Module 9 Lipid Management in Diabetic Patients

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[1].
- In Hong Kong one-third of patients hospitalised for stroke, myocardial infarction and coronary heart failure have diabetes[2,3].
- Dyslipidaemia is a major risk factor for diabetes macrovascular complications[4].
- 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 [5], 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

Management

Lifestyle modification[6,7]

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

Drug treatment (Table 1)

(1) Statins (HMG - CoA reductase inhibitors)[8-10]

- ↓ LDL-C ≥50% if high intensity and 30-50% if moderate intensity, ↓ TG 10-20%, ↑ HDL-C 1-10%[7]
- 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

- ↓ TG 50%, ↑ HDL-C ≤ 20%, ↓ LDL-C ≤ 20%[7]
- There is no strong evidence for using fibrate therapy in primary prevention of cardiovascular disease[7,12]. The use of fibrates in these patients should only be considered when statins are contraindicated.
- Combination therapy of statin and fibrate is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and renal insufficiency and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate)[12,13]. Hence, gemfibrozil should not be initiated in patients on statin therapy and fenofibrate is the preferred agent when used in combination with statin but should be used with cautions and under close monitoring.

(3) Ezetimibe

- ↓ TG 8%, ↑ HDL-C 3%, ↓ LDL-C 15-22% if using ezetimibe alone. Adding ezetimibe to an ongoing statin reduces LDL-C levels by an additional 21-27%. In statin naive patients, combined therapy with ezetimibe and statin reduces LDL-C levels by around an additional 15%[7].
- 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[7,11].
- Life-threatening liver failure with ezetimibe as monotherapy or in combination with statins is extremely rare. The addition of ezetimibe to statin therapy does not appear to increase the incidence of elevated CK levels.[7]

(4) Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

- ↓ TG 26%, ↑ HDL-C 9%, ↓ LDL-C 60%, depending on dose, largely independent of any background therapy[7]
- Have been approved as adjunctive therapy for patients with atherosclerotic cardiovascular disease (ASCVD) or familial hypercholesterolaemia who are receiving maximally tolerated statin therapy but require additional lowering of LDL-C[12].
- Requires subcutaneous injection
- Adverse events were minimal and tolerable[14]. Among the most frequently reported side effects are itching at the site of injection and flu-like symptoms[7].

Figure 1. Practical algorithm of statin usage

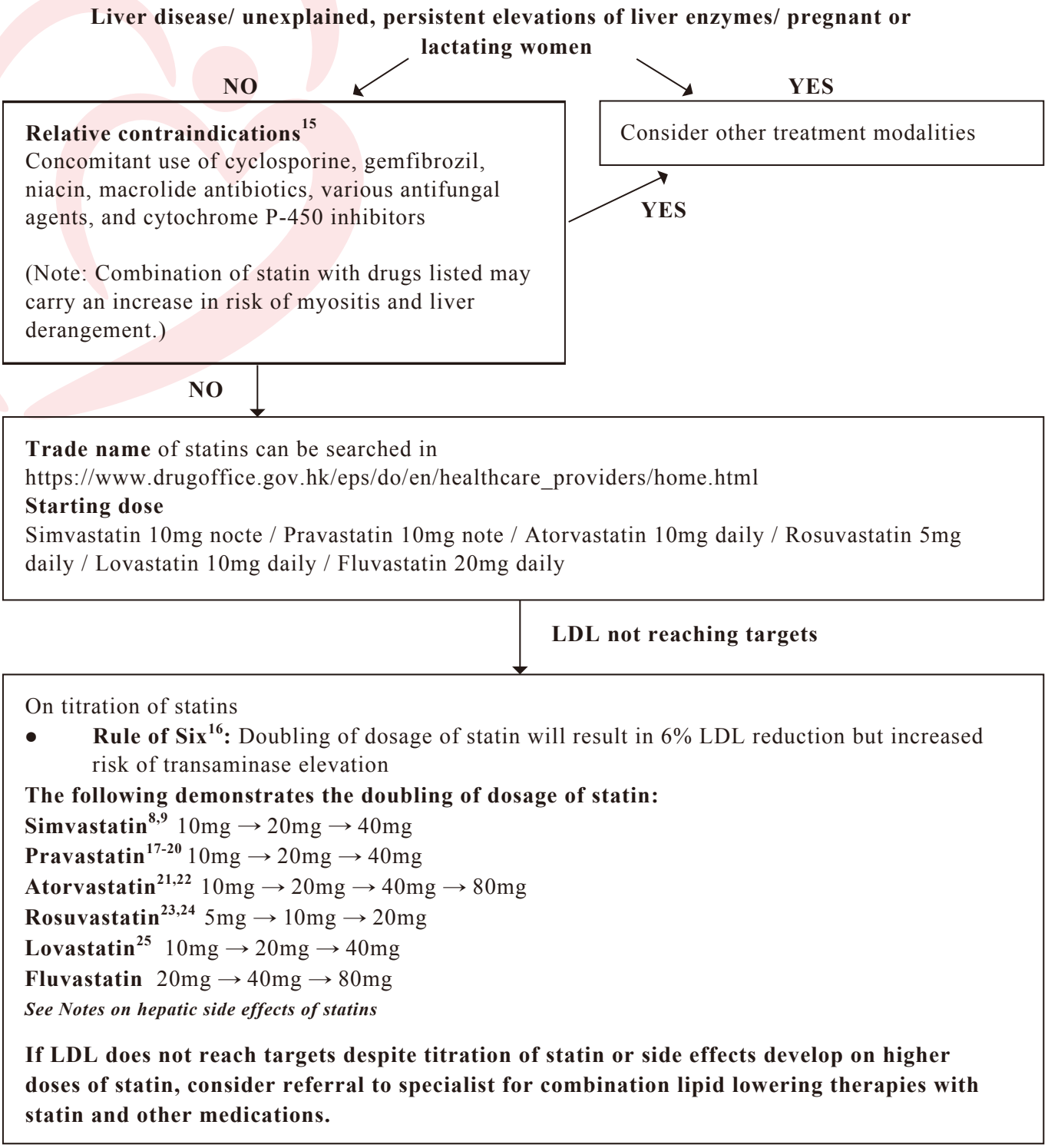

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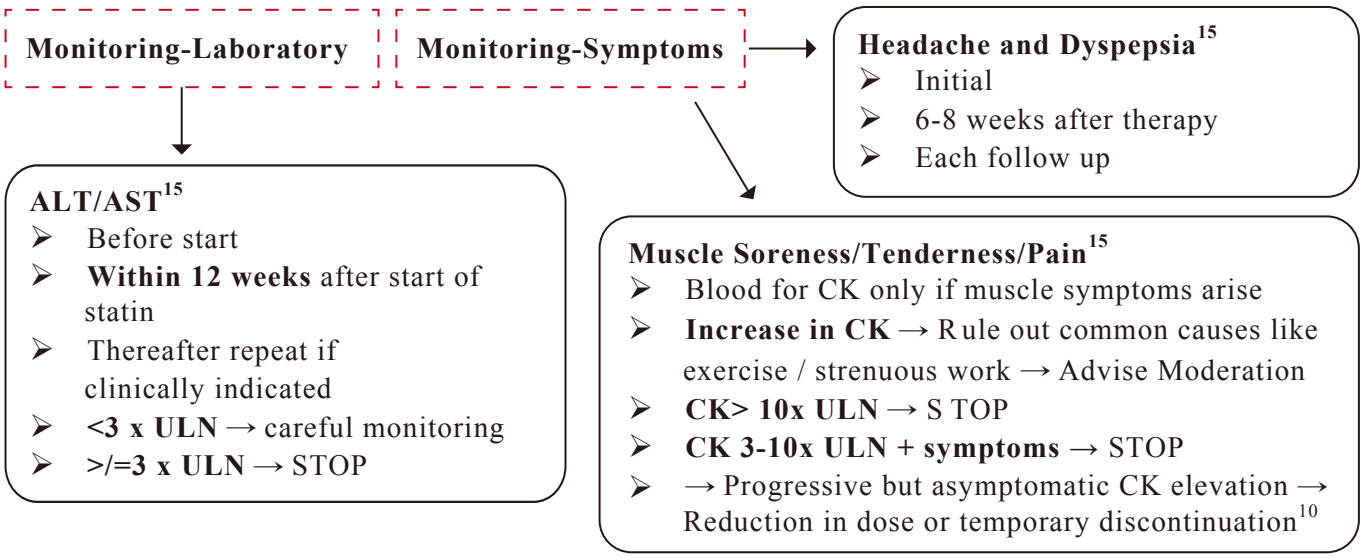
Figure 1. Practical algorithm of statin usage (Continued)



Abbreviations:

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

Notes on hepatic side effects of statin:

- Elevated hepatic transaminase generally occurs in 0.5%-2% of cases and is dose dependent [26,27], 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 [28]
- 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 [29,30]

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.

New simvastatin label
Contraindicated with simvastatin: • Itraconazole • Ketoconazole • Posaconazole (New) • Erythromycin • Clarithromycin • Telithromycin • HIV protease inhibitors • Nefazodone • Gemfibrozil • Cyclosporine • Danazol
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.
http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm

Table 1. Management of diabetic dyslipidaemia[12]

I. Lifestyle modification and glycaemic control optimisation:
- Recommend lifestyle modification to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease (ASCVD):
  - weight loss (if indicated)
  - application of a Mediterranean diet or Dietary Approaches to Stop Hypertension (DASH) dietary pattern
  - reduction of saturated fat and trans fat
  - increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/ sterols intake
  - increased physical activity
- Intensify lifestyle therapy and optimise glycaemic control for patients with elevated triglyceride levels (≥1.7 mmol/L) and/or low HDL cholesterol (<1.0 mmol/L for men, <1.3 mmol/L for women)

II. LDL-C lowering and cardioprotection:
- Statins are the drugs of choice in ASCVD primary and secondary prevention.

III. Add-on therapy in association with statins when the therapeutic target is not achieved at the maximum tolerated statin dose:
- Ezetimibe, PCSK9 inhibitor[12,13]
- Fibrates are not recommended to be add-on drugs to statin therapy for lowing LDL-C[13].

IV. Control of hypertriglyceridaemia:
- Fasting or non-fasting triglycerides (TG) 1.7-5.6 mmol/L:
  - address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise TG.
- Fasting TG levels ≥ 5.7 mmol/L:
  - evaluate for secondary causes of hypertriglyceridaemia and consider medical therapy (fibrate and/or fish oil) to reduce the risk of pancreatitis.
  - if 10-year ASCVD risk is ≥7.5%, consider to initiate statin therapy or increase statin dosage. More potent statins (atorvastatin, rosuvastatin and pitavastatin) demonstrate a robust lowering of TG levels, especially at high doses and in patients with hypertriglyceridaemia[7].
- Combination therapy with statin and fibrate is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk is higher when statins are combined with gemfibrozil (compared with fenofibrate). Hence, fenofibrate is the preferred agent when used in combination with statin but should be used with cautions and under close monitoring.

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