Module 9  Lipid Management in Hypertensive Patients

Aims of this module

To provide recommendations on lipid management in adult hypertensive patients for primary prevention of cardiovascular disease (CVD) in primary care setting\(^\text{Note}\).

Screening

Screening of lipid profile should be performed for all newly diagnosed hypertensive patients, and as a part of the annual assessment\(^1\). This information, together with information on other risk factors, is useful in determining the individual’s cardiovascular risk and provides insight into the subsequent management.

Global risk assessment

In addition to hypertension and dyslipidaemia, there are other major cardiovascular risk factors, such as advancing age, male gender, cigarette smoking, obesity, physical inactivity, and family history of premature cardiovascular disease\(^2\). The total risk of developing CVD is determined by the combined effect of cardiovascular risk factors, which commonly coexist and act multiplicatively. An individual with several mildly raised risk factors may be at a higher total risk of CVD than someone with just one elevated risk factor\(^3\). Therefore, the global risk approach should be considered in every cardiovascular risk assessment including patients with hypertension. For all identified modifiable cardiovascular risk factors, they should be managed as possible. Periodic review of the cardiovascular risk is also necessary.

\(^{Note}\) For lipid management in diabetic patients, please refer to Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care Settings.
Cardiovascular risk assessment Tools

**Background**
Cardiovascular risk assessment tools aim at helping physicians to estimate the risk of cardiovascular events for individuals without known cardiovascular diseases, based on the presence of different risk factors. The predicted risk of an individual can be a useful guide for making clinical decisions on the intensity of interventions, which should always be individualised. These multivariate cardiovascular risk assessment tools can usually be interpreted easily by referring simplified charts or tables, or by web-based calculators, and most of them can be accessed easily on the internet. There is currently no tool specifically designed for Chinese populations.

It has to emphasise that estimation of the cardiovascular risk is not necessary for individuals with known very high or high risk conditions (Table 1). Lipid lowering therapy should be considered for these individual unless contraindicated.

Table 1. Individuals at very high and high risk of developing future coronary events

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Clinical presentation of individuals</th>
</tr>
</thead>
</table>
| Very high risk | (1) Individuals with established coronary artery disease, atherosclerotic cerebrovascular disease, aortic aneurysm or peripheral artery disease  
(2) Individuals with diabetes mellitus with chronic kidney disease  
(3) Individuals with familial hypercholesterolemia |
| High risk | (1) Individuals with moderate to severe chronic kidney disease (estimated glomerular filtration rate [eGFR] <60ml/min/1.73 m²)  
(2) Individuals with diabetes mellitus without established coronary artery disease, atherosclerotic cerebrovascular disease, aortic aneurysm, peripheral artery disease or chronic kidney disease |
**Examples of cardiovascular risk assessment tools** *(Table 2)*

1. **Framingham-based**
   - The original Framingham risk score (published in 1998) derived from Framingham Heart Study, a prospective cohort of largely Caucasian population, were widely adapted worldwide, such as in National Cholesterol Education Program (NCEP), Joint British Societies 2 (JBS2) and the New Zealand Cardiovascular Risk Charts; the former two guidelines had been widely used as reference in the public sectors in Hong Kong (information as at Feb 2017).
   - The Framingham system had been recalibrated for Asian populations for different cohorts, for example,
     - Singapore-adapted Framingham Risk Score: adjusted for Chinese, Malay and Indian populations in Singapore
     - Asia Pacific Cohort Studies Collaboration: cohorts from Japan, Korea, Singapore and China
     - The Chinese Multi-Provincial Cohort Study: Chinese cohorts from mainland China
   - It had been suggested that Framingham equation can be applied to the Hong Kong Chinese population but requires recalibration in men due to overestimation of the risk. There is currently no recalibrated tool available for local use.

