Cardiovascular Risk & Prevention

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Disclosures

Speaker fees, travel grants and consultancy fees from Amgen and Sanofi
Research funding from Regeneron
Speaker fees from Bayer
Outline

1. CVD Prevention Landscape

2. Assessment of CVD Risk

3. Risk factors and Risk Reduction
   • Lipids and LDL lowering
   • Hypertension
   • Diabetes
CVD – Problem Solved?

Luepke Circ 2016

Berg BMC CVD 2014

Jousilahti BMJ 2016
The Problem

Recent Analysis from ONS:

CVD caused 44% of “avoidable” deaths in 2014

IHD was most common cause of avoidable death – 17%
Atherosclerosis
Risk Factors

15k cases/15k controls in 52 countries

Most of the risk of MI worldwide in both sexes and at all ages in all regions are attributable to

- Abnormal lipids
- Smoking
- Hypertension
- Diabetes
- Abdominal obesity
- Psychosocial factors
- Consumption of fruits, vegetables
- Alcohol
- Regular physical activity

90% PAR for MI

References:
1. INTERHEART Yusuf Lancet 2004
Going in Reverse?

U.S. life expectancy declines for the first time since 1993

By Lenny Bernstein

December 8, 2016 at 12:01 AM
Obesogenic Environment

75 to 80 per cent of middle-aged men are overweight in Australia.

Obesity soared 80% in the last 33 years.

25% of Children are Classified as Overweight.

Who's to blame for obesity? Policy makers, the food industry, or individuals?
Government Policy

- 10 Year Plan – focus on CVD prevention

- PHE Initiatives
  - Familial Hypercholesterolaemia

- NHS Health Checks

- Childhood Obesity Plan

- Diabetes Prevention Program
Outline

1. CVD Prevention Landscape

2. Assessment of CVD Risk

3. Risk factors and Risk Reduction
   1. Lipids and LDL lowering
   2. Hypertension
   3. Diabetes
Question

Which of the following about CVD risk assessment is incorrect?

A. The SCORE system includes diabetes in its algorithm
B. Relative Risk is a ratio of absolute risks
C. 10 year risk may underestimate risk in young women
D. Risk scores should not be used in people with FH
E. The SCORE system estimates 10 year risk of fatal CVD only
Guidelines
## Assess CV Risk

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic CV risk assessment is recommended in individuals at increased CV risk, i.e. with family history of premature CVD, familial hyperlipidaemia, major CV risk factors (such as smoking, high BP, DM or raised lipid levels) or comorbidities increasing CV risk.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>It is recommended to repeat CV risk assessment every 5 years, and more often for individuals with risks close to thresholds mandating treatment.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Systematic CV risk assessment may be considered in men &gt;40 years of age and in women &gt;50 years of age or post-menopausal with no known CV risk factors.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Systematic CV risk assessment in men &lt;40 of age and women &lt;50 years of age with no known CV risk factors is not recommended.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
NICE

1.1.1 For the primary prevention of CVD in primary care, use a systematic strategy to identify people who are likely to be at high risk. [2008, amended 2014]

1.1.2 Prioritise people on the basis of an estimate of their CVD risk before a full formal risk assessment. Estimate their CVD risk using CVD risk factors already recorded in primary care electronic medical records. [2008]

1.1.3 People older than 40 should have their estimate of CVD risk reviewed on an ongoing basis. [2008]

1.1.4 Prioritise people for a full formal risk assessment if their estimated 10-year risk of CVD is 10% or more. [2008, amended 2014]
How?

1.1.7 Be aware that all CVD risk assessment tools can provide only an approximate value for CVD risk. Interpretation of CVD risk scores should always reflect informed clinical judgement. [2008]

1.1.8 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. [new 2014]

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CV risk estimation, using a risk estimation system such as SCORE, is recommended for adults &gt;40 years of age, unless they are automatically categorised as being at high-risk or very high-risk based on documented CVD, DM (&gt;40 years of age), kidney disease or highly elevated single risk factor.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
Risk Scores

https://www.nice.org.uk/guidance/CG181 - Accessed 30/01/17
Example – QRISK2

60 year old male
◦ Heavy Smoker
◦ Cholesterol 7
◦ BP 160/95

QRisk 33.5%

Your results

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

33.5%

In other words, in a crowd of 100 people with the same risk factors as you, 34 are likely to have a heart attack or stroke within the next 10 years.
Framingham 10 year Risk

**Framingham Risk Score for Hard Coronary Heart Disease**
Estimates 10-year risk of heart attack.

**INSTRUCTIONS**
There are several distinct Framingham risk models. MDCalc uses the ‘Hard’ coronary Framingham outcomes model, which is intended for use in non-diabetic patients age 30-79 years with no prior history of coronary heart disease or intermittent claudication, as it is the most widely applicable to patients without previous cardiac events. See the official Framingham website for additional Framingham risk models.

**When to Use**

<table>
<thead>
<tr>
<th>Age</th>
<th>60 years</th>
</tr>
</thead>
</table>

29.5 %
10-year risk of MI or death for this patient

20 %
Average 10-year risk of MI or death

[Copy Results] [Next Steps]
SCORE chart: 10-year risk of fatal cardiovascular disease in populations of countries at high cardiovascular risk

Women

<table>
<thead>
<tr>
<th>Age</th>
<th>Non-smoker</th>
<th>Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>107 11 12 13 14 15 16</td>
<td>7 8 9 10 11 12 13</td>
</tr>
<tr>
<td>60</td>
<td>100 106 112 120 130 136 142</td>
<td>5 6 7 8 9 10 11</td>
</tr>
<tr>
<td>55</td>
<td>100 103 106 110 114 118 122</td>
<td>3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>50</td>
<td>100 101 103 105 107 109 111</td>
<td>2 3 4 5 6 7 8</td>
</tr>
<tr>
<td>40</td>
<td>100 100 100 100 100 100 100</td>
<td>1 2 3 4 5 6 7</td>
</tr>
</tbody>
</table>

Men

<table>
<thead>
<tr>
<th>Age</th>
<th>Non-smoker</th>
<th>Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>26 30 35 41 47</td>
<td>10 12 14 16 18</td>
</tr>
<tr>
<td>60</td>
<td>21 25 29 34 39</td>
<td>8 10 12 14 16</td>
</tr>
<tr>
<td>55</td>
<td>13 16 19 22 26</td>
<td>5 7 9 11 13</td>
</tr>
<tr>
<td>50</td>
<td>12 15 17 20 24</td>
<td>4 6 8 10 12</td>
</tr>
<tr>
<td>40</td>
<td>11 13 15 18 20</td>
<td>3 4 5 6 8</td>
</tr>
</tbody>
</table>

Systolic blood pressure

Cholesterol (mmol/L)

SCORE

- 15% and over
- 10%-14%
- 5%-9%
- 3%-4%
- 2%
- 1%
- <1%

10-year risk of fatal CVD in populations at High CVD risk


www.escardio.org/guidelines
<table>
<thead>
<tr>
<th>Data</th>
<th>Framingham</th>
<th>SCORE</th>
<th>ASSIGN – SCORE</th>
<th>QRSK &amp; QRSK</th>
<th>PROGAM</th>
<th>Pooled Cohort Studies Equations</th>
<th>CUORE</th>
<th>Globorisk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prospective studies: Framingham Heart Study and Framingham offspring study. Latest version includes both.</td>
<td></td>
<td>SHHEC Prospective Study</td>
<td>QRESEARCH database.</td>
<td>Prospective study: 4 Pooled prospective studies ARIC, CHS, CARDIA Framingham (original and offspring studies).</td>
<td>CUORE: Derivation cohort: 8 pooled prospective studies - Atherosclerosis Risk in Communities, Cardiovascular Health Study, Framingham Heart Study original cohort and offspring cohort, Honolulu Program, Multiple Risk Factor Intervention Trial, Puerto Rico Heart Health Program, and Women’s Health Initiative Clinical Trial.</td>
<td>Globorisk: 10 year risk of fatal cardiovascular Disease.</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>3969 men and 4522 women.</td>
<td>117,996 men and 88,000 women.</td>
<td>5540 men and 6757 women.</td>
<td>128 million (GRRK1) 2.23 million (GRRK2)</td>
<td>18,460 men and 6515 women.</td>
<td>11,240 white women, 5090 white men, 2541 African-American women and 1647 African-American men.</td>
<td>7520 men and 13,127 women.</td>
<td>33,323 men and 16,806 women.</td>
</tr>
<tr>
<td>Calculates</td>
<td>10-year risk of CAD events.</td>
<td>10-year risk of CVD events.</td>
<td>10-year risk of CVD events.</td>
<td>10-year risk of CVD events.</td>
<td>20-year risk of major coronary events and cerebrovascular events.</td>
<td>10-year risk for a first atherosclerotic CVD event.</td>
<td>Lifetime risk.</td>
<td>10-year probability of developing a first major CVD event (myocardial infarction or stroke).</td>
</tr>
<tr>
<td></td>
<td>Framingham</td>
<td>SCORE</td>
<td>Asserton – SCORE</td>
<td>QRISK &amp; QRISK</td>
<td>PROCAM</td>
<td>Pooled Cohort Studies Equations</td>
<td>CUMORE</td>
<td>Glorobiskr</td>
</tr>
<tr>
<td>----------------------</td>
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<td>-----------</td>
<td>-------------------------------</td>
<td>--------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Age range (years)</strong></td>
<td>30–75</td>
<td>40–65</td>
<td>30–74</td>
<td>35–74</td>
<td>20–75</td>
<td>20–79</td>
<td>35–69</td>
<td>40–64</td>
</tr>
<tr>
<td><strong>Variables</strong></td>
<td>Sex, age, total cholesterol, HDL-C, SBP, smoking status, DM, hypertensive treatment.</td>
<td>Sex, age, total cholesterol or total cholesterol/ HDL-C ratio, SBP, smoking status. Versions for use in high and low-risk Countries.</td>
<td>Sex, age, total cholesterol, HDL-C, SBP, smoking - no cigs, DM, area based index of deprivation, family history.</td>
<td>QRISK1 - sex, age, total cholesterol to HDL-C ratio, SBP, smoking status, DM, area based index of deprivation, family history, BMI, BP treatment, ethnicity and chronic diseases.</td>
<td>Age, sex, LDL-C, HDL-C, DM, smoking, SBP.</td>
<td>Age, sex, race (White or Other/African American), total cholesterol, HDL-C, SBP, antihypertensive treatment, DM, smoking.</td>
<td>Age, sex, SBP, total cholesterol, HDL-C, smoking, DM, systolic BP.</td>
<td>Age, sex, smoking, total cholesterol, DM, systolic BP.</td>
</tr>
<tr>
<td><strong>Comments/develop.</strong></td>
<td>Latest version includes version based on non-laboratory values only, substituting BMI from lipid measurements.</td>
<td>National, updated Recalibrations.</td>
<td>QRISK2 includes interaction terms to adjust for the interactions between age and some of the Variables.</td>
<td>Report change in the methods (Weibull) allows extension of risk estimation to women and broader age range.</td>
<td>Race specific beta coefficients for risk factors have been incorporated. Calculate shown to overestimate risk in external validations - this may indicate the need for recalibration in certain populations.</td>
<td>Recalibrations have been undertaken for 11 countries.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.1.26 Offer people information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period. This information should be in a form that:

   presents individualised risk and benefit scenarios and
   presents the absolute risk of events numerically and
   uses appropriate diagrams and text. [2008]
The Problem with 10 Year Risk

40 year old female
- Heavy Smoker
- Cholesterol 6.5
- BP 148/95
- Overweight

QRisk 3.9%

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

3.9%

In other words, in a crowd of 100 people with the same risk factors as you, 4 are likely to have a heart attack or stroke within the next 10 years.

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

Your body mass index was calculated as 31.25 kg/m².
Most of us have coronary disease

32 Year Old Female

Atherosclerosis (%)<br>
<20 37% 60% 71% 85% 17% 60% 71% 85%

Age (years) <20-29 30-39 40-49 ≥50

Tuzcu Circ 2001
Atherosclerosis Starts Early

Post mortem aorta specimens

CIMT & Risk factors measured at ages 12-18yrs

Pathobiological Determinants of Atherosclerosis in Youth Study Group, unpublished observation.

Raitakari JAMA 2003
Lifetime Risk

The Value of Starting Early

$5,000 invested each year for 10 years, with no additional contributions. Graph assumes an 11% annual return.

<table>
<thead>
<tr>
<th>Investor</th>
<th>Ending Age 65 Savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>$787,176</td>
</tr>
<tr>
<td>B</td>
<td>$364,615</td>
</tr>
<tr>
<td>C</td>
<td>$166,887</td>
</tr>
<tr>
<td>D</td>
<td>$83,227</td>
</tr>
</tbody>
</table>

Lloyd-Jones Circ. 2006; 113: 791-798
A particular problem relates to young people with high levels of risk factors, where a low absolute risk may conceal a very high relative risk requiring intensive lifestyle advice. Several approaches to communicating about risk to younger people are presented below (refer also to section 2.5.1). These include use of the relative risk chart or ‘risk age’ or ‘lifetime risk’. The aim is to communicate that lifestyle changes can reduce the relative risk substantially as well as reduce the increase in risk that occurs with ageing.
Absolute versus Relative risk

**Absolute risk:** the probability that a person experiences an event

\[
\text{Number needed to treat} = \frac{1}{\text{Absolute risk difference}}
\]

**Relative risk:** ratio of absolute risks for a patient with and without a particular condition
Possibly standardised / adjusted for other factors

e.g. a young smoker has a *high age-standardised relative risk* of heart disease even if *absolute risk* is low
Relative Risk

Figure 3: Relative risk chart, derived from SCORE. Conversion of cholesterol mmol/L to mg/dL: 8 = 310; 7 = 270; 6 = 230; 5 = 190; 4 = 155.
### SCORE chart: 10-year risk of fatal cardiovascular disease in populations of countries at low cardiovascular risk

#### Women

<table>
<thead>
<tr>
<th>Age</th>
<th>Non-smoker</th>
<th>Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>4 5 6 7 8 9 10 11 12 13 14</td>
<td>9 10 11 12 13 14 15 16 17 18 19</td>
</tr>
<tr>
<td>160</td>
<td>2 3 4 5 6 7 8 9 10 11 12</td>
<td>6 7 8 9 10 11 12 13 14 15 16</td>
</tr>
<tr>
<td>140</td>
<td>1 2 3 4 5 6 7 8 9 10 11</td>
<td>4 5 6 7 8 9 10 11 12 13 14</td>
</tr>
<tr>
<td>120</td>
<td>1 2 3 4 5 6 7 8 9 10 11</td>
<td>2 3 4 5 6 7 8 9 10 11 12</td>
</tr>
</tbody>
</table>

#### Men

<table>
<thead>
<tr>
<th>Age</th>
<th>Non-smoker</th>
<th>Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>8 9 10 11 12 13 14 15 16 17 18</td>
<td>5 6 7 8 9 10 11 12 13 14 15</td>
</tr>
<tr>
<td>160</td>
<td>4 5 6 7 8 9 10 11 12 13 14</td>
<td>3 4 5 6 7 8 9 10 11 12 13</td>
</tr>
<tr>
<td>140</td>
<td>2 3 4 5 6 7 8 9 10 11 12</td>
<td>1 2 3 4 5 6 7 8 9 10 11</td>
</tr>
<tr>
<td>120</td>
<td>1 2 3 4 5 6 7 8 9 10 11</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

#### Systolic blood pressure

<table>
<thead>
<tr>
<th>Cholesterol (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 5 6 7 8 9 10 11 12 13 14 15</td>
</tr>
</tbody>
</table>

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## QRISK Report

<table>
<thead>
<tr>
<th>Your score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Your 10-year QRISK®2 score</td>
<td>26.7%</td>
</tr>
<tr>
<td>The score of a healthy person with the same age, sex, and ethnicity*</td>
<td>12.5%</td>
</tr>
<tr>
<td>Relative risk**</td>
<td>2.1</td>
</tr>
<tr>
<td>Your QRISK® Healthy Heart Age***</td>
<td>76</td>
</tr>
</tbody>
</table>

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

The risk age concept

The risk of this 40 year old male smoker with risk factors is the same (3%) as that of a 60 year old man with ideal risk factor levels—the therefore his risk age is 60 years.
Heart Age

https://www.bhf.org.uk/heart-health/risk-factors/check-your-heart-age

Patel BMJ Open 2016
Caveats to be aware of

- **Risk Scores Not used** if type 1 DM, Known CHD, CKD GFR <60, Familial Hypercholesterolaemia

- May underestimate risk for some:
  - HIV, mental illness, medications, autoimmune dx

- Will underestimate CVD risk if already taking BP meds, lipid meds, recent stopped smoking

- Morbid obesity increases risk and >85
A 36 year old Indian man comes to you for assessment of his cardiac risk. His father died of an MI at the age of 38. He doesn’t smoke, is not known to have diabetes and has a BMI of 22kg/m2. Blood pressure is 124/77mmHg. He eats well and exercises regularly.

Which of the following is an appropriate course of action?

A. Request a panel of biomarkers including homocysteine
B. Request a Carotid IMT scan
C. Request a genetic CAD risk score including 9p21
D. Measure his lipid profile and check for FH
E. Advise weight loss given he is South Asian and at risk of diabetes
### Recommendation for individuals <50 years of age

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended to screen all individuals under 50 year of age with a family history of premature CVD in a first degree relative (under 55 year of age in males, under 65 year of age in females) for familial hypercholesterolaemia using a validated clinical score.</td>
<td>I</td>
<td>B</td>
<td>187–189</td>
</tr>
</tbody>
</table>

### Recommendations for assessment of family history/(epi)genetics

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of family history of premature CVD (defined as a fatal or non-fatal CVD event or an established diagnosis of CVD in a first degree male relative before 55 years or female relatives before 65 years) is recommended as part of cardiovascular risk assessment.</td>
<td>I</td>
<td>C</td>
<td>71</td>
</tr>
<tr>
<td>The generalized use of DNA-based tests for CVD risk assessment is not recommended.</td>
<td>III</td>
<td>B</td>
<td>72, 73</td>
</tr>
</tbody>
</table>
Other Considerations

### Recommendations for imaging methods

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery calcium scoring may be considered as a risk modifier in CV risk assessment.</td>
<td>IIb</td>
<td>B</td>
<td>120–125</td>
</tr>
<tr>
<td>Atherosclerotic plaque detection by carotid artery scanning may be considered as a risk modifier in CV risk assessment.</td>
<td>IIb</td>
<td>B</td>
<td>126–128</td>
</tr>
<tr>
<td>ABI may be considered as a risk modifier in CV risk assessment.</td>
<td>IIb</td>
<td>B</td>
<td>129–132</td>
</tr>
<tr>
<td>Carotid ultrasound IMT screening for CV risk assessment is not recommended.</td>
<td>III</td>
<td>A</td>
<td>128, 133</td>
</tr>
</tbody>
</table>

ABI = ankle–brachial index; CV = cardiovascular; IMT = intima–media thickness.

*Class of recommendation.
Level of evidence.
Reference(s) supporting recommendations.

### Recommendation for assessment of circulating and urinary biomarkers

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine assessment of circulating or urinary biomarkers is not recommended for refinement of CVD risk stratification.</td>
<td>III</td>
<td>B</td>
<td>114, 115</td>
</tr>
</tbody>
</table>

Class of recommendation.
Level of evidence.
Reference(s) supporting recommendations.
So risk is High, now what?

- Interpretation of CVD risk scores should always reflect informed clinical judgement
- Lifestyle modifications
First – Lifestyle!

- **Diet**
  - Total fat <30%; Saturated/ trans<7%
  - More mon-unsaturated fats
  - Wholegrain, Sugar, 5-day, 2 portions fish, 4-5 nuts/seeds/legumes

- **Activity**
  - 150mins week moderate, 75 minutes intense activity

- **Smoking cessation**
- **Alcohol reduction**
- **Weight management**
## Healthy diet characteristics

- Saturated fatty acids to account for <10% of total energy intake, through replacement by polyunsaturated fatty acids.
- Trans unsaturated fatty acids: as little as possible, preferably no intake from processed food, and <1% of total energy intake from natural origin.
- <5 g of salt per day.
- 30–45 g of fibre per day, preferably from wholegrain products.
- ≥200 g of fruit per day (2–3 servings).
- ≥200 g of vegetables per day (2–3 servings).
- Fish 1–2 times per week, one of which to be oily fish.
- 30 grams unsalted nuts per day.
- Consumption of alcoholic beverages should be limited to 2 glasses per day (20 g/d of alcohol) for men and 1 glass per day (10 g/d of alcohol) for women.
- Sugar-sweetened soft drinks and alcoholic beverages consumption must be discouraged.
## Classification of physical activity intensity and examples of absolute and relative intensity levels

<table>
<thead>
<tr>
<th>Intensity</th>
<th>MET</th>
<th>Examples</th>
<th>%HR max</th>
<th>RPE (Borg scale score)</th>
<th>Talk Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light</td>
<td>1.1-2.9</td>
<td>Walking &lt;4.7 km/h, light household work.</td>
<td>50-63</td>
<td>10-11</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3-5.9</td>
<td>Walking briskly (4.8–6.5 km/h), slow cycling (15 km/h), painting/decorating, vacuuming, gardening (mowing lawn), golf (pulling clubs in trolley), tennis (doubles), ballroom dancing, water aerobics.</td>
<td>64-76</td>
<td>12-13</td>
<td>Breathing is faster but compatible with speaking full sentences.</td>
</tr>
<tr>
<td>Vigorous</td>
<td>≥6</td>
<td>Race-walking, jogging or running, bicycling &gt;15 km/h, heavy gardening (continuous digging or hoeing), swimming laps, tennis (single).</td>
<td>77-93</td>
<td>14-16</td>
<td>Breathing very hard, incompatible with carrying on a conversation comfortably.</td>
</tr>
</tbody>
</table>
“To prevent heart attack, take one aspirin every day. Take it out for a run, then take it to the gym, then take it for a bike ride...”
Lifestyle fixed (!), next?

• Primary prevention
  ◦ Atorvastatin 20mg
    ◦ 10 year risk >=10%
    ◦ Diabetes
    ◦ CKD

• Secondary prevention
  ◦ Atorvastatin 80mg
<table>
<thead>
<tr>
<th>Total CV risk (SCORE) %</th>
<th>LDL-C levels</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>Lifestyle advice</td>
<td>Lifestyle advice</td>
</tr>
<tr>
<td>Class/Level</td>
<td>I/C</td>
<td>I/C</td>
</tr>
<tr>
<td>≥1 to &lt;5</td>
<td>Lifestyle advice</td>
<td>Lifestyle advice, consider drug if uncontrolled</td>
</tr>
<tr>
<td>Class/Level</td>
<td>I/C</td>
<td>Ila/A</td>
</tr>
<tr>
<td>≥5 to &lt;10, or high-risk</td>
<td>Lifestyle advice</td>
<td>Lifestyle advice and drug treatment for most</td>
</tr>
<tr>
<td>Class/Level</td>
<td>Ila/A</td>
<td>Ila/A</td>
</tr>
<tr>
<td>≥10 or very high-risk</td>
<td>Lifestyle advice, consider drug</td>
<td>Lifestyle advice and concomitant drug treatment</td>
</tr>
<tr>
<td>Class/Level</td>
<td>Ila/A</td>
<td>Ia</td>
</tr>
</tbody>
</table>
Outline

1. CVD Prevention Landscape

2. Assessment of CVD Risk

3. Risk factors and Risk Reduction
   1. Lipids and LDL lowering
   2. Hypertension
   3. Diabetes
Lipid Management Guidelines

Cardiovascular disease: risk assessment and reduction, including lipid modification

Clinical guideline [CG181] Published date: July 2014 Last updated: September 2016
Post-truth

“Relating to or denoting circumstances in which objective facts are less influential in shaping public opinion than appeals to emotion and personal belief”
The Cholesterol Story

Rudolph Virchow 19th Century

Nikolai Anitschkow 1913

Technology to measure lipids ~1930s
1. Observational Evidence

- Ancel Keys Seven Countries Study 1960s
- Framingham & MRFIT Studies 1970s
Prospective Studies Collaboration

900K subjects; IHD mortality >30K
2. Genetic Evidence

- Mendelian Genetics
  - Familial Hypercholesterolaemia
    - Risk of premature fatal/ non fatal MI

- Common Polymorphisms
  - Risk Scores
  - Mendelian Randomization

1. Willer Nat Gen 2013
2. Ference JACC 2012
Lipid Lowering Agents & Mechanisms

- Triparanol
- Nicotinic acid
- Resins/ Bile acid sequestrants
- Probucol
- Fibrates
- Statins
- Ezetemibe
- PCSK9i
3. Therapeutic Evidence

WHO Cooperative Trial
- Clofibrate: 10,577 (Lancet 1980)

LRC Coronary Primary Prevention Trial
- Cholestyramine: 3806 (JAMA 1984)

Helsinki Heart Study
- Gemfibrozil: 4081 (NEJM 1987)

- Some reduction in coronary events but not CVD mortality
- Overall increase in deaths from non CVD causes!
Statins

• 1976 Akira Endo isolates “compactin” from *penicillium citrinum*

• Merck develops levostatin FDA approved 1987

• Mechanism
  ◦ Competitively inhibits HMG-CoA reductase
  ◦ Reduces synthesis of cholesterol
  ◦ Increases uptake by increasing expression of LDL-R (Goldstein & Brown)
Primary Prevention Trials

WOSCOPS
- Pravastatin 40mg v Placebo
- 6595 men (45-64yrs)
- TC >6.5mmol/l
- No prior CHD

- ~26% ↓ LDL
- ~30% ↓ MI/CHD/CVD deaths
- ~22% ↓ All deaths
Secondary Prevention Trials

- 4S Study

- 4444 patients with known CHD

- Simvastatin 40mg v Placebo

- Men with TC of 5.5 - 8mmol/l
4S Study

At ~ 5.4 years
- 35% ↓ LDL
- 42% ↓ CHD deaths
- 30% ↓ All deaths

Figure 1: Kaplan-Meier curves for all-cause mortality
Number of patients at risk at the beginning of each year is shown below the horizontal axis.
### CTTC 2005

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Events (%)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (45 954)</td>
<td>Control (45 002)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>2081 (4.4%)</td>
<td>2769 (6.2%)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1548 (3.4%)</td>
<td>1960 (4.4%)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3337 (7.4%)</td>
<td>4420 (9.8%)</td>
</tr>
<tr>
<td>CABG</td>
<td>712 (1.6%)</td>
<td>1006 (2.2%)</td>
</tr>
<tr>
<td>PTCA</td>
<td>510 (1.1%)</td>
<td>658 (1.5%)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1357 (3.1%)</td>
<td>1776 (3.9%)</td>
</tr>
<tr>
<td>Any coronary revascularisation</td>
<td>2620 (5.8%)</td>
<td>3434 (7.6%)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>105 (0.2%)</td>
<td>99 (0.2%)</td>
</tr>
<tr>
<td>Presumed ischaemic stroke</td>
<td>1235 (2.7%)</td>
<td>1518 (3.4%)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1340 (3.0%)</td>
<td>1617 (3.7%)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>6354 (14.1%)</td>
<td>7994 (17.8%)</td>
</tr>
</tbody>
</table>

22% reduction in risk for 1 mmol reduction in LDL
Higher intensity > Lower intensity statins
Statin risk

• Muscle pain/ Myopathy/ Rhabdomyolysis

• Haemorrhagic Stroke

• Diabetes

• Cancer

Collins Lancet 2016
Today's Random Medical News

Can cause:
- Exercise
- Coffee
- Computer
- Fatty foods
- Stress
- Red wine
- Talcum powder
- Nerve damage
- Glaucoma
- Hypothermia
- Depression
- Arthritis
- twins
- 7 out of 10 men
- Two-income families

According to a report released today...
A 60 year old man with 2 prior MIs and CABG 2 years ago comes for review. He has a BMI of 30kg/m2. His TC is 5.0 and LDL 3.1 mmol/L. He is on rosuvastatin 40mg and states good adherence.

What would you do next?

A. Nothing, continue for now
B. Increase rosuvastatin to 80mg
C. Switch to atorvastatin 80mg and add a fibrate
D. Consider a cholesterol absorption inhibitor
E. Add in Red Yeast Rice Supplements
Ezetimibe

Intestine:
- 1. Inhibition of cholesterol absorption

Liver:
- 2. Reduced cholesterol transport to liver
- 3. Up-regulation of LDL receptors

Peripheral tissue:
- 4. Increased clearance of atherogenic lipoproteins

Statin monotherapy:
- Inhibits endogenous cholesterol synthesis
- Ezetimibe monotherapy:
  - Inhibits dietary cholesterol absorption
  - Enhances re-absorption of biliary cholesterol
- Statin + ezetimibe:
  - Inhibits cholesterol synthesis and absorption
  - Leads to greater LDL-C reduction
Ezetimibe

IMPROVE-IT Enrolled 18,144 patients

- ACS with LDL 1.3 to 2.6mmol/l

- Randomized to
  - Simvastatin 40mg / ezetimibe 10mg
  - Simvastatin 40mg alone

- Primary endpoint: CV death, MI, stroke, UA, revascularisation
IMPROVE-IT - 1° Endpoint

Median LDL ↓ from 1.8 to 1.4mmol/l

Absolute risk ↓ 2%

Relative risk ↓ 6.7%
Ezetimibe

IMPROVE-IT
7% reduction in risk for 0.4mmol reduction in LDL – As predicted

NICE TA 385, 2016

1.2 Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults in whom initial statin therapy is contraindicated.
1.3 Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who cannot tolerate statin therapy (as defined in section 1.6).
Question

A 60 year old man with 2 prior MIs and CABG 2 years ago comes for review. He has a BMI of 30kg/m². His TC is 6.0 and LDL 4.1 mmol/L. He is on rosuvastatin 40mg and ezetimibe 10mg.

What would you do next?

A. Encourage use of plant stanols
B. Eat more nuts and fresh fruit
C. Switch to atorvastatin 80mg and add a fibrate
D. Add colesevelam
E. Refer for PCSK9 monoclonal antibody therapy
PCSK9

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

An enzyme that activates other proteins

A pro-protein convertase
PCSK9 Mechanism

1. LDL Receptors function to remove LDL from the circulation

2. PCSK9 promotes degradation of LDL Receptors (not good – as decreases ability of liver/tissue to remove LDL from circulation)
PCSK9 inhibition

Gene Silencing
- Antisense oligonucleotides (ASO)
- Small interfering RNA (SiRNA)

LDLR mimics - Small peptide inhibitors

Vaccination – Virus Like Particles (VLPs)

Monoclonal antibodies
- Different Types
- PCSK9 inhibitors
  - Alirocumab (Sanofi)
  - Evolocumab (Amgen)
  - Bococizumab (Pfizer)

Potential for Immunogenicity
PCSK9i Efficacy

Sabatine NEJM 2015

Robinson NEJM 2015

Blom NEJM 2014

~60% ↓ in LDL
Very Low Levels & Plaque Regression

Nicholls JAMA 2006

Puri EHJ 2013

<2.0 mmol/L
FOURIER - Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

Evolocumab SC
140 mg Q2W or 420 mg QM

RANDOMIZED DOUBLE BLIND

Placebo SC
Q2W or QM

Follow-up Q 12 weeks

Primary Endpoint

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001

Evolocumab vs Placebo

Sabatine MS et al. NEJM 2017
ODYSSEY – Trial Design

N=18,924

- Post-ACS patients (1 to 12 months)
- Run-in period of 2–16 weeks on high-intensity or maximum-tolerated dose of atorvastatin or rosuvastatin
- At least one lipid entry criterion met

- Randomization

- Alirocumab SC Q2W
- Placebo SC Q2W
Primary Endpoint

![Graph showing Primary Endpoint: MACE (%) over years since randomization. The graph compares Placebo and Alirocumab treatments. The Hazards Ratio (HR) is 0.85, with a 95% CI of 0.78 to 0.93, and a P-value of 0.0003. The graph is presented at ACC 2018.](image)
NICE & PCSK9i (TA 2016)

With Familial Hypercholesterolaemia
- LDL > 3.5mmol/l if also has CVD
- LDL > 5mmol/l if no CVD

With established CVD and uncontrolled LDL
- LDL > 4 mmol/l
- LDL > 3.5 mmol/l (recurrent or very high risk CVD)

High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.

Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease)

1. https://www.nice.org.uk/guidance/TA394 - Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia, Accessed 30/03/2019
2. https://www.nice.org.uk/guidance/TA393 - Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia, Accessed 30/03/2019
ESC Consensus

2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia


Landmesser EHJ 2018
ESC Consensus

Patients with familial hypercholesterolaemia without clinically diagnosed ASCVD on maximally tolerated statin plus ezetimibe therapy

Check for additional indices of risk severity
- Diabetes mellitus with target organ damage (e.g. proteinuria), or with a major risk factor (e.g. marked hypertension)
- Lipoprotein(a) >50 mg/dL
- Major risk factors: smoking, marked hypertension
- >40 years of age without treatment
- Premature ASCVD (<55 years in males and <60 years in females) in first-degree relatives
- Imaging indicators (refer to text)

No additional indices of risk severity
LDL-C >4.5 mmol/L (>180 mg/dL)

Additional indices of risk severity
LDL-C >3.6 mmol/L (>140 mg/dL)*

* Confirmed on two consecutive occasions

Consider a PCSK9 inhibitor

Landmesser EHJ 2018
LDL Lowering by any means reduces risk

Relative risk reduction per 1-mmol/L (38.7-mg/dL) reduction in LDL-C:
23% (relative risk, 0.77 [95% CI, 0.75-0.79]; P<.001)

Interpretation of the evidence for the efficacy and safety of statin therapy

Caveats

- Not everyone with high TC gets CHD
- Not everyone with CHD has high TC
- Some FH patients don’t have CHD
- Many factors affect retention of LDL in plaque – high circulating LDL is a requisite but not the only factor
- **Any** level of LDL may be too high for a given individual

---

Castelli AJC 1998

Virmani ATV 2000
A 65 year old man with a recent MI and CABG comes for review at 3 months. He has a BMI of 32kg/m². His TC at baseline before treatment was 5.0 and LDL 3.6 with a non-HDL of 4mmol/L. He is on atorvastatin 80mg. You send him for a repeat lipid profile.

Which of the following is incorrect?

A. His LDL target should ideally be below 1.8mmol/L
B. His Non-HDL target should ideally be 2.4mmol/L or below
C. A repeat lipid profile is not required as there are no formal lipid targets in secondary prevention once high dose statin is started
D. A non fasting lipid profile is acceptable and sufficient to assess response to therapy
E. If his LDL remains high compliance may be an issue
NICE – use statins whatever the baseline LDL/non-HDL

• **Primary prevention**
  ◦ Atorvastatin 20mg
    ◦ 10 year risk $\geq 10\%$
    ◦ Diabetes
    ◦ CKD

• **Secondary prevention**
  ◦ Atorvastatin 80mg

• **Aim** $>40\%$ reduction in non-HDL

https://www.nice.org.uk/guidance/CG181 - Accessed 30/01/17
NICE “Targets”

1.3.28 Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment (both primary and secondary prevention, including atorvastatin 20 mg for primary prevention) at 3 months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol. If a greater than 40% reduction in non-HDL cholesterol is not achieved:

- discuss adherence and timing of dose
- optimise adherence to diet and lifestyle measures
- consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement. [new 2014]
Statin Response Variation

A. Prava 40mg, LIPID
B. Rosuva 20mg, JUPITER
C. Atorva 10-80mg, TNT
D. Placebo, AFCAPS-TexCAPS

Boekholdt, JACC 2014
ESC Targets

Risk Categories

LDL targets guided by these categories

3 LDL targets:
- 1.8mmol/L
- 2.6mmol/L
- 3.0mmol/L
## ESC LDL Targets

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients at VERY HIGH CV risk, an LDL-C goal &lt;1.8 mmol/L (&lt;70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients at HIGH CV risk, an LDL-C goal &lt;2.6 mmol/L (&lt;100 mg/dL), or a reduction of at least 50% if the baseline is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In the remaining patients on LDL-C lowering treatment, an LDL-C goal &lt;3.0 mmol/L (&lt;115 mg/dL) should be considered.</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>
Question

A 50 year old man with a prior MI, complains he can no longer take his atorvastatin 80mg as he has muscle aches. He stopped his statin 4 weeks ago and feels better. His GP confirms CK was normal while on statins.

What would be your next step?

1. Try him on rosuvastatin 20mg
2. Try him on simvastatin 40mg
3. Add a fibrate such as fenofibrate
4. Replace the statin with ezetimibe
5. Refer for PCSK9 as he is at high risk
Statin Intolerance

Establish causality - washout

Re-challenge lower dose in same intensity group

Alternate day or 1-2x weekly dosing (Atorva/rosvuva)

Change to lower intensity group

3 different statins before specialist referral
ESC - Statins

*Note suggested use of bile acid absorption inhibitors and fibrates – and LDL goal directed

Can use ezetimibe if statin not tolerated – both NICE and ESC recommend this
Question

Which of the following is considered a high intensity or potent statin?

A. Atorvastatin 20mg
B. Simvastatin 20mg
C. Pravastatin 40mg
D. Fluvastatin 40mg
E. Simvastatin 40mg
## Statin Intensity

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>-</td>
<td>-</td>
<td>21%</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>-</td>
<td>20%</td>
<td>24%</td>
<td>29%</td>
<td>-</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>-</td>
<td>27%</td>
<td>32%</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>-</td>
<td>37%</td>
<td>43%</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>38%</td>
<td>43%</td>
<td>48%</td>
<td>53%</td>
<td>-</td>
</tr>
</tbody>
</table>

1. 20\%–30\%: low intensity.
2. 31\%–40\%: medium intensity.
3. Above 40\%: high intensity.
4. Advice from the MHRA: there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80 mg 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 the benefits are expected to outweigh the potential risks.
Question

A 55 year old man has TC 6, LDL 4 and TG 3.5mmol/L. He had an MI 1 year ago and has a family history of premature MI. You switch his simvastatin to atorvastatin 80mg and he responds well initially. He now presents for review and you notice his TG level has risen to 15mmol/L, LDL unmeasurable. There are no clear secondary causes, he does not drink alcohol and is not diabetic.

What would you do next?

A. Add in ezetimibe
B. Add in gemfibrozil
C. Add in fenofibrate
D. Refer for apheresis
E. Consider PCSK9 therapy

For CV risk reduction or pancreatitis risk reduction?
Other agents for CVD risk?

**NICE**
- Fibrates
- Nicotinic acid
- Bile acid sequestrants
- Omega-3 fatty acids
- Stanols/Stanols
- Co-enzyme Q10

**ESC**

Use fibrates with statins if TG >2.3mmol/L and high risk IIa/B (mixed dyslipidaemia)

Can also add n-3 fatty acids if needed but evidence lacking at time of guidelines

Avoid gemfibrozil + statin

A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided.

If TG are not controlled by statins or fibrates, prescription of n-3 fatty acids may be considered to decrease TG further, and these combinations are safe and well tolerated.
REDUCE-IT

• 8179 Patients with CVD (or diabetes) on statin therapy with TGs 1.52-5.63mmol/L and LDL 1.06-2.59mmol/L

• 4g daily* of icosapent ethyl (omega-3 oil eicosapentaenoic acid, pure EPA)

• 8179 patients enrolled, double blind RCT, followed median f/u 4.9 years

• 25% relative risk reduction first events (>40% recurrent events)

• Possible AF and bleeding signals

* Most studies 1 g daily of mixed omega-3 oils. JELIS trial 1.8-g with 19% benefit (post hoc)

STRENGTH Trial due 2020
Drugs for High Triglycerides

**To treat risk of pancreatitis not CVD risk under NICE**

### Lipid Effects of Drug Classes in Dyslipidemia and Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Type of Dyslipidemia/medication</th>
<th>TG</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Non-HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Range, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed dyslipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>-10 to -37</td>
<td>-26 to -63</td>
<td>+5 to +16</td>
<td>-44 to -60</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>-19 to -44</td>
<td>-6 to +25</td>
<td>-5 to +7</td>
<td>-1 to -7</td>
</tr>
<tr>
<td>Fenofibrate, fenofibric acid, and gemfibrozil</td>
<td>-24 to -36</td>
<td>-5 to -31</td>
<td>+10 to +16</td>
<td>-17</td>
</tr>
<tr>
<td>Niacin</td>
<td>-5 to -38</td>
<td>-3 to -17</td>
<td>+10 to +26</td>
<td>NR</td>
</tr>
<tr>
<td>Isolated hypertriglyceridemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>-21 to -52</td>
<td>-27 to -45</td>
<td>+3 to +22</td>
<td>-29 to -52</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>-26 to -52</td>
<td>+17 to +49</td>
<td>+9 to +14</td>
<td>-10 to -14</td>
</tr>
<tr>
<td>Fenofibrate, fenofibric acid, and gemfibrozil</td>
<td>-46 to -62</td>
<td>+3 to +47</td>
<td>+18 to +23</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported.

Exclude Secondary Causes

<table>
<thead>
<tr>
<th></th>
<th>Lipid Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cholesterol</td>
</tr>
<tr>
<td>Alcohol excess</td>
<td>↑</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>↑</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>↑↑</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>↑</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>↑↑</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>↑/↑↑↑</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>↑↑</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>↑/-</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>↑/↑↑↑</td>
</tr>
<tr>
<td>Beta blockers</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>↑</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>↑</td>
</tr>
<tr>
<td>HIV antiretroviral agents</td>
<td></td>
</tr>
<tr>
<td>Oral oestrogens</td>
<td>↑</td>
</tr>
<tr>
<td>Retinoids</td>
<td>↑↑/↑</td>
</tr>
</tbody>
</table>

Poor diet and lack of physical activity may also have an adverse effect on lipid profile.
Dyslipidaemias

Fredrickson Classification of the Hyperlipidemias

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Lipoprotein(s) elevated</th>
<th>Serum cholesterol concentration</th>
<th>Serum triglyceride concentration</th>
<th>Relative frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>Normal to ↑</td>
<td>↑↑↑↑↑</td>
<td>&lt;1</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>↑↑</td>
<td>Normal</td>
<td>10</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL and VLDL</td>
<td>↑↑</td>
<td>↑↑</td>
<td>40</td>
</tr>
<tr>
<td>III</td>
<td>IDL</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>&lt;1</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>Normal to ↑</td>
<td>↑↑</td>
<td>45</td>
</tr>
<tr>
<td>V</td>
<td>VLDL and chylomicrons</td>
<td>↑ to ↑↑</td>
<td>↑↑↑↑↑</td>
<td>5</td>
</tr>
</tbody>
</table>
Lipid Pathways
Question

A 40 year old male presents with a STEMI. His BMI is 27. His TC is 9.8 and LDL is 8mmol/L with a TG of 1.1mmol/L. He has no other risk factors aside from a brother who had CABG at 48 years of age.

What is the most likely underlying problem?

A. Homozygote risk carrier at 9p21
B. Deletion of chromosome 8
C. Mutation in LDLR
D. Missense mutation in SORT1
E. Poor diet and lifestyle
Familial Hypercholesterolaemia
FH: A treatable cause of CHD

- Autosomal dominant disorder of lipid metabolism
- Leads to high levels of LDL cholesterol from early childhood
- Treatable cause of premature CHD and CVD
- Several mutations – most in LDLR or ApoB genes (currently able to find 80%)
FH and CVD Risk

Nordestgaard EHJ 2013
Question

A 40 year old man with TC 7.7 and LDL 5.2mmol/L, presents for review of his cholesterol. He has 2 uncles who dies from MI in their 40s.

According to the S-B criteria he has:

A. Possible FH
B. Definite FH
C. Unlikely FH
D. Need to measure 3 lipid profiles first
## Simon-Broome & DLCN

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Total cholesterol concentration above 7.5 mmol/L in adults or a total cholesterol concentration above 6.7 mmol/L in children aged less than 16 years, or low-density lipoprotein cholesterol concentration above 4.9 mmol/L in adults or above 4.0 mmol/L in children</td>
</tr>
<tr>
<td>b</td>
<td>Tendinous xanthomata in the patient or a first-degree relative</td>
</tr>
<tr>
<td>c</td>
<td>DNA-based evidence of mutation in the LDLR or APOB gene</td>
</tr>
<tr>
<td>d</td>
<td>Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative</td>
</tr>
<tr>
<td>e</td>
<td>Family history of raised total cholesterol concentration above 7.5 mmol/L in a first- or second-degree relative</td>
</tr>
</tbody>
</table>

### Diagnosis

A ‘definite’ FH diagnosis requires either criteria a and b or criterion c. A ‘probable’ FH diagnosis requires criteria a and d or criteria a and e.

### Parameter | Points
---|---
Familial history
First-degree relative with early vascular/ coronary disease (male <45 y, female <55 y)
OR
Adult first-degree relative with LDL-C > 160 mg/dL
First-degree relative with xanthoma and/or corneal arcus
OR
First-degree relative <18 y with LDL-C > 130 mg/dL
Clinical history
Patient with early coronary artery disease (male <45 y, female <55 y)
Patient with early cerebral or peripheral arterial disease (male <45 y, female <55 y)
Physical examination
Xanthoma
Corneal arcus (<45 y)
Level of LDL-C (mg/dL)
≥330
250–329
190–249
155–189
Genetic testing
Presence of functional mutation of LDL-R, ApoB-100, or PCSK9 gene
(Diagnostic of FH)
Definite FH
Probable FH
Possible FH
FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.
Why you should be aware FH?

• Know it exists & measure lipid profiles
• Look for TC>7.7, LDL >4.9 and usually some sort of family or personal history of CHD
• A high TG suggests a mixed dyslipidaemia – still high risk but its unlikely FH
• Atorva 40 or 80mg not enough – may need newer agents (recheck LDL)
• Will require genetic testing to confirm diagnosis but importantly permit family cascading – prevention!
**Box 7** Individuals who should be considered for lipoprotein(a) screening

<table>
<thead>
<tr>
<th>Individuals with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Premature CVD</td>
</tr>
<tr>
<td>• Familial hypercholesterolaemia</td>
</tr>
<tr>
<td>• A family history of premature CVD and/or elevated Lp(a)</td>
</tr>
<tr>
<td>• Recurrent CVD despite optimal lipid-lowering treatment</td>
</tr>
<tr>
<td>• $\geq 5%$ 10-year risk of fatal CVD according to SCORE</td>
</tr>
</tbody>
</table>
Outline

1. CVD Risk & Prevention

2. Risk factors
   1. Lipids
   2. Hypertension
   3. Diabetes
Hypertension

Every 10mmHg reduction in systolic BP reduces the risk of major cardiovascular events by 20%.

4 out of 10 people with hypertension — (that’s 25,000 people in the average CCG) are not treated to target.

Between 50-80% of patients with high blood pressure do not take all of their prescribed medicine.
Definitions of Hypertension

NICE

140/90

150/90 – Over 80s

ABPM/ HBPM

135/85

145/85

Table 9 Definitions of hypertension according to office, ambulatory, and home blood pressure levels

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office BP*</td>
<td>≥140 and/or ≥90</td>
<td></td>
</tr>
<tr>
<td>Ambulatory BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime (or awake) mean</td>
<td>≥135</td>
<td>≥85</td>
</tr>
<tr>
<td>Night-time (or asleep) mean</td>
<td>≥120</td>
<td>≥70</td>
</tr>
<tr>
<td>24 h mean</td>
<td>≥130</td>
<td>≥80</td>
</tr>
<tr>
<td>Home mean</td>
<td>≥135</td>
<td>≥85</td>
</tr>
</tbody>
</table>

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
*Refers to conventional office BP rather than unattended office BP.
Targets

**NICE**

Just aim below 140/90 or 150/90 in over 80s

**ESC**

More aggressive in latest guidance (120-129mmHg in young; 130-139mmHg in >65) but not below 120 in any group
Lifestyle

- Salt intake
- Alcohol
- Diet
- Weight loss
- Exercise
- Smoking
- Caffeine intake
# ESC Classification of BP

## Table 3  Classification of office blood pressure and definitions of hypertension grade

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120</td>
<td>and</td>
</tr>
<tr>
<td>Normal</td>
<td>120–129</td>
<td>80–84</td>
</tr>
<tr>
<td>High normal</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Grade 1 hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

BP = blood pressure; SBP = systolic blood pressure.

*BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.

*Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.

The same classification is used for all ages from 16 years.
Figure 3: Initiation of blood pressure-lowering treatment (lifestyle changes and medication) at different initial office blood pressure levels. BP = blood pressure; CAD = coronary artery disease; CVD = cardiovascular disease; HMOD = hypertension-mediated organ damage.
Aged under 55 years

Aged over 55 years or black person of African or Caribbean family origin of any age

Step 1

A

C

Step 2

A + C

Step 3

A + C + D

Resistant hypertension
A + C + D + consider further diuretic

or

alpha-blocker

or

beta-blocker

Consider seeking expert advice

Step 4

A – ACE inhibitor or angiotensin II receptor blocker (ARB)

C – Calcium-channel blocker

D – Thiazide-like diuretic
Figure 4  Core drug treatment strategy for uncomplicated hypertension. The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMOD = hypertension-mediated organ damage; MI = myocardial infarction; o.d. = omni die (every day); PAD = peripheral artery disease.
Outline

1. CVD Risk & Prevention

2. Risk factors
   • Lipids
   • Hypertension
   • Diabetes
Diabetes

Almost 3.7 million people have been diagnosed with diabetes in the UK.

12.3 million people are at increased risk of Type 2 diabetes.

4.6 million people are living with diabetes in the UK.

DIABETES BY THE NUMBERS

- 2-3x increased risk for heart disease
- 30% of coronary stents implanted in 2011
- 280,000 heart attacks annually
- 2-4x higher heart disease morbidity and mortality rates
- 60% chance of dying from heart disease

© TheDiabetesCouncil.com
Diabetes

**DCCT Units = %**

**IFTT = mmol/mol**

- **6 = 42**
- **6.5 = 48**
- **7.8 = 62**
- **11.1 = 98**
Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

1. **IF HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions**
   - Offer additional non-metformin intervention.
   - Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%).
   - **FIRST INTENSIFICATION**
     - If triple therapy is not effective (7.5%):
       - Consider dual therapy with:
         - metformin and a DPP-4i
         - metformin and a GLP-1R agonist
         - metformin and an SGLT-2i
     - Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%).

2. **IF HbA1c rises to 58 mmol/mol (7.5%)**
   - Consider triple therapy with:
     - a DPP-4i and an SU
     - a GLP-1R agonist and an SU
     - an SGLT-2i and an SU
   - Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%).

3. **IF HbA1c rises to 58 mmol/mol (7.5%)**
   - Consider insulin-based treatment.
   - Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%).

**METFORMIN CONTRAINDICATIONS OR NOT CONSIDERED**
- Type 2 diabetes who have a BMI of 35 kg/m² or higher (weight loss is usually more effective).
- Allergy to metformin.
- Pregnancy.
- Severe hepatic or renal impairment.
- Severe systemic conditions (e.g., heart failure, liver failure).
- History of lactic acidosis.
- History of hypoglycaemia.

**Insulin-based treatment**
- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies.
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine if the person needs assistance to inject insulin. Lifetime is restricted by recurrent symptomatic hypoglycaemic episodes or would otherwise need to discontinuate NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem or blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.
- Monitor people on insulin for the need to change the treatment.

**SGLT-2i in combination with insulin with or without other antihyperglycaemic drugs is an option**.

---

**Type 2 diabetes in adults management**, NICE guideline NG82. Published December 2015, last updated April 2017. © National Institute for Health and Care Excellence 2015. All rights reserved.
Diabetes & CV Outcomes

Historically no benefit from diabetes control for macrovascular complications

Some new agents increased risk of CV outcomes

- FDA mandated close monitoring

<table>
<thead>
<tr>
<th>Study</th>
<th>Diabetes type</th>
<th>CV composite</th>
<th>MI</th>
<th>CV mortality</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT/EDIC (17,26,27)</td>
<td>Type 1</td>
<td>←</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
</tr>
<tr>
<td>UKPDS</td>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main randomization (SU or insulin vs. conventional therapy) (18,28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional randomization of overweight patients (metformin vs. SU vs. conventional therapy) (19,28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD (20,30)</td>
<td>Type 2</td>
<td>←</td>
<td>↓</td>
<td>←</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE (21)</td>
<td>Type 2</td>
<td>←↑</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>VADT (22,29)</td>
<td>Type 2</td>
<td>←</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
</tbody>
</table>

Left columns show initial results; right columns show long-term follow-up. ←, Neutral effect; ↓, decrease; ↑, increase; ---, not assessed/reported; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; SU, sulfonylurea. Adapted from Bergenstal et al. (97). *Metformin group only. †A decrease was reported in a combined CV/microvascular composite but was found to be mostly attributable to nephropathy.
# Clinical Goals for CVD Risk Factors

<table>
<thead>
<tr>
<th>Smoking</th>
<th>No exposure to tobacco in any form.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish.</td>
</tr>
<tr>
<td>Physical activity</td>
<td>At least 150 minutes a week of moderate aerobic PA (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination thereof.</td>
</tr>
<tr>
<td>Body weight</td>
<td>BMI 20–25 kg/m². Waist circumference &lt;94 cm (men) and or &lt;80 cm (women).</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;140/90 mmHg. Or Lower but not &lt;120mmHg</td>
</tr>
</tbody>
</table>

## Lipid

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Very high-risk: &lt;1.8 mmol/L (&lt;70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-risk: &lt;2.6 mmol/L (&lt;100 mg/dL) or a reduction of at least 50% if the baseline is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL). Low to moderate risk: &lt;3.0 mmol/L (115 mg/dL).</td>
</tr>
</tbody>
</table>

### Non-HDL-C<sup>b</sup>

<2.6, <3.3 and <3.8 mmol/L (<100, <130 and <145 mg/dL) are recommended for very high, high and low to moderate risk subjects, respectively

### HDL-C

No target but >1.0 mmol/L (>40 mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicate lower risk.

### Triglycerides

No target but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.

## Diabetes

HbA1c: <7% (<53 mmol/L). NICE <6.5% or <7% if hypo; 7.5%
Thank You