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[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[3], 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[4]

Risk level	**Clinical presentation of individuals**
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 hypercholesterolaemia
High risk	(1) Individuals with moderate to severe chronic kidney disease (estimated glomerular filtration rate [eGFR] <60ml/min/1.73 m^2) (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)*

A. Tools available as paper-based tables or charts

1. *Framingham-based*
   - The original Framingham risk score (published in 1998) derived from Framingham Heart Study[5], a prospective cohort of largely Caucasian population, was widely adapted worldwide, such as in National Cholesterol Education Program (NCEP)[6] and Joint British Societies 2 (JBS2)[7].
   - The Framingham system had been recalibrated for Asian populations for different cohorts, for example,
     - Singapore-adapted Framingham Risk Score[4]: adjusted for Chinese, Malay and Indian populations in Singapore
     - Asia Pacific Cohort Studies Collaboration[8]: cohorts from Japan, Korea, Singapore and China
     - The Chinese Multi-Provincial Cohort Study[9]: Chinese cohorts from Chinese Mainland
   - 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[10]. There is currently no recalibrated tool available for local use

2. *Systemic Coronary Risk Evaluation (SCORE)*[11]
   - Based on European cohorts
   - Recommended by European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS)[12, 13]

B. Tools available as web-based calculators

1. *QRISK2*[14]
   - 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)[15]

2. *JBS3 Risk Calculator*[16]
   - Based on QRISK Lifetime cardiovascular risk calculator
   - Recommended by Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3)[17]

3. *Pooled Cohort Equations*[18]
   - Derived from Whites and African Americans cohorts
   - Recommended by American College of Cardiology/ American Heart Association (ACC/AHA)[19]
   - 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[10]

Table 2. Examples of the cardiovascular risk assessment tools

Risk estimation system	Recommending guideline	Variables	Endpoint	Remarks
Paper-based tables or charts				
Framingham-based	● NCEP guidelines[6] ● JBS2 guidelines[7] ● Singapore guideline[4]	Sex, age, total cholesterol, HDL-C, SBP, smoking status, DM, HT treatment	10-year risk of CAD events (in original version)	NCEP and JBS2 guidelines are commonly used as reference in public sectors
SCORE[11]	● ESC/EAS Guidelines for the management of dyslipidaemias[12] ● European Guidelines on cardiovascular disease prevention in clinical practice[13]	Sex, age, total cholesterol or total cholesterol/HDL-C ratio, SBP, smoking status	10-year risk of CVD mortality	Web-based interactive tool (HeartScore) is available
Web-based calculators				
QRISK2[14]	● NICE guidelines on lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease[15]	Sex, age, race, total cholesterol/HDL-C ratio, SBP, smoking status, DM, HT treatment, family history, BMI, chronic disease	10-year risk of CVD events	
JBS3 isk calculator[16]	● Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3)[17]	Sex, age, race, non-fasting total cholesterol and HDL-C, SBP, smoking status, DM, HT treatment, family history, BMI, chronic disease	10-year and lifetime risk of CVD events	
Pooled Cohort Equations[18]	● 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol[19]	Sex, age, race (white or other/African American), total cholesterol, HDL-C, SBP, smoking status, DM, HT treatment	10-year risk for the first atherosclerotic CVD event	Poor Calibration for Hong Kong Chinese[10]

Abbreviations:
CVD: Cardiovascular disease
BMI: Body mass index
CAD: Coronary artery disease
HT: Hypertension
DM: Diabetes mellitus
HDL-C: High-density lipoprotein cholesterol
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 3.

For lipid management in diabetic patients, please refer to Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care Settings.

Table 3. Treatment target levels of lipid (if available) for primary prevention in some of the international guidelines

Guideline	Risk Category	Lipid Target (if any)/ treatment strategies	Remarks
NCEP (2004)[20]	*Low*: 0-1 risk factor†	LDL-C < 4.1 mmol/L	Lipid targets are commonly used as reference in public sectors
	Moderate: ≥ 2 risk factors and 10-year CHD risk < 10%	LDL-C < 3.4 mmol/L	
	Moderately high: ≥ 2 risk factors and 10-year CHD risk 10 to 20%	LDL-C < 3.4 mmol/L (optional goal: < 2.6 mmol/L)	
	High: CHD equivalent‡ or 10-year CHD risk > 20%	LDL-C < 2.6 mmol/L (optional goal: < 1.8 mmol/L for very high risk)	
JBS2 (2005)[7]	*High:* 10-year CVD risk ≥ 20%	*Optimal targets:* LDL-C < 2.0mmol/L and TC < 4.0mmol/L, or 30% LDL-C reduction and 25% TC reduction *Audit (minimum) standard:* LDL-C < 3.0mmol/L and TC < 5.0mmol/L	Prediction charts are commonly used as reference in public sectors
JBS3 (2014)[17]	*Cholesterol lowering drug therapy is recommended in the following conditions:* • established CVD • high risk of CVD: DM age > 40 years, CKD stages 3–5, or familial hyperlipidemia • high 10-year CVD risk (threshold to be defined by NICE guidance, i.e. ≥ 10%) • high lifetime CVD risk estimated from JBS3 calculator, in whom lifestyle changes alone are considered insufficient by the physician and person concerned	Non-HDL-C of < 2.5 mmol/L (equivalent to <1.8 mmol/L for LDL-C)	A non-fasting