2. **Systemic Coronary Risk Evaluation (SCORE)**
   - Based on European cohorts
   - Recommended by European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS)

3. **QRISK**
   - Based on patient data from England and Wales in the United Kingdom
   - Included more medical variables such as type 2 diabetes, chronic renal disease, atrial fibrillation, and rheumatoid arthritis
   - Recommended by the National Institute of Clinical Excellence (NICE)

4. **Pooled Cohort Studies Equations**
   - Derived from Whites and African Americans cohorts
   - Recommended by American College of Cardiology/ American Heart Association (ACC/AHA)
   - Study had questioned its validity in Hong Kong Chinese due to poor discrimination power and calibration when applied to the Chinese population in Hong Kong
Table 1. Examples of the cardiovascular risk assessment tools (information as at Feb 2017)

<table>
<thead>
<tr>
<th>Risk estimation system</th>
<th>Recommending guideline</th>
<th>Variables</th>
<th>Endpoint</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham-based</td>
<td>• NCEP guidelines&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Sex, age, total cholesterol, HDL-C, SBP, smoking status, DM, HT treatment</td>
<td>10-year risk of CAD events (in original version)</td>
<td>NCEP and JBS2 guidelines are commonly used as reference in public sectors</td>
</tr>
<tr>
<td></td>
<td>• JBS2 guidelines&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• New Zealand guidelines&lt;sup&gt;8&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td></td>
<td>• Singapore guideline&lt;sup&gt;9&lt;/sup&gt;</td>
<td></td>
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</tr>
<tr>
<td>SCORE&lt;sup&gt;13&lt;/sup&gt;</td>
<td>• ESC/EAS Guidelines for the management of dyslipidaemias&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Sex, age, total cholesterol or total cholesterol/HDL-C ratio, SBP, smoking status</td>
<td>10-year risk of CVD mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• European Guidelines on cardiovascular disease prevention in clinical practice&lt;sup&gt;15&lt;/sup&gt;</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>QRISK2&lt;sup&gt;16&lt;/sup&gt;</td>
<td>• NICE guidelines on lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Sex, age, race, total cholesterol/HDL-C ratio, SBP, smoking status, DM, HT treatment, family history, BMI, chronic disease</td>
<td>10-year risk of CVD events</td>
<td></td>
</tr>
<tr>
<td>Pooled Cohort Studies Equations&lt;sup&gt;18&lt;/sup&gt;</td>
<td>• ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Sex, age, race (white or other/African American), total cholesterol, HDL-C, SBP, smoking status, DM, HT treatment</td>
<td>10-year risk for the first atherosclerotic CVD event</td>
<td>Poor Calibration for Hong Kong Chinese&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- BMI: Body mass index
- CAD: Coronary artery disease
- CVD: Cardiovascular disease
- DM: Diabetes mellitus
- HDL-C: High-density lipoprotein cholesterol
- HT: Hypertension
- LDL-C: Low-density lipoprotein cholesterol
- SBP: Systolic blood pressure
**Treatment targets**

The treatment target should be individualised for different patients. In general, the higher the cardiovascular risk, the more worthwhile to start lipid lowering therapy. For patients who have very high risk or high risk conditions (*Table 1*), lipid lowering therapy should be considered unless contraindicated. Many of the guidelines recommend different treatment goals for patients who have been stratified under different risk categories. There are also guidelines recommending the use of lipid lowering drugs for patients considered as high risk and do not recommend specific treatment targets. The treatment targets (if available) for primary prevention of some of the international guidelines are listed for reference in table 2.

For lipid management in diabetic patients, please refer to Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care Settings.
### Table 2. Treatment target levels of lipid (if available) for primary prevention in some of the international guidelines (information as at Feb 2017)

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Risk Category</th>
<th>Lipid Target (if any)/ treatment strategies</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP (2004)</td>
<td>Low: 0-1 risk factor</td>
<td>LDL-C &lt; 4.1mmol/L</td>
<td>Lipid targets are commonly used as reference in public sectors</td>
</tr>
<tr>
<td></td>
<td>Moderate: ≥ 2 risk factors and 10-year CHD risk &lt; 10%</td>
<td>LDL-C &lt; 3.4mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderately high: ≥ 2 risk factors and 10-year CHD risk 10 to &lt; 20%</td>
<td>LDL-C &lt; 3.4mmol/L (optional goal: &lt; 2.6mmol/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High: CHD equivalent or 10-year CHD risk &gt; 20%</td>
<td>LDL-C &lt; 2.6mmol/L (optional goal: &lt; 1.8mmol/L for very high risk)</td>
<td></td>
</tr>
<tr>
<td>JBS2 (2005)</td>
<td>High: 10-year CVD risk ≥ 20%</td>
<td>Optimal targets: LDL-C &lt; 2.0mmol/L and TC &lt; 4.0mmol/L, or 30% LDL-C reduction and 25% TC reduction</td>
<td>Prediction charts are commonly used as reference in public sectors</td>
</tr>
<tr>
<td></td>
<td>For original recommendation, optimal targets were recommended.</td>
<td>Audit (minimum) standard: LDL-C &lt; 3.0mmol/L and TC &lt; 5.0mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-year CVD risk ≥ 15%</td>
<td>LDL-C &lt; 2.0mmol/L, TC &lt; 4.0mmol/L, HDL-C ≥ 1.0mmol/L, TG &lt;1.7mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subsequent update does not recommended specific targets.</td>
<td>TC ≥ 8mmol/L or TC:HDL-C ratio ≥ 8</td>
<td>Recommend drug treatment irrespective of CVD risk</td>
</tr>
<tr>
<td></td>
<td>Combined CVD risk &gt; 20%</td>
<td>Recommend drug treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined CVD risk 10-20%</td>
<td>Shared decision-making approach on drug treatment</td>
<td></td>
</tr>
<tr>
<td>New Zealand (2012 and 2013)</td>
<td>Combined CVD risk ≥ 20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC/ AHA (2013)</td>
<td>Recommendations the use of high or moderate intensity statin in different risk. No recommendations on specific treatment targets.</td>
<td>Primary LDL-C ≥ 4.9mmol/L</td>
<td>High intensity statin</td>
</tr>
<tr>
<td></td>
<td>Age 40-75 years without diabetes and 10-year ASCVD risk ≥ 7.5%</td>
<td>Moderate to high intensity statin</td>
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<tr>
<td></td>
<td>Remarks: Moderate-intensity statin: 30% to &lt; 50% LDL-C reduction. High-intensity statin: ≥ 50% LDL-C reduction</td>
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</tr>
</tbody>
</table>

(Table continued on next page)
### Table 2. Treatment target levels of lipid (if available) for primary prevention in some of the international guidelines. (Continued)

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Risk Category</th>
<th>Lipid Target (if any)/ treatment strategies</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE (2014)¹⁷</td>
<td>High: 10-year CVD risk ≥ 10%</td>
<td>&gt; 40% non-HDL-C reduction</td>
<td>Fasting blood is not required for non-HDL-C</td>
</tr>
<tr>
<td>ESC/ EAS (2016)¹⁴</td>
<td>Moderate:</td>
<td>LDL-C &lt; 3.0mmol/L</td>
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<tr>
<td></td>
<td>• SCORE ≥ 1% to &lt; 5%</td>
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<tr>
<td></td>
<td>High:</td>
<td>LDL-C &lt; 2.6mmol/L</td>
<td>≥ 50% reduction on LDL-C if baseline is between 2.6 and 5.1mmol/L</td>
</tr>
<tr>
<td></td>
<td>• markedly elevated single risk factors (e.g. familial dyslipidaemia, severe HT) or</td>
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<tr>
<td></td>
<td>• most other people with DM (some young people with type 1 diabetes may be at low or moderate risk) or</td>
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<tr>
<td></td>
<td>• moderate CKD or</td>
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<tr>
<td></td>
<td>• SCORE ≥ 5% to &lt; 10%</td>
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<tr>
<td></td>
<td>Very high:</td>
<td>LDL-C &lt; 1.8mmol/L</td>
<td>≥ 50% reduction on LDL-C if baseline is between 1.8 and 3.5 mmol/L</td>
</tr>
<tr>
<td></td>
<td>• documented CVD or</td>
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<td></td>
<td>• DM with target organ damage or</td>
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<tr>
<td></td>
<td>• severe CKD or</td>
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<td></td>
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<tr>
<td></td>
<td>• SCORE ≥ 10%</td>
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</tbody>
</table>

**Abbreviations:**
- ASCVD: Atherosclerotic cardiovascular disease
- CVD: Cardiovascular disease
- CHD: Coronary heart disease
- DM: Diabetes mellitus
- CKD: Chronic kidney disease
- HT: Hypertension
- HDL-C: High-density lipoprotein cholesterol
- LDL-C: Low-density lipoprotein cholesterol
- Non-HDL-C: Non high-density lipoprotein cholesterol
- TC: Total cholesterol
- TG: Triglycerides
Management

Dyslipidaemia can be modified by dietary change, increase in physical activity and lipid lowering drugs. In case of any secondary causes of dyslipidaemia such as hypothyroidism, diabetes, liver disease, nephrotic syndrome or steroid treatment, they should be identified and treated accordingly. Lifestyle modification is recommended in all hypertensive patients with dyslipidaemia. Use of lipid lower drugs should be commenced in patients who are considered having high cardiovascular risk or when lifestyle modification alone fails.

Lifestyle modification\textsuperscript{6,14}

- Reduction of dietary fat intake
- Total fat <30% of total calorie/day
- Saturated fat <7%, cholesterol <200 mg, trans fat <1% of total calorie intake/day

Drug treatment (Figure 1)

There are some patient groups who are more likely to discontinue their lipid-lowering medications after prescription. Recent studies performed in Hong Kong found that younger subjects (<50 years), patients who paid their first clinic visit and those without any comorbidities were more likely non-adherent or discontinuing their medications\textsuperscript{23,24}. These subjects should receive more meticulous monitoring of their medication-taking behaviour.

(1) Statins (HMG - CoA reductase inhibitors)\textsuperscript{25-27}
- ↓ LDL-C 25-55%, ↓ TG 15-30%, ↑ HDL-C 5-10%
- 25-55% risk reduction in cardiovascular diseases (coronary heart disease, stroke) in primary and secondary prevention studies
- Practical algorithm of statin usage is illustrated in Figure 1

(2) Fibrates\textsuperscript{28}
- ↓ TG 25-50% + ↑ HDL-C 10-20%
- There is no strong evidence for using fibrate therapy in primary prevention of cardiovascular disease. The use of fibrates in these patients should only be considered when statins are contraindicated.
- Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis\textsuperscript{19}. Fenofibrate is the preferred agent when used in combination with statins but should be used with cautions and under close monitoring

(3) Ezetimibe
- Can be used as an add-on drug in association with statins when the therapeutic target is not achieved at the maximum tolerated statin dose, or as an alternative to statins in patients who are intolerant of statins or with contraindications to statins\textsuperscript{4}
- No major adverse effects have been reported; the most frequent adverse effects are moderate elevations of liver enzymes and muscle pain\textsuperscript{14}
Figure 1. Practical algorithm of statin usage

Liver disease/ unexplained, persistent elevations of liver enzymes/ pregnant or lactating women

Relative contraindications
Concomitant use of cyclosporine, gemfibrozil, niacin, macrolide antibiotics, various antifungal agents, and cytochrome P-450 inhibitors

NO

YES

Consider other treatment modalities

YES (Note: Combination of statin with drugs listed may carry an increase in risk of myositis and liver derangement.)

Trade name of statins can be searched in https://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/home.html

Starting dose
Simvastatin 10mg nocte / Pravastatin 10mg note / Atorvastatin 10mg daily / Rosuvastatin 5mg daily / Lovastatin 10mg daily / Fluvastatin 20mg daily

LDL not reaching targets

On titration of statins

- **Rule of Six**: Doubling of dosage of statin will result in 6% LDL reduction but increased risk of transaminase elevation.

The following demonstrates the doubling of dosage of statin:

- **Simvastatin**
  - 10mg → 20mg → 40mg

- **Pravastatin**
  - 10mg → 20mg → 40mg

- **Atorvastatin**
  - 10mg → 20mg → 40mg → 80mg

- **Rosuvastatin**
  - 5mg → 10mg → 20mg

- **Lovastatin**
  - 10mg → 20mg → 40mg

- **Fluvastatin**
  - 20mg → 40mg → 80mg

See Notes on hepatic side effects of statins

If LDL does not reach targets despite titration of statin or side effects develop on higher doses of statin, consider referral to specialist for combination lipid lowering therapies with statin and other medications.

(Figure continued on next page)
Figure 1. Practical algorithm of statin usage (Continued)

**Muscle Soreness/Tenderness/Pain**
- Blood for CK only if muscle symptoms arise
- Increase in CK → Rule out common causes like Exercise / Strenuous work → Advise Moderation
- CK > 10x ULN → STOP
- CK 3-10x ULN + symptoms → STOP
- Progressive but asymptomatic CK elevation → Reduction in dose or temporary discontinuation

**Headache and Dyspepsia**
- Initial
- 6-8 weeks after therapy
- Each follow up

**Monitoring-Laboratory**
- ALT/AST
  - Before start
  - 12 weeks after start of statin
  - Thereafter repeat if clinically indicated
  - <3 x ULN → careful monitoring
  - ≥=3 x ULN → STOP

**Monitoring-Symptoms**

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**Abbreviations:**

ALT: Alanine transaminase
AST: Aspartate aminotransferase
CK: Creatine kinase
ULN: Upper limit of normal

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**Notes on hepatic side effects of statin:**

- Elevated hepatic transaminase generally occurs in 0.5%-2% of cases and is dose dependent, with ↑ relative risk 2 – 4 fold at higher doses of statin
- Progression to liver failure specifically due to statin is exceedingly rare if ever occurs
- Reversal of transaminase elevation is frequently noted with a reduction in dose, and elevations do not often recur with either re-challenge or selection of another statin
Simvastatin dose limitations
When used with simvastatin, the following medications can raise the levels of simvastatin in the body and increase the risk of myopathy. Taking no more than the recommended dose of simvastatin with these medications will help keep simvastatin levels in the body at a safer level.

<table>
<thead>
<tr>
<th>New simvastatin label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindicated with simvastatin:</td>
</tr>
<tr>
<td>• Itraconazole</td>
</tr>
<tr>
<td>• Ketoconazole</td>
</tr>
<tr>
<td>• Posaconazole (New)</td>
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<tr>
<td>• Erythromycin</td>
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<tr>
<td>• Clarithromycin</td>
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<tr>
<td>• Telithromycin</td>
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<tr>
<td>• HIV protease inhibitors</td>
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<tr>
<td>• Nefazodone</td>
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<tr>
<td>• Gemfibrozil</td>
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<tr>
<td>• Cyclosporine</td>
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<tr>
<td>• Danazol</td>
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<tr>
<td>Do not exceed 10 mg simvastatin daily with:</td>
</tr>
<tr>
<td>• Verapamil</td>
</tr>
<tr>
<td>• Diltiazem</td>
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<tr>
<td>Do not exceed 20 mg simvastatin daily with:</td>
</tr>
<tr>
<td>• Amiodarone</td>
</tr>
<tr>
<td>• Amlodipine (New)</td>
</tr>
<tr>
<td>• Ranolazine (New)</td>
</tr>
<tr>
<td>Avoid large quantities of grapefruit juice (&gt;1 quart daily)</td>
</tr>
</tbody>
</table>

FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. 15 Dec 2011.
Reference:


