LIPID DISORDERS

Background

LIPID disorders are important for three reasons:
• They contribute to cardiovascular disease, still the number one cause of death in our society, by aggravating atherosclerosis.
• They are common and are treatable, mainly with statins, which have revolutionised preventive medicine in the last few decades.
• In Australia, more than a million adults take lipid-modifying drugs, at an annual cost of about $1.1 billion to the PBS.

Indications for lipid-modifying drugs
The indications for using lipid-modifying drugs are to:
• Reduce the incidence of CVD through primary and secondary prevention.
• Reduce itching in obstructive jaundice, due to deposition of bile acids in the skin, by the use of bile-acid sequestrants (resins).
• Prevent acute pancreatitis, a potentially fatal complication of very high triglyceride (TG) levels (>11mmol/L).
• Induce regression of lesions caused by high levels of low-density lipoprotein...
Lipid levels for PBS subsidy

**TC >9mmol/L or TG >8mmol/L**

 Patients with high-risk diabetes mellitus include those with:
- **Symptomatic CVD**
- **High-risk diabetes mellitus.**
  - A family history of premature CVD (CVD before age 55 in two or more first-degree relatives, or CVD before age 45 in one or more first-degree relatives).

 Patients not eligible under the above criteria:
- **Men aged 35-75**
- **Postmenopausal women aged up to 75**
- **Patients not otherwise included**

**Table 1: Criteria for reimbursement of lipid drugs for those patients not at very high risk**

<table>
<thead>
<tr>
<th>Patient category</th>
<th>Lipid levels for PBS subsidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus (not high-risk)</td>
<td>TC &gt;6.5mmol/L</td>
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<tr>
<td>Aboriginal or Torres Strait Islander Hypertension</td>
<td>TC &gt;6.5mmol/L</td>
</tr>
<tr>
<td>or</td>
<td>TC &gt;5.5mmol/L and HDL-C &lt;1.0mmol/L</td>
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<tr>
<td>Familial hypercholesterolaemia identified by:</td>
<td>If aged ≤18 at treatment initiation, LDL-C &gt;4mmol/L</td>
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<tr>
<td>DNA mutation</td>
<td>If aged &gt;18 at treatment initiation:</td>
</tr>
<tr>
<td>Tendon xanthomas in the patient or a first- or second-degree relative</td>
<td>• LDL-C &gt; 5mmol/L, or</td>
</tr>
<tr>
<td>Family history of symptomatic CHD</td>
<td>• TC &gt; 6.5mmol/L, or</td>
</tr>
<tr>
<td>• Before age 60 in one or more first-degree relatives</td>
<td>• TC &gt;5.5mmol/L and HDL-C &lt;1.0mmol/L</td>
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<tr>
<td>• Before age 50 in one or more second-degree relatives</td>
<td>Patients not eligible under the above criteria:</td>
</tr>
<tr>
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<td>• TC &gt;7.5mmol/L or TG &gt;4mmol/L</td>
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<tr>
<td>HDL-C &lt;1.0mmol/L</td>
<td>Patients not otherwise included</td>
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</table>

**Symptoms of lipid disorders**

Most lipid disorders are asymptomatic. Symptoms may arise from associated comorbidities, some of which are caused by the lipid disorder (eg, angina from coronary atherosclerosis secondary to high LDL-C levels; acute abdominal pain from acute pancreatitis secondary to high TG levels).

**Clinical presentation**

**Figure 1:** Mixed tendon and cutaneous xanthomas of Achilles’ tendons; cutaneous xanthoma of foot lateral to the fifth toe. (Source: MEDPED program, the late Professor RR Williams.)

**Figure 2:** Tendon xanthoma of the extensor tendon of the third finger, dorsal to the metacarpophalangeal joint. Other xanthomas may be observed during finger flexion and extension (‘playing the piano’). (Source: MEDPED program, the late Professor RR Williams.)

**Figure 3:** Irregularity of outline of the extensor tendons of the second and third fingers due to tendon xanthomas. (Source: MEDPED program, the late Professor RR Williams.)

**Figure 4:** Tendon xanthoma of the extensor tendon of the third finger, dorsal to the metacarpophalangeal joint. Other xanthomas may be observed during finger flexion and extension (‘playing the piano’). (Source: MEDPED program, the late Professor RR Williams.)

**Figure 5:** Bilateral yellow-white xanthelasmas on the medial upper and lower eyelids near the inner canthus. (Source: MEDPED program, the late Professor RR Williams.)

**Figure 6:** Advanced arcus senilis (dense circular opacity around the periphery of the cornea) and xanthelasma (flat, yellow maculopapular lesion above the upper eyelid). (Source: MEDPED program, the late Professor RR Williams.)

**Figure 7:** Earlier arcus senilis with peripheral corneal opacity superiorly and inferiorly. (Source: Professor S Humphries and HEART-UK.)
Investigations

Table 2: Patterns of lipid profile according to underlying aetiology

<table>
<thead>
<tr>
<th>Primary causes</th>
<th>Secondary causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mutation of LDL-receptor gene (familial hypercholesterolaemia)</td>
<td>• Hyperlipidaemias</td>
</tr>
<tr>
<td>• Mutation of apoB gene (familial defective apoB)</td>
<td>• Hypothyroidism</td>
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Table: Standard lipid investigations

<table>
<thead>
<tr>
<th>Lipid disorder</th>
<th>Primary causes</th>
<th>Secondary causes</th>
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</thead>
<tbody>
<tr>
<td>Hypercholesterolaemia:</td>
<td>• Tg increased</td>
<td>• Hypercholesterolaemia:</td>
</tr>
<tr>
<td>• Tg increased</td>
<td></td>
<td>• Tg increased</td>
</tr>
<tr>
<td>• LDL-C near-normal</td>
<td></td>
<td>• HDL-C near-normal</td>
</tr>
<tr>
<td>• HDL-C low-reduced</td>
<td></td>
<td>• LDL-C reduced</td>
</tr>
<tr>
<td>Combined hyperlipidaemia:</td>
<td>• Tg increased</td>
<td>• LDL-C, HDL-C targets are largely</td>
</tr>
<tr>
<td>• Tg increased</td>
<td></td>
<td>achieved to lower LDL-C</td>
</tr>
<tr>
<td>• HDL-C near-normal (direct assay)</td>
<td></td>
<td>when apoB may detect the</td>
</tr>
<tr>
<td>• LDL-C reduced</td>
<td></td>
<td>presence of small dense LDL-C,</td>
</tr>
<tr>
<td>Isolated low LDL-C:²</td>
<td>• Apo A-1 deficiency³</td>
<td>widespread and recommended strat-</td>
</tr>
<tr>
<td>• HDL-C low</td>
<td>• ABCA-1 deficiency (Tanger disease)</td>
<td>egies based on current US guidelines,</td>
</tr>
<tr>
<td>• Neat-normal Tg, TC, LDL-C</td>
<td>• LCAT deficiency⁴</td>
<td>which are conveniently performed</td>
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</table>

Figure 8: Percentage reduction in CVD events according to achieved LDL-C levels in statin trials. Adapted from: Cholesterol Treatment Trials Collaboration, University of Oxford, 2000 (www.chl.s.usc.ac.uk/projects/ctt/)

LDL-C targets

<table>
<thead>
<tr>
<th>Treatment targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIBBE depend on the patient’s base-line global cardiovascular risk:</td>
</tr>
<tr>
<td>• High risk (&gt;15% five-year CVD risk): &lt;1.8mmol/L (no lower limit recognised) The lowest mean LDL- C level so far achieved in clinical trials is 1.4mmol/L (JUPITER trial with 20mg rosuvastatin).</td>
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</tbody>
</table>
### Table 3: Dietary therapy for lipid disorders

<table>
<thead>
<tr>
<th>Lipid disorder</th>
<th>Diet</th>
<th>Dietary supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>High LDL-C</td>
<td>Low total or saturated fat</td>
<td>Plant sterols (margarine) &lt;br&gt; Soluble fibre</td>
</tr>
<tr>
<td>Combined hyperlipidaemia</td>
<td>Low saturated fat</td>
<td>Plant sterols</td>
</tr>
<tr>
<td>High TG</td>
<td>Low total fat</td>
<td>Fish oils</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>Mediterranean-type diet</td>
<td><strong>MCT if severe</strong>&lt;br&gt; Fish oils</td>
</tr>
</tbody>
</table>

*Adapted from Colquhoun D. How to Treat Hyperlipidaemia, 2006

**Medium-chain triglycerides (MCT) are not converted by the intestine into lipoproteins (especially chylomicrons), and may be used to supply non-essential fatty acids in those with very high TG levels.

### Table 4: Use of lipid drugs in clinical practice

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Initial treatment</th>
<th>LDL-C at goal</th>
<th>TG or HDL-C at goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary prevention and high-risk primary prevention</td>
<td>Statin</td>
<td>1. Exclude or control secondary causes</td>
<td>1. Exclude or control secondary causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Add ezetimibe</td>
<td>2. Fenofibrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Add low-dose resin</td>
<td>3. Fish oil (moderate dose)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Add fenofibrate</td>
<td>4. Nicotinic acid* or refer†</td>
</tr>
<tr>
<td></td>
<td>Statin*</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Other primary prevention, TG &lt;4.5mmol/L</td>
<td>Fibrate</td>
<td>1. Exclude or control secondary causes</td>
<td>1. Exclude or control secondary causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Statin (only with fenofibrate)</td>
<td>2. Increase doses of statin/fish oil/niacinic acid*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Nicotinic acid* or refer†</td>
<td>3. Consider other combinations or refer†</td>
</tr>
</tbody>
</table>

*Losses of over-the-counter fish oil: moderate 2–4 capsules (each 1g, containing ~30% DHA/EPA); high 6–12 capsules (1g). High-dose capsules (Maccan), 1g each, containing ~84% DHA/EPA, are likely to become available on prescription in the near future for post-MI patients (1g bd) and for hypertensive/cholesterolaemia (2–4 daily) or equivalent liquid formula.

**Use of immediate-release nicotinic acid requires specific protocol; highest tolerated dose recommended to maximise 3g/day (see text).

†Refer may be considered at earlier stages, especially with very abnormal lipid levels or with adverse events

### Global risk targets

Lipid intervention is one component of global intervention, in which CVD risk can be reduced independently and additively by multiple risk factor intervention, including:

- Lowering blood pressure (BP).
- Stopping cigarette smoking.
- Improving glucose tolerance.
- Lowering LDL-C and raising HDL-C levels.

The role of lowering TG level is less clear but recent meta-analyses suggest an independent benefit.

Figure 9 shows that global, especially global lifetime, risk can be dramatically reduced by simultaneously, multiple risk factor intervention, even with small changes in individual risk factors, which become amplified in the longer term. Targets for global risk have yet to be introduced in guidelines, but it is reasonable to treat to the lowest achievable global risk. Calculation of global risk using risk scores can demonstrate to patients the theoretical benefit of interventions and assist compliance with therapy.

Figure 9 shows a key relationship between age and CVD risk; while changes in relative risk for different interventions are similar across the age spectrum, changes in absolute risk are much greater at older compared with younger ages. At age 80, multiple intervention lower risk by 34% while at age 50 it lowers risk only by 7%.

### Dietary therapy and lipid targets

Lipid disorders require specific diets depending on the lipid profile, as shown in table 3. Maintaining ideal body weight improves most lipid disorders. Referral to a diettian is always advisable.

The National Heart Foundation recommended dietary guidelines are listed in the box above.
**HOW TO TREAT**  
**Lipid disorders**

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**from page 30**

**Table 5: How to manage adverse events with statin therapy**

<table>
<thead>
<tr>
<th>Event</th>
<th>Initial treatment</th>
<th>Subsequent treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased transaminase levels (AST, ALT)</td>
<td>Withdraw or reduce statin dose if &lt;3 x ULN</td>
<td>Repeat CK after 1-2 weeks, withdraw dose or lower dose if symptoms persist</td>
</tr>
<tr>
<td>Myalgia (pain, stiffness) with CK &lt;3 x ULN</td>
<td>Continue statin and check secondary cause and treat if indicated*</td>
<td>Repeat CK if &lt;3 x ULN, withdraw dose or lower dose</td>
</tr>
<tr>
<td>Myalgia with CK &gt;3 x ULN</td>
<td>Withdraw statin and check secondary cause and treat if indicated</td>
<td>As above</td>
</tr>
<tr>
<td>Myositis (more severe symptoms, including weakness with CK &gt;10 x ULN)</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Rhabdomyolysis (severe symptoms, CK &gt;10 x ULN with myoglobinuria and impaired renal function)</td>
<td>As above</td>
<td>As above</td>
</tr>
</tbody>
</table>

**CPT = ICD9 code/pathway number**

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**Possible contributors to residual risk in patients on statin therapy**

- **Cigarette smoking**
- **Uncontrolled hypertension**
- **Impaired glucose tolerance**
- **Reduced physical exercise**
- **Central abdominal obesity**
- **Hypertriglyceridaemia**
- **Increased CRP**
- **Pro-thrombotic tendency**
- **Increased fibrinogen**
- **Myocardial ischaemia**
- **Left ventricular hypertrophy**
- **Reduced HDL-C**
- **Increased LDL-C**
- **Atherogenic dyslipidaemia**
- **Increased apoA and small dense LDL**
- **Increased apoB and TG-rich lipoproteins**

---

**Residual risk**

Residual risk refers to CVD events that occur despite statin therapy. In controlled trials, statins reduce CVD events by 30–40% compared with placebo and reduce overall mortality by 20–30%.

**Lifestyle measures**

As a means of improving residual risk is likely to be significant.

**Possible contributing factors**

- **Stopping smoking**
- **Increased aerobic capacity through exercise**
- **Loss of visceral fat mass through diet and exercise**

**CVD or diabetes, 42% were untreated and only 59% of those being treated reached target LDL-C levels**.

**Of those without CVD or diabetes, 48% achieved target LDL-C levels, and 31% of patients with high CVD risk did not receive lipid treatment for primary prevention**.

**Lifestyle**

Lifestyle measures as a means of improving residual risk is likely to be significant.

- **Stopping smoking**
- **Increased aerobic capacity through exercise**
- **Loss of visceral fat mass through diet and exercise**

**Possible contributing factors**

- **Lifestyle**
- **Medications**
- **Other medical conditions**

**To refer**

Some lipid disorders are difficult to treat because of genetic factors (e.g., isolated low HDL-C and FH with extremely high LDL-C levels due to inherited environmental factors (uncontrolled diabetes, excess alcohol)).

**References**

- **Recent lipid guidelines**
- **Residual risk**
- **Lifestyle measures as a means of improving residual risk is likely to be significant.**

---

**continued page 34**
**GP’s contribution**

**Case study**

MS MC, 45, is an obese woman who presents to you for a checkup. Her 50-year-old brother was recently admitted to hospital and needed coronary stenting. The patient is a regular smoker (five pack years) with a sedentary lifestyle. She has consistently failed attempts at diet and exercise and has a BMI of 31. She rarely attends the practice except for fulfilling her oral contraceptive script.

Her fasting lipids are:
- TC: 8.0mmol/L
- HDL-C: 0.7mmol/L
- LDL-C: 6.6mmol/L
- TG: 1.5mmol/L

**Questions for the author**

1. Which TWO statements are correct?
   - a) Statins effectively treat the pruritus of obstructive jaundice
   - b) Lipid-lowering drugs are indicated for the prevention of pancreatitis due to very high triglyceride (TG) levels
   - c) Patients with symptomatic CVD or a family history of premature CVD are eligible for PBS subsidised lipid-lowering drugs only if total cholesterol (TC) level is >5.5 mmol/L
   - d) Patients aged >60 years, with DM or significant micro-albuminuria are eligible for PBS subsidised lipid-lowering therapy irrespective of their lipid levels

2. Which TWO statements are correct?
   - a) Eruptive xanthomas tend to occur in those with very high low-density lipoprotein–cholesterol (LDL-C) levels
   - b) Lapaena retinalis is due to the presence of TG-rich lipoproteins
   - c) The presence of arcus senilis, tendon xanthomas or xanthelasmata is associated with familial hypercholesterolaemia
   - d) Fasting is required before lipid blood testing to avoid high postprandial total TC levels

3. Which TWO statements are correct?
   - a) The Friedewald formula used to calculate LDL-C level is valid when TG is <4.5mmol/L
   - b) LDL-C level may be measured in non-fasting plasma if direct methods are available
   - c) In patients combined hyperlipidaemia (CHL) and hypertriglyceridaemia (HTG), a reciprocal relationship often exists between HDL-C and TG levels
   - d) Patients with hyperalphalipoproteinaemia (elevated apoA-I) level, tend to have low levels of HDL-C

4. Which THREE statements are correct?
   - a) Secondary causes of hypercholesterolaemia include hypothyroidism and myeloma
   - b) Familial dysalphalipoproteinaemia is suspected when TG level is raised and TC level is normal
   - c) Insulin resistance disorders and alcohol excess are common secondary causes of hyperlipidaemia
   - d) Isolated low HDL-C level is associated with cigarette smoking and a high-carbohydrate diet

5. Which TWO statements are correct?
   - a) Lipoprotein (a) is a protective against CVD
   - b) Statins are effective in lowering LDL levels
   - c) ApoB and apoA-1 may be better CVD risk discriminators than LDL-C and HDL-C
   - d) LDL and triglyceride-rich lipoproteins (very low-density lipoprotein in metabolic syndrome, intermediate-density lipoproteins) contain apoB

6. Which TWO statements are correct?
   - a) Measurement of apoB is most useful in combined hyperlipidaemia to detect the presence of small dense LDL-C
   - b) ApoB-1 is protective against CVD
   - c) Patients with very high CVD risk, the target level of LDL-C = <3.0mmol/L
   - d) Patients with low CVD risk, the target level of LDL-C = <2.0mmol/L

7. Which TWO statements are correct?
   - a) The fire-and-forget treatment strategy has the disadvantage of being more expensive than a treat-to-target strategy
   - b) A modified fire-and-forget strategy stratifies patients into higher and lower five-year CVD risk groups, with a different standard treatment for each group
   - c) When compared with an intensive treat-to-target strategy, the modified fire-and-forget strategy prevents fewer CVD events and mortality
   - d) For TG levels >1.7mmol/L, the nature of LDL particles changes from large and light (safe) LDL to small and dense (harmful) LDL

8. Which TWO statements are correct?
   - a) Non-HDL-C is a measure of atherogenic cholesterol, when high TG makes the Friedewald formula inaccurate
   - b) Lowering TG levels may provide benefit in reducing CVD risk, independent of lowering LDL-C and raising HDL-C levels
   - c) The reduction in CVD absolute risk with multiple risk factor interventions is similar across the age spectrum
   - d) Fish oils are the most effective dietary supplement to lower LDL-C level

9. Which TWO statements are correct?
   - a) Fenofibrate is the first-line pharmacotherapy for TG level >4.5 mmol/L
   - b) For elevated LDL-C level insufficiently responsive to a statin alone, ezetimibe is the drug of first choice in combination with the statin
   - c) With statins, start with a low dose and titrate up as needed
   - d) No dose adjustment of statin is necessary in patients with low muscle mass

10. Which TWO statements are correct?
    - a) If a patient on a statin has myalgia and CK level >3 × upper limit of normal, the statin should be continued
    - b) Additional reduction in CVD risk by adding a fibrate to statin therapy is confined to patients with high TG and low HDL-C levels
    - c) Nicotinic acid reduces TG and LDL-C, and increases HDL-C levels
    - d) Patients with raised LDL-C and HDL-C levels and a normal TC/HDL ratio do not need treatment with a statin

**How to Treat Quiz**

Lipid disorders—9 July 2010

**Instructions**

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points for the 2008-10 triennium. You can complete this online along with the quiz at www.australiandoctor.com.au. Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

**Online only**


**CPS Quiz update**

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2008-10 triennium. You can complete this online along with the quiz at www.australiandoctor.com.au. Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

**References**

Available on request from: julian.mcalan@reedbusiness.com.au

**Online resources**

www.theheart.org — the best site for CVD issues
- Heart Foundation, for local references: www.heartfoundation.org.au

**How to treat**

Dr Giovanna Zingarelli

How to treat looks at pelvic organ prolapse in women, which is a major cause of reduced quality of life in older women particularly. Advances in conservative and surgical management are examined. The authors are Dr David Knight and Dr Peter Scott, senior staff specialists in obstetrics and gynaecology, Canberra Hospital, and clinical lecturers in obstetrics and gynaecology, Australian National University, Canberra, ACT.

**How to treat**

Editor: Dr Giovanna Zingarelli

Co-editor: Julian McAlan

Quiz: Dr Giovanna Zingarelli

**How to treat**

Editor: Dr Giovanna Zingarelli

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