Lipids for Medics in Primary Care

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Format

1. CV Risk and lipid lowering
2. Familial Hypercholesterolaemia
3. Hypertriglyceridaemia
4. Lipoprotein(a)
Case 1

- 59 year old male
- Barrister
- Asymptomatic
- No Family History of CVD

- Total cholesterol 7.2 mmol/L
- HDL-c 1.4 mmol/L
- LDL 4.1 mmol/l
- TG 1.4 mmol/l
- Non-HDL 5.8 mmol/l
Non-HDL-C captures cholesterol in all atherogenic (apoB-containing) lipoproteins

Non-HDL-C = Total cholesterol – HDL-C
Case 1

• 59 year old male
• Barrister
• Asymptomatic
• No Family History of CVD
• Total cholesterol 7.2 mmol/L
• HDL-c 1.4 mmol/L
• LDL 4.1 mmol/L
• TG 1.4 mmol/L
• Non-HDL 5.8 mmol/L

Does he need a statin?
Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014]


Obviously:
• Exclude secondary causes of hypercholesterolaemia
  (drugs, hypothyroidism, nephrotic syndrome, anorexia etc)

Do not use a risk assessment tool in people with:
• Secondary prevention
• type 1 diabetes
• eGFR less than 60 and/or albuminuria
• familial hypercholesterolaemia

Underestimates risk in people:
• treated for HIV
• with serious mental health problems
• taking medicines that can cause dyslipidaemia
  (eg antipsychotics, steroids or immunosuppressant)
• with autoimmune disorders such as SLE
Your heart age is about 66 compared to a person of the same age, gender and ethnicity with optimal risk factors.
On average, expect to survive to age 79 without a heart attack or stroke.

Your risk of a heart attack or stroke in the next 10 years is 11% assuming you don’t die of anything else.

Interventions:
- Future smoking category: I quit
- Systolic Blood Pressure: 130 → 130
- Total Cholesterol: 7.2 → 7.2
- HDL Cholesterol: 1.4 → 1.4
- NonHDL Cholesterol: 5.8
- BMI: 26.0

Reset
On average, expect to survive to age 81 without a heart attack or stroke gaining 2.0 years through interventions.

Your risk of a heart attack or stroke in the next 10 years is 6.4% assuming you don’t die of anything else.
• What target lipids are we aiming for?
Aim for a greater than 40% reduction in non-HDL cholesterol.

Aim for non-HDL-c of <2.5 mmol/L (broadly equivalent to an LDL-c of <1.8 mmol/l)
LDL in nature

Hochholzer W & Giugliano RP. Ther Adv Cardiovasc Dis 2010;
LDL and CV risk

Eur Heart J. 2017
LDL-C and atheroma formation
Statin intolerance

Consider if statin-attributed symptoms and individual CVR favor statin continuation/reinitiation

- Muscle symptoms
  - Pravastatin or Rosuvastatin

- Liver dysfunction
  - Try pravastatin or rosuvastatin

- Sleep disturbance/ headache/ amnesia/other neuro sx

CK < 4xULN

- 6 week washout of statin
- Symptoms persist-
  - Statin re-challenge
  - Symptom free-
    - Continue statin
  - Symptoms Re-occur
    - 1) Low dose third statin
    - 2) Potent statin alternate day/ once/ twice weekly

CK > 4xULN +/- rhabdomyolysis

- 6 week washout of statin until Normal CK/Cr
- Symptoms improve-
  - Second statin at usual/low dose
  - Symptoms persist-
    - Statin re-challenge

Achieve LDL-C goal with maximally tolerated dose of statin
SAMSON
Self-assessment toolkit trial
for people who have stopped statins due to adverse symptoms

4 months nothing
4 months placebo
4 months statin

www.samson-trial.org
## Statins and LDL reduction

<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>
Statins!

