Background

Accelerated atherosclerosis is multifactorial and begins years/decades prior to the diagnosis of type 2 diabetes:

- Risk for atherosclerotic events is two to four-fold greater than in non-diabetic subject.
- Responsible for 80% of diabetic mortality. (75% due to coronary heart disease and 25% due to stroke and peripheral vascular disease).
- >75% of all hospitalisations for diabetic complications.
- In Hong Kong one-third of patients hospitalised for stroke, myocardial infarction and coronary heart failure have diabetes.
- Dyslipidaemia is a major risk factor for diabetes macrovascular complications.
- Typical characteristics of dyslipidaemia in type 2 diabetes include hypertriglyceridaemia and low HDL-Cholesterol, the LDL-Cholesterol level is similar to that in non-diabetic, but qualitatively more atherogenic (increased glycation, triglyceride enrichment with increased proportion of small dense LDL-Cholesterol), thus leading to accelerated atherosclerosis.

Screening

At least annual screening of lipid profile, and more frequently if needed for treatment modification.

- Optimal treatment target of various lipid components:
  - LDL-Cholesterol (LDC-C): < 2.6 mmol/L
    - <1.8 mmol/L (for patients with pre-existing cardiovascular diseases)
  - HDL-Cholesterol (HDL-C): >1.0 mmol/L for male
    - >1.3 mmol/L for female
  - Triglyceride (TG): <1.7 mmol/L

1. HK Reference Framework for Diabetes Care for Adults in Primary Care Settings
Management

Lifestyle modification

- 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 (Table 1)

1. Statins (HMG - CoA reductase inhibitors) $^{6,7,8}$
   - ↓ 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 $^9$
   - ↓ TG 25-50% + ↑ HDL-C 10-20%
   - 24 % risk reduction in cardiovascular diseases (MI, stroke) in diabetes subgroup
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

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.
ALT/AST\textsuperscript{10}
- Before start
- \textbf{12 weeks} after start of statin
- Thereafter repeat if clinically indicated
- $< 3 \times \text{ULN} \rightarrow$ careful monitoring
- $\geq 3 \times \text{ULN} \rightarrow$ STOP

**Muscle Soreness/Tenderness/Pain\textsuperscript{10}**
- Blood for CK only if muscle symptoms arise
- **Increase in CK** $\rightarrow$ Rule out common causes like exercise / strenuous work $\rightarrow$ Advise Moderation
- CK $> 10 \times \text{ULN} \rightarrow$ STOP
- CK $3-10 \times \text{ULN} +$ symptoms STOP
- $\rightarrow$ Progressive but asymptomatic CK elevation $\rightarrow$ Reduction in dose or temporary discontinuation\textsuperscript{10}

**Headache and Dyspepsia\textsuperscript{10}**
- Initial
- 6-8 weeks after therapy
- Each follow up

**Monitoring-Laboratory**
- **Monitoring-Symptoms**

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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\textsuperscript{23,24}, 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\textsuperscript{25}
- 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\textsuperscript{26,27}

\textsuperscript{\#} Combination of statin with drugs listed may carry an increase in risk of myositis and liver derangement.

\textsuperscript{\^} (i) LDL lowering efficacy on ezetimibe + lowest-dose statin is comparable to maximum dose of every statin (up to 60\% lowering) but there is slightly higher percentage of patients having elevated ALT/AST compared with statin monotherapy (~1\%); all were asymptomatic, transient and reverted to baseline with discontinuation of drugs\textsuperscript{28–30}.

(ii) Niaspan can slow down the progression of the atherosclerosis, regression the atherosclerotic plaque volume and decrease the cardiovascular morbidity and mortality (surrogate and hard endpoints)\textsuperscript{31–35}. The side effect of most concern of Niaspan is flushing.
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>
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<tbody>
<tr>
<td>Contraindicated with simvastatin:</td>
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<tr>
<td>● Itraconazole</td>
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<tr>
<td>● Ketoconazole</td>
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<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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<td>● Cyclosporine</td>
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<td>● Danazol</td>
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Do not exceed 10 mg simvastatin daily with:
● Verapamil
● Diltiazem

Do not exceed 20 mg simvastatin daily with:
● Amiodarone
● Amlodipine (New)
● Ranolazine (New)

Avoid large quantities of grapefruit juice
(>1 quart daily)

FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. 15 Dec 2011.
Table 1. Management of diabetic dyslipidemia *(in order of priorities)* *(Adopted from American Diabetes Association)*

<table>
<thead>
<tr>
<th>I. LDL-C lowering</th>
<th>II. HDL-C raising</th>
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<tbody>
<tr>
<td>– HMG-CoA reductase inhibitor (statin)</td>
<td>– Behavioural interventions such as weight loss, increased physical activity and smoking cessation may be useful</td>
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<td>– Fibrates (gemfibrozil, fenofibrate) or nicotinic acid</td>
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<th>III. Triglyceride lowering</th>
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<tr>
<td>– Glycaemic control</td>
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<tr>
<td>– Fibrates</td>
</tr>
<tr>
<td>– Statins moderately effective at high dose in hypertriglyceridaemia subjects who also have high LDL-C</td>
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<th>IV. Combined hyperlipidemia</th>
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<tr>
<td>– First choice - Improved glycaemic control plus high dose statin</td>
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<tr>
<td>– Second choice - Improved glycaemic control plus statin plus fibrates* (gemfibrozil, fenofibrate)</td>
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<tr>
<td>– Third choice - Improved glycaemic control plus statin plus nicotinic acid* (glycaemic control must be monitored carefully)</td>
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* The combination of statins with gemfibrozil or fenofibrate, or even nicotinic acid may carry an increased risk of myositis.
Reference:


