The relation of serum cholesterol to CHD deaths in 361,662 men aged 35 to 57 years during an average follow-up of 6 years in MRFIT screenings. Each point represents median value for 5% of the population.

Gotto AM Jr et al. *Circulation*. 1990;81:1721-1733.

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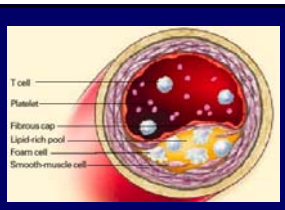
## Secondary

- IHD
- CVA
- PVD




**GOAL**

LDL < 1.8 mmol/l
Or
Non HDL chol. < 2.5mmol/l
Or
At least a >50% reduction of LDL

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

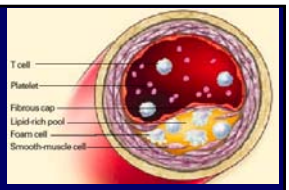
| Modifiable risk factors | OR (99% CI) | PAR (99% CI)* |
|---|---|---|
| Hyperlipidaemia | 3.25 (2.81 to 3.76) | 49.2% (43.8 to 54.5) |
| Smoking (current and former) | 2.04 (1.86 to 2.25) | 35.7% (32.5 to 39.1) |
| Hypertension | 1.91 (1.74 to 2.10) | 17.9% (15.7 to 20.4) |
| Abdominal obesity | 1.62 (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

## Total Cholesterol

HDL, LDL, VLDL, IDL, Liprotein (a), Chlomicrons and remnants




- HDL carry cholesterol back to the liver for excretion.
- Atherogenic cholesterol → VLDL, IDL, LDL, Lipoprotein (a)

Apolipoprotein B

**Total cholesterol - HDL = atherogenic cholesterol**

## 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*



## JBS 3 - General Recommendations

1. Risk Model Refinement Recommendations
2. Lifestyle Recommendations
3. Childhood and Adult Obesity Recommendations
4. Lipid Recommendations
5. Blood Pressure Recommendations
6. Established CVD Recommendations
7. Post Myocardial Infarction Recommendations
8. Stroke Recommendations
9. Peripheral Arterial Disease Recommendations
10. Diabetes Mellitus Recommendations
11. Chronic Kidney Disease Recommendations
12. Chronic Inflammatory Disease Recommendations
13. Chronic Obstructive Sleep Apnoea/Hypopnoea Recommendations
14. Implementation Recommendations

**Primary**

↓

- **FH** (familial hypercholesterolaemia)
- **Others**

**GOAL**

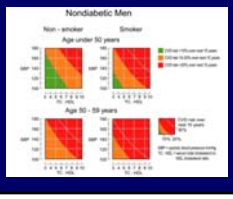
**Very high risk, LDL < 1.8 mmol/l or at least a >50% reduction of LDL (non-HDl chol. < 2.5 mmol/l)**

**High risk, LDL < 2.5 mmol/l (non-HDl chol < 3 mmol/l)**

**Low-moderate risk, LDL < 3 mmo/L (non-HDl chol < 3.8 mmol/l)**

**Risk Scores**

- **Framingham**
- **QRISK2**
- **JBS**
- **ESC Heart Score**
- **Scottish ASSIGN**




Daily Express Friday July 18 2014 7

Give statins to 17m, says NHS watchdog

By Jo Willey

Tragedy

Heart

Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3)

JBS3 Board

**1 April 2014**

*Heart* 2014 100: ii1-ii67
doi: 10.1136/heartjnl-2014-305693

**http://www.jbs3risk.com**

**The JBS3 risk calculator complements the NHS Health Check programme in England.**

**Offer CVD risk factor measurement from the age of 40 years.**

**Use JBS3 risk calculator to estimate both 10-year risk and lifetime risk of CVD in all individuals, except pts. with CVD or high risk diseases i.e. diabetes age >40 yrs., CKD stages 3-5, or familial hypercholesterolaemia (FH).**

**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.

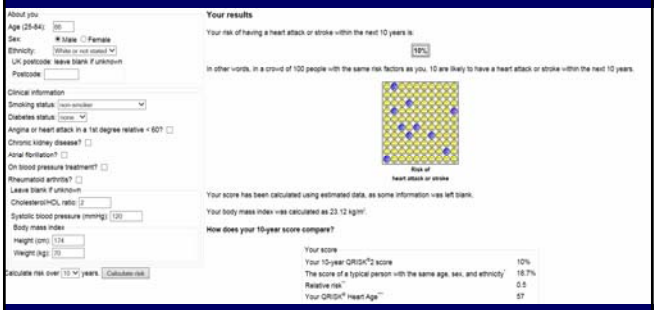
**NICE. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. July 2014**

- 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.

## 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**

## Q Risk 2 Score




## 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 |

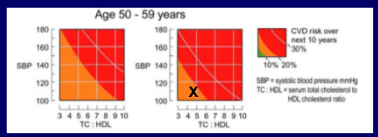
↑ **Benecol**

## Cases

## Case 6

**10-year QRISK®2 score**
**Non smoker = 9%,**
**Smoker = 15.7%**

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



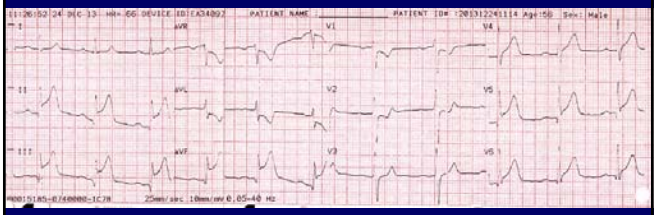

**10-year JBS score**
**Non smoker = 12%,**
**Smoker = 19%**

**10-year ESC Heart score**
**Non smoker = 1%,**
**Smoker = 2%**
**Very high risk** SCORE ≥10%, high risk ≥ 5 but < 10, moderate risk ≥ 1 but < 5

## 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**

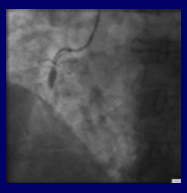


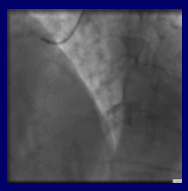
**•57 year old male**
**•Total Chol. = 4.2 mmo/l, HDL 1.01 mmol/l, LDL 2.7, TGL = 1.9 mmol/l, TC/HDL = 4.2**
**•BP 112/79 Weight 97 kg Height 183 cms. BMI = 29**
**•Risk factors: hypertension, smoker >20/day, > 20yrs.**

**Heart age 65 yrs.**


**10-year QRISK®2 score**
**Non smoker = 9%,**

## Case 6





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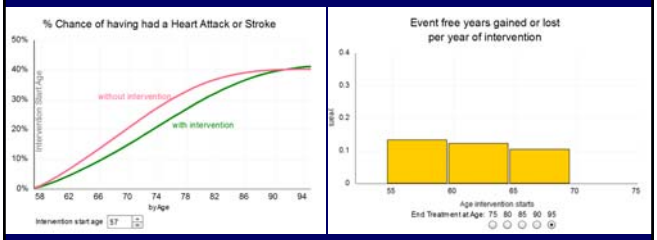
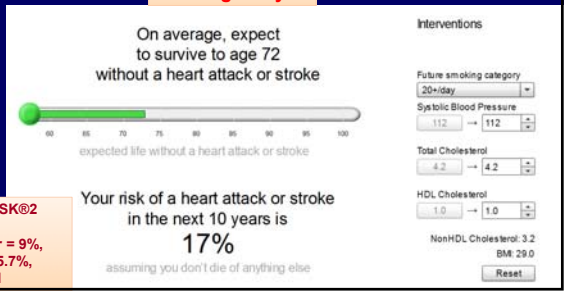



**•57 year old male**
**•Total Chol. = 4.2 mmo/l, HDL 1.01 mmol/l, LDL 2.7, TGL = 1.9 mmol/l, TC/HDL = 4.2**
**•BP 112/79 Weight 97 kg Height 183 cms. BMI = 29**
**•Risk factors: hypertension, smoker >20/day, > 20yrs.**

**Heart age 72 yrs.**




**10-year QRISK®2 score**
**Non smoker = 9%,**
**Smoker = 15.7%,**
**heart age 61**

## Learning Point

Case 6

**JBS 3 or QRISK 2 score is useful in predicting cardiovascular risk**

•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

Triple vessel disease

10-yr JBS3 Risk = 2.1%
10-yr. Qrisk 2 = 2%
Lifetime risk (80yrs.) = 59.1

•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

Normal coronary arteries on coronary angiography

10-yr JBS3 Risk = 9.3 %
10-yr. Qrisk 2 = 8.2 %
Lifetime risk (80yrs.) = 20.3

## 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 |
|---|---|
| 10-year QRISK®2 score | 13.5% |
| The score of a typical person with the same age, sex, and ethnicity* | 9.7% |
| Relative risk** | 1.4 |
| QRISK® Heart Age*** | 61 |

Case 3

# Learning Point

- 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

**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.

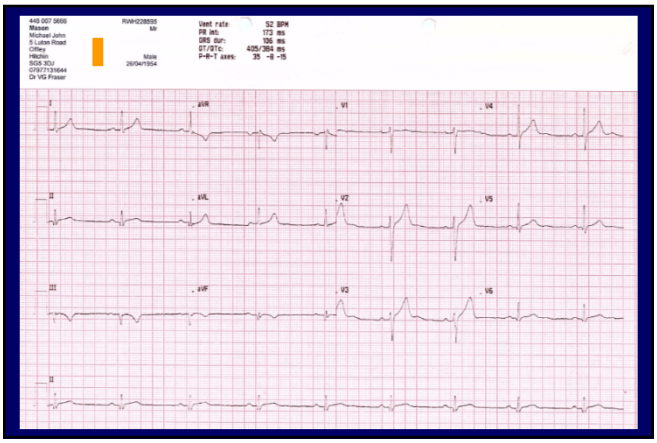
**Examination:** Blood pressure 168/96 mmHg. Heart sounds are normal.
ECG is normal sinus rhythm with rate of 53 beats per minute with T-wave inversion in III and aVF and a Q-wave in lead III and aVF.

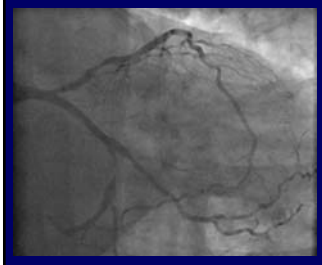
His Duke score showed a probability of coronary disease as 73% (male, hypertension and ECG changes). I have discussed Mr Mason's symptoms and ECG changes with Dr Azad Ghuran, Dr Ghuran believes Mr Mason has been investigated with a coronary angiogram quoting a 1 in 1000 risk of death, MI, stroke and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

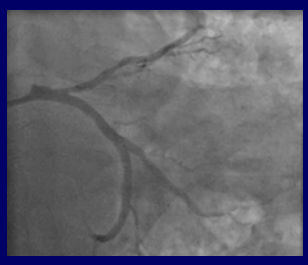
I have explained to Mr Mason even though he is now asymptomatic since the commencement of Omeprazole because of the ECG changes and risk factors we need to completely exclude there is no cardiovascular reason for his symptoms. He is happy to go ahead with his angiogram. I have made no changes to his 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.

## 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







## ~12 months later after PCI, 4th June 2014

Case 7

| | |
|---|---|
| Diagnosis: | Ischaemic heart disease – stented 2013<br>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 Bencool. 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. |

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**

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

## 3 months later, 04/12/13

| | |
|---|---|
| Diagnosis: | Ischaemic heart disease – stented 2013<br>Intolerant to lipid lowering medication |
| Medication: | Aspirin, Clopidogrel |
| Results: | BP 150/76 Weight 83 kg Height 176 cm BMI 27<br>Creatinine 78, Cholesterol 5.4, Triglycerides 1.33, Fasting Glucose 6.0<br>Albumin 45, Haemoglobin 35 |

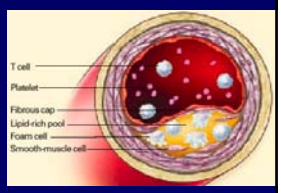
It had pleasure in reviewing this patient at the cardiovascular risk clinic on 4th December 2013. As you mention he has significant coronary disease, however, he has had a bad experience with Atorvastatin that led to severe muscle pains and also he felt depressed. His symptoms started approximately two 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.

Case 7

## 24th September 2014 - Dr. Ghuran

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

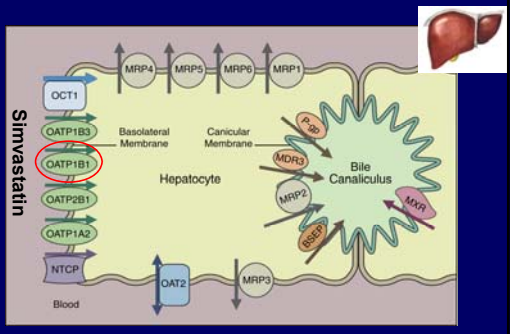



**Future options:**

- Fluvastatin
- Ezetimibe
- PCSK 9 inhibitors

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

Gene *SLCO1B1* encodes for OATP1B1




## Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

NICE clinical guideline 181

**Consider use of Ezetimibe treatment in line with NICE technology appraisal guidance (TAG) 132**

**The population groups covered by the ezetimibe NICE TAG 132 are:**

**adults with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their CVD status or risk and**

**whose condition is not appropriately controlled with a statin alone or**

**in whom a statin is considered inappropriate or is not tolerated**

**The term "not appropriately controlled with a statin alone" is defined as failure to achieve a target lipid level that is appropriate for a particular group or individual. It also assumes that statin therapy is optimised and tolerated.**


Issued: July 2014 last modified: September 2014
http://www.nice.org.uk/guidance/cg181

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

## 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% | - |

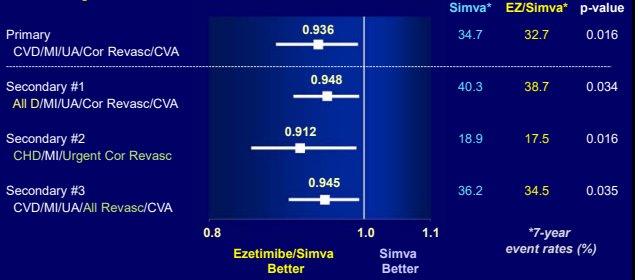
- Low intensity; 20%-30%
- Medium intensity; 31%-40%
- High intensity; above 40%

* 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

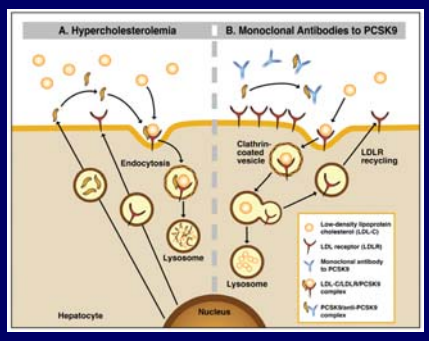
CARD-1131919-0000

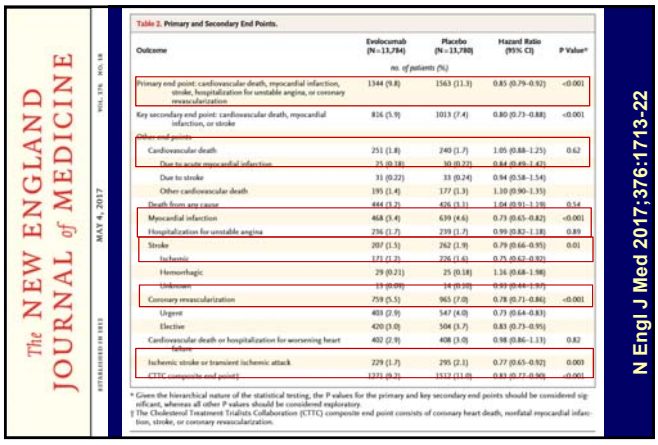
## Primary and 3 Prespecified Secondary Endpoints — ITT




*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)*

## Proprotein convertase subtilisin/kexin type 9 (PCSK9)





The NEW ENGLAND JOURNAL of MEDICINE

MAY 4, 2017

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

## 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%**

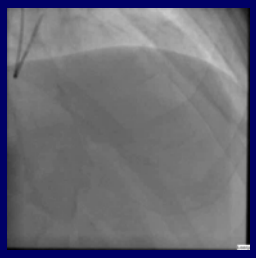
**Dr Azad Ghuran MB ChB, MRCP, MD**
**Consultant Cardiologist**

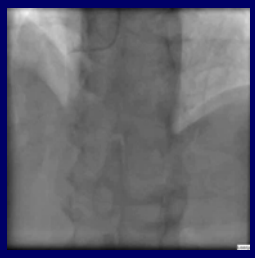
## Case 7

# 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**

## Case 11





## 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.

## Case 11

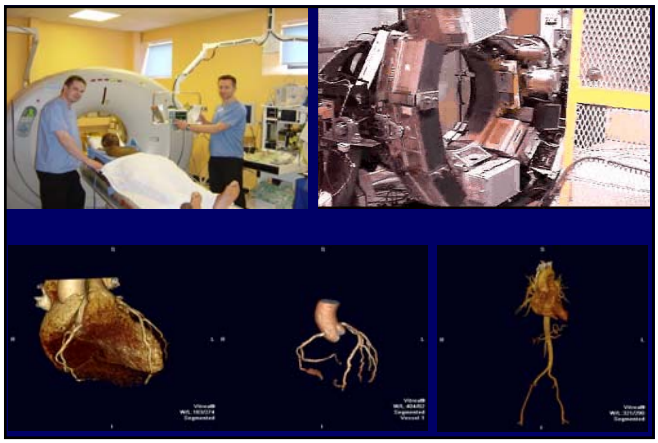
Coronary Angiography: 21/03/2014
Typed: 22/03/2014

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,

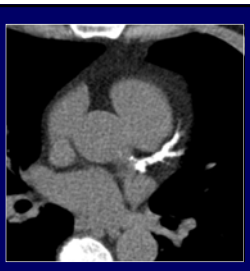
**Dr Azad Ghuran MB ChB, MRCP, MD**

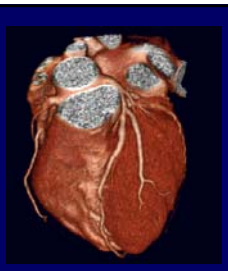


## Comparative Effective Dose of Radiological Investigations

- 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**





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

NICE National Institute for Health and Care Excellence

**Update November 2016**

1.3.4 Diagnostic testing for people in whom stable angina cannot be excluded by clinical assessment alone

The Guideline Development Group emphasised that the recommendations in this guideline are to make a diagnosis of chest pain, not to screen for CAD. Most people diagnosed with non-anginal chest pain after clinical assessment need no further diagnostic testing. However in a very small number of people, there are remaining concerns that the pain could be ischaemic.

1.3.4.1 Include the typicality of anginal pain features (see recommendation 1.3.3.1) in all requests for diagnostic investigations and in the person's notes. [2010, amended 2016]

1.3.4.2 Use clinical judgement and take into account people's preferences and comorbidities when considering diagnostic testing. [2010]

1.3.4.3 Offer 64-slice (or above) CT coronary angiography if:

- clinical assessment (see recommendation 1.3.3.1) indicates typical or atypical angina or
- clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves. [new 2016]

## *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.

Case 11

## Learning Point

- **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 data to suggest coronary artery disease risk reduction by commencing a statin – on going studies**

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 = 1.4%**
**10-yr. Qrisk 2 = 1.2%**
**Lifetime risk (80yrs.) = 14%**

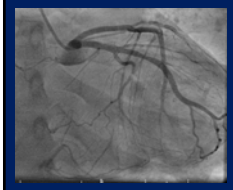
# Clinical Case 2

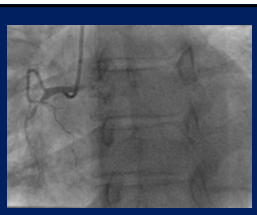
**56 year old lady. Asymptomatic.**
**Full medical: TC 7 mmol/l, HDL 2 mmol/l, LDL 4 mmol/l, triglycerides 2.2 mmol/l and a TC:HDL ratio of 3.5.**

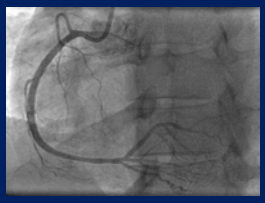
**FHx: ischaemic heart disease. Her father is alive and had a stroke 59 yrs. Her mother died at age 60 but had three previous MI and CABG prior to her death. Her younger sister died of ovarian cancer at age 35. Maternal uncle died at age 56 with an MI. Maternal grandmother died of an MI at age 36 and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

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

# Case 5A







Case 2

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

# 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.**

Case 2

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.

## Five months later

Case 2

[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

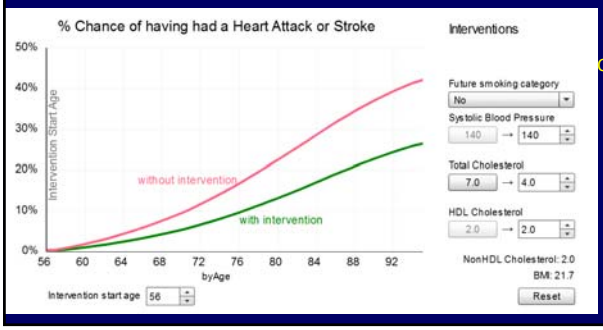
I reviewed Fiona today in clinic. She remains asymptomatic from a cardiac point of view. Her fasting lipid profile showed a total cholesterol of 6.8 mmol/L, triglycerides 1.48 mmol/L, HDL cholesterol 2.25 mmol/L, LDL cholesterol 3.95 mmol/L and a total cholesterol to HDL ratio of 3.02. Her Apolipoprotein 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**

•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

Case 2

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**

## 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

•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.

**Heart age 62 yrs.**


Case 2

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

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

*European Heart Journal (2016) 37, 3569–3575*

## 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

## 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[28] | 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.

*European Heart Journal (2016) 37, 3569–3575*

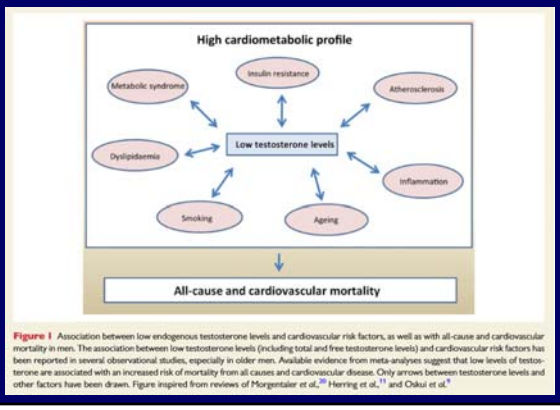



**Figure 1** Association between low endogenous testosterone levels and cardiovascular risk factors, as well as with all-cause and cardiovascular mortality in men. The association between low testosterone levels (including total and free testosterone levels) and cardiovascular risk factors has been reported 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.,[30] Herring et al.,[11] and Oskui et al.[9]

*European Heart Journal (2016) 37, 3569–3575*

## 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*

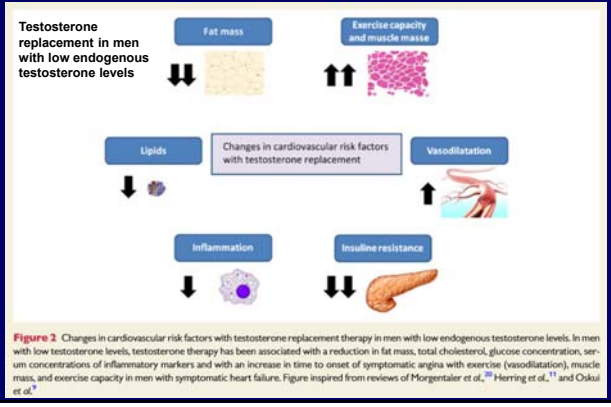



**Figure 2** Changes in cardiovascular risk factors with testosterone replacement therapy in men with low endogenous testosterone levels. In men with low testosterone levels, testosterone therapy has been associated with a reduction in fat mass, total cholesterol, glucose concentration, serum concentrations 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.,[30] Herring et al.,[11] and Oskui et al.[9]

*European Heart Journal (2016) 37, 3569–3575*

## 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.**

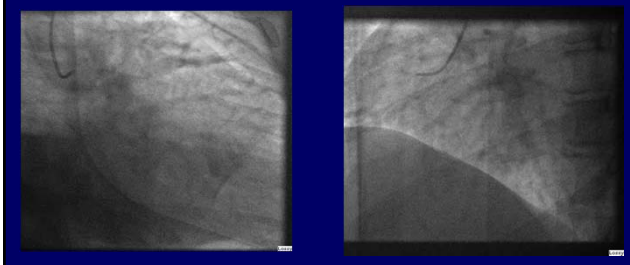
# Case 1

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

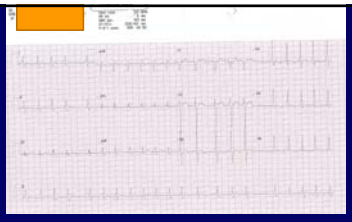
HB mildly elevated at 171 gm/L with a normal MCV, CRP, ferritin, TFT's, haemoglobin A1c, beta-2 microglobulin, ANA and anti-cardiolipin antibody. Although lupus anticoagulant screen was done it could not be interpreted given that he was on Apixaban. Creatinine was mildly elevated at 135 mmol/L, with 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.

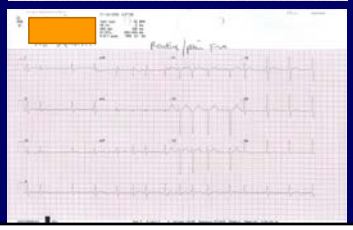
His ventricular rate was adequately controlled on bisoprolol 10 mg daily. He was also commenced on Ramipril and the dose was slowly titrated up to 5 mg bd, and Apixaban 5mg BD

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.



**Cardiac MRI**
**Echo**
**DC cardioversion**





Case 1

Over a 3.5 years

# Case 1

Started with DNP (dinitrophenol)

Ephhedrine 30-90mg
Caffeine 200-400 mg,
Aspirin

ECA stack. Daily. Occasionally omit stack 1-2 wks. up to 4 times over 3 years

T3 50mcg OD
Clembuterol 40-120 mcg OD

Stack for 3 wks. Six times over 3 yrs.

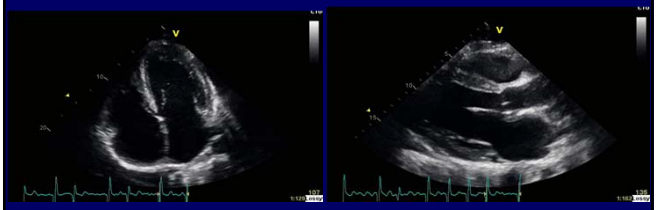
Test 250 (fast and slow acting testosterone)
Decabolin
Winstrol

Stack, twice wkly for 16 wks. Then stop for 3 mont

Alternate

Test 300/400
Tren (trenbolone)
Anavar (oxandrolone)

# Case 1



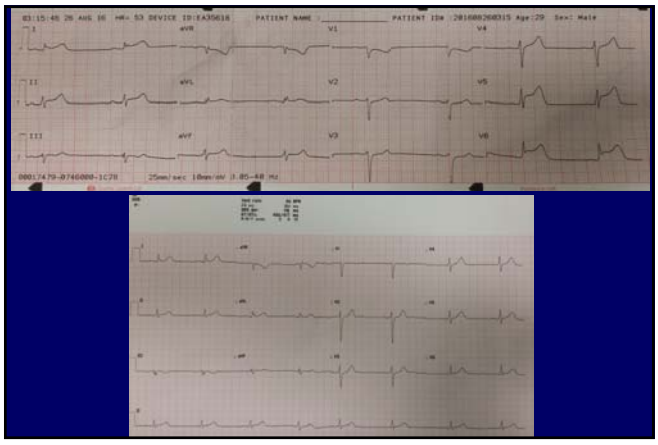
# Case 2

29 year male. Admitted in the early hours of the morning after awakening with acute onset heavy chest pain associated wit sweating.

Smoker. Denied recreational drugs. No FHx of IHD

PMHx: Nil. Admits to using Test 400 and Stanvar (oxandrolone and stanozol) Winstrol

Paramedics ECG ST↑ I, Avl, V5, V6.



# Case 3

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

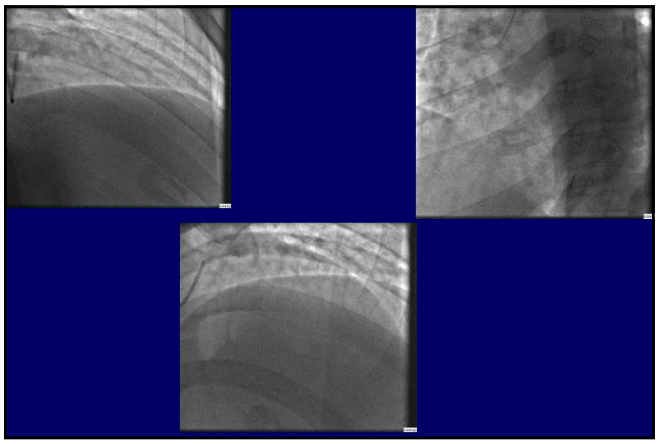
RF: pre-diabetic 2 yrs. on metformin. Choleterol 5.4 mmol/l, LDL 3.5 mmol/l, HDL 1.2 mmol/l, TGL 1.5 mmol/l. Ex-smoker 25 years.. No FHx.

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**



# 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.