- For every 10000 patients treated with statins, 500 CVD events will be avoided but 1 case rhabdomyolysis, 5 cases myopathy and 75 cases diabetes mellitus.
- Annual glucose / HbA1c recommended
- Benefit of statin outweighs risk of DM
- Mechanism unclear but higher risk in patients with prediabetes
- Starting statin doesn’t affect DM management
Summary Case 1

- Use QRISK to estimate risk of CV event
- If risk >10%, recommend atorvastatin 20mg od
- Aim for non-HDL-C <2.5 mmol/l
Case 2 19 yo man

- Referred by plastic surgeon
- Fit and well
- Professional footballer
- FHx: Father MI aged 40, died aged 46

- Total cholesterol 10.2 mmol/L
- HDL-c 1.4 mmol/L
- TG 1.1
Case 2 Questions

• What is his LDL-c?

• Friedewald equation

\[
\text{LDL-C} = \text{Total cholesterol} - \text{HDL-C} - \frac{\text{TG}}{2.2}
\]

\[
10.2 - 1.4 - \frac{1.1}{2.2}
\]

\[
= 8.3 \text{ mmol/l}
\]
Case 2 Questions

- What is the genetic basis of his hypercholesterolaemia?
1. CV Risk and lipid lowering
2. Familial Hypercholesterolaemia
3. Hypertriglyceridaemia
4. Lipoprotein(a)
Familial hypercholesterolaemia

- The most common dominantly inherited disorder
- Autosomal dominant disorder
- High levels of low density lipoprotein cholesterol
- Early coronary artery disease
- Heterozygous ~1 in 250
- Homozygous ~1/1,000,000
An unrecognised, potentially fatal, treatable disease

- **Genetic disorder** – we know the genes involved
- **Common** – as Type 1 DM
- 50% men will have MI by age of 50 and 60% of women by age of 60
- Treatable
- Underdiagnosed
Genetics of FH

What genes are affected in FH?

- LDL-R mutations 93% chromosome 19
- ApoB 5% chromosome 2
- PCSK9 2% chromosome 1

LDL removed from blood

PCSK9 (Proprotein convertase subtilisin/kexin 9)

LDL-r

ApoB
Why do FH patients have such premature CHD?

FH patients have high LDL-C from Birth → high LDL-C BURDEN

LDL-Burden = LDL-C level x years exposure

Like smoking pack-years

By 45y FH patient has accumulated LDL-C exposure of non-FH 70y old, explaining high CHD risk and need for aggressive lipid-lowering

Starr et al; 2008
Elevated LDL cholesterol → Atherosclerosis → Coronary heart disease

Liver with only 50% functional LDL receptors

Mutations in LDL receptor, apolipoprotein B or PCSK9

Myocardial infarction, Angina pectoris
Presentation

• After a CV event
• Routine cholesterol testing
• Cascade screening
• Via dermatology clinic
Presentation

- Cholesterol 7.0-14 mmol/L

- Tendon xanthomata are virtually diagnostic of heterozygous familial hypercholesterolaemia, and occur in about 70% of affected individuals after the age of 20 years
Presentation

xanthelasma and premature corneal arcus are commonly found but are less specific signs.
Diagnosis

- Exclude secondary causes of hypercholesterolaemia
- Phenotypic and/or genetic testing
- Genetic testing increases diagnostic accuracy
Simon-Broome criteria

- *TC > 7.5mmol/l or LDL > 4.9mmol/l in adults
- *TC > 6.7mmol/l or LDL > 4.0mmol/l in children
- PLUS tendon xanthoma (absence does not exclude)
- OR PLUS DNA confirmation

- Biochemical criteria as above
- PLUS family history of CVD (<50 2nd degree relative, <60 1st degree relative) OR of high cholesterol

• NOTE – mutation identified in ~80% of „clinically definite“ FH, only 30% of „possible“ FH!
Assess additional CVD risk factors

• Presence of additional CVD risk factors should guide the intensity of management
  • Hypertension, diabetes, obesity, smoking
  • Lipoprotein(a)
  • Level and duration of untreated LDL cholesterol
  • Prematurity of the family & personal history of CVD
  • Framingham and other CVD risk equations should not be used

• Cardiovascular imaging may be useful for assessing asymptomatic patients
  • Cardiac computed tomography
  • Carotid ultrasonography
Management

• Lifestyle modification
• LDL lowering drugs
• LDL-Apheresis
Can LDL be lowered in FH patients?

Hadfield et al; 2007
LDL-lowering

• Therapy should ideally aim for at least 50% reduction in plasma LDL cholesterol, followed by
  • LDL cholesterol < 2.5 mmol/L (no CVD or other risk factors)
  • LDL cholesterol < 1.8 mmol/L (with CVD or other risk factors)
• Statin therapy - monitor hepatic aminotransferases, glucose and creatinine
• Drug combinations
  – ezetemibe
  – bile acid sequestrants
  – PCSK9 inhibitors
Statins decrease mortality in FH

![Graph showing standardised mortality ratio comparison between pre and post statin usage in 20-59 year olds, with a 2-fold decrease and an 8.1 reduction in life expectancy, suggesting approximately 9 years gained by statins.]

Simon Broome UK FH Registry papers; Athero, 1999
LDL-lowering in women

• All women of child-bearing age should receive pre-pregnancy counselling
  • Appropriate advice on contraception before starting a statin
• Statins and other systemically absorbed lipid regulating drugs should be discontinued 3 months before conception, as well as during pregnancy and lactation
PCSK-9 inhibitors

- Binding of PCSK9 to LDLR promotes lysosomal degradation of LDLR
- Degradation of LDLR

LDLR

PCSK9

Endosome

Lysosome

LDL-C uptake

Plasma membrane

LDL-C
PCSK-9 inhibition in FH

Raal et al, Lancet. 2014
Effect on the coronaries

Primary Endpoint: PAV

![Graph showing change in PAV for Statin Monotherapy and Statin-Evolocumab treatments.]

- **Yellow** = lumen
- **Blue** = external elastic membrane
- **Green** = atheroma

Nicholls et al, JAMA, 2016
### PCSK-9 inhibition and NICE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Without CVD</th>
<th>With CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary non-familial hypercholesterolaemia or mixed dyslipidaemia</td>
<td>Not recommended at any LDL–C concentration</td>
<td>Recommended only if LDL–C concentration is persistently above 4.0 mmol/litre</td>
</tr>
<tr>
<td>Primary heterozygous-familial hypercholesterolaemia</td>
<td>Recommended only if LDL–C concentration is persistently above 5.0 mmol/litre</td>
<td>Recommended only if LDL–C concentration is persistently above 3.5 mmol/litre</td>
</tr>
</tbody>
</table>

1. High risk of CVD
2. Very high risk of CVD
Lipoprotein apheresis

• LA should be considered in patients with heterozygous FH with CHD who cannot achieve LDL cholesterol targets or have progressive disease despite maximal drug therapy
Cascade screening

It is Common - Frequency FH \(~1/500\)  →  120,000 in UK

Same as childhood diabetes

It is underdiagnosed < 15,000 known, particularly in the < 35 years group (600/14,000 children)

Marks, et al 2004
HEARTUK 2008
PRIMIS Familial Hypercholesterolaemia FH Case-Finder tool

https://www.nottingham.ac.uk/primis/

The FHC tool is designed to help practices case find patients who may have FH and also may be missing a coded diagnosis.

FHC tool is quick and simple to run within practices, and free to download for any PRIMIS registered users.

Developed in collaboration with the Primary Care Stratified Medicine (PRISM) research group (formerly the Applied Genetics and Ethnicity Research Group) at the University of Nottingham. This tool is based on the FAMCAT algorithm\(^1\) developed by academics in the Applied Genetics and Ethnicity research group.
Homozygous FH
Case 3

Patient F
29 y
Xanthomas age 2
TC 29mmol/l age 2
Statins since age 5
Apheresis since 6y
CP 3rd trimester age 19
CP during labour age 23 PCI
Supravalvular aortic stenosis
Bilateral carotid plaques

Patients’ permission obtained

Patient F’s son
Heterozygous FH

Patient F’s husband
Heterozygous FH

Patient F’s daughter, age 6
Homozygous FH, apheresis at the Evelina.
Homozygous FH

- Cholesterol 15-30 mmol/L
- Two major genetic defects in LDL metabolism
- Tendon and cutaneous xanthomomas often before age 10 years
- CHD onset in childhood
- Poorly responsive to drugs; apheresis often indicated
Lipoprotein apheresis

• Lipoprotein apheresis should be considered in all patients with homozygous or compound heterozygous FH

• Apheresis should be considered in children with homozygous FH by the age of 5 and no later than 8 years
- Homozygous FH
- Before and after 6 years of apheresis
Format

1. CV Risk and lipid lowering
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3. Hypertriglyceridaemia
4. Lipoprotein(a)
Case 4

- 25 year old lady
- TC 5.2 mmol/l
- **TG 14.1 mmol/l**
- HDL 1.1 mmol/l
- non-HDL 4.1 mmol/l
- HbA1C 31 mmol/mol
- BMI 22
- Tee total
- No meds
HyperTG and CVD

N=93410 (cardiac events=7183)
Median follow-up 6 years
Copenhagen City Heart Study and
Copenhagen General Population Study

N=302430 (cardiac events=12785)
Median follow-up 8 years
Emerging Risk Factors Collaboration
HyperTG and acute pancreatitis

Multivariable and Alcohol Intake Adjusted
(P for Trend $8 \times 10^{-8}$)

**TG mmol/l**
- <1.00
- 1.00-1.99
- 2.00-2.99
- 3.00-3.99
- 4.00-4.99
- >5.00

**HR (95% CI)**

JAMA intern med 2016
Primary

TG only
• Familial chylomicronaemia syndrome
• Familial HyperTG

Mixed
• Familial dysbetalipoproteinaemia
• Familial combined hyperlipidaemia

With permission from Prof GR Thompson
TG response to a meal..

Assumptions:
- Complete digestion and absorption of dietary fat
- Clearance is zero (e.g. LPL deficiency)
- Ignore VLDL production
- Fasting triglycerides are 4 mmol/L
- Plasma volume of 3 L
- 1 mol triglycerides $\approx$ 885 g

Take-away meal: Triglyceride content
- Double hamburger with cheese 42 g
- French fries (large) 30 g
- Chocolate triple thick shake (supersize) 28 g

Total meal is 100 g of triglyceride $\rightarrow$ 113 mmol

Change in triglycerides: 113 mmol of triglyceride / 3 L plasma volume: 37.66 mmol/L

Triglycerides can rise from 4 mmol/L to over 40 mmol/L

Cholesterol consumed: 255 mg ($\approx$ 0.7 mmol)
## Secondary causes of hyperTG

<table>
<thead>
<tr>
<th>Condition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Mild hypertriglyceridaemia frequent in metabolic syndrome. Increased waist circumference highly predictive of mild hypertriglyceridaemia</td>
</tr>
<tr>
<td>Diet</td>
<td>See Box 1 for the effect of dietary fat in patients with lipolytic defects</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Most common secondary cause in our experience. Controlling diabetes mellitus often lowers TGs substantially</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Alcohol can increase VLDL synthesis. Pancreatitis risk from alcohol and TGs</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Mild hypertriglyceridaemia frequently seen in uremia</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Increased VLDL production may expose lipolytic effect. Pancreatitis has high fatality rate in pregnancy</td>
</tr>
<tr>
<td>Paraproteins</td>
<td>May inhibit lipolytic proteins</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td>Systemic lupus erythematosus (SLE) may generate auto-antibodies to LPL</td>
</tr>
<tr>
<td>Other disorders</td>
<td>Glycogen storage disorders may have mild hypertriglyceridaemia</td>
</tr>
</tbody>
</table>

...and drugs

Blom et al, 2014
# Drugs associated with hyperTG

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestrogen</td>
<td>Oral oestrogen elevate TGs more than transdermal preparations</td>
</tr>
<tr>
<td></td>
<td>May cause marked hypertriglyceridaemia in susceptible individuals</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Variable lipid phenotypes, may cause predominant hypercholesterolaemia</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Severe hypertriglyceridaemia possible</td>
</tr>
<tr>
<td></td>
<td>Check baseline TGs before therapy and once on treatment</td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td>Protease inhibitors, especially ritonavir, most often implicated</td>
</tr>
<tr>
<td></td>
<td>Hypertriglyceridaemia often severe</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>May aggravate hypertriglyceridaemia</td>
</tr>
<tr>
<td></td>
<td>Avoid prescription when TGs are increased</td>
</tr>
<tr>
<td>Immunosuppressant drugs</td>
<td>Sirolimus frequently implicated</td>
</tr>
<tr>
<td>Beta blockers, thiazides</td>
<td>Increase in TGs usually minor</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>Weight gain, insulin resistance and diabetes</td>
</tr>
<tr>
<td></td>
<td>commonly accompany rise in TGs</td>
</tr>
</tbody>
</table>

Blom et al, 2014
Treatment

• **Acute:**
  – dietary intervention
  – insulin,
  – heparin,
  – plasmapheresis,
  – drug therapy (e.g., fibrates, omega-3 fatty acids and statins)

• **Non-acute:**
  – dietary intervention
  – drug therapy (e.g., fibrates, omega-3 fatty acids and statins)
Format

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Case 5

36 year old architect
Presented with AMI
- non-smoker
- runs 5 times per week, cycles

- TC 4.2 mmol/l
- TG 1.1 mmol/l
- HDL 1.2 mmol/l
- non-HDL 3.0mmol/l
- HbA1C 24 mmol/mol
- BP 124/84
Lipoprotein(a)

- Kringle IV type 2 repeats (variable number) (KIV-2)
- KIV-1
- Cysteine rich
- Phospholipid
- Free cholesterol
- KIV-3 to 10
- Disulphide bridge (Apo-B100-Lp(a))
- ApoB100
- NH2
- COOH
- LDL receptor binding
- KV
- Protease domain
Lp(a) distribution

Men

Women

Fraction of population

Lp(a) (mg/dL)

20%

Kamstrup JAMA 2009
Lp(a) and CV risk

Meta-analysis
Adjustment for age and sex only
Nonfatal MI and coronary death

Mendelian Randomization
Multivariable adjusted

Genome-Wide Association

ERF Collab JAMA 2009
Kamstrup JAMA 2009
Clarke NEJM 2009
Lp(a) Pathophysiology

**Pro-inflammatory**
- ↑ oxidised phospholipids
- ↑ monocyte trafficking
- ↑ monocyte cytokine release

**Proatherogenic**
- ↑ arterial infiltration
- ↑ SMC proliferation
- ↑ foam cell formation
- ↑ necrotic core formation

**Prothrombotic**
- ↓ plasminogen activation
- ↓ fibrin degradation
- ↑ platelet aggregation
Treatment of Lp(a)

The management of patients with raised lipoprotein(a) levels (> 90 nmol/l), should include:

– 1) reducing residual atherosclerotic risk
– 2) controlling dyslipidaemia and
– 3) consideration of:
  a) aspirin therapy
  b) lipoprotein apheresis
When and whom to refer:

- Patients with familial hyperlipidaemias
- Patients who fail to respond adequately to diet and first-line drug therapy
- Patients with severe hypertriglyceridaemia who are at risk of pancreatitis
- Patients for whom there is any uncertainty about diagnosis
Take home messages:

• Lipids are a key target in CVD prevention and statins are the first line drugs
• Consider FH in patients with TC>7.5mmol/l or LDL>4.9mmol/l
• Raised TG: Think: Acute risk: Pancreatitis and Chronic risk: CVD
• Consider raised Lp(a) as a mediator of CV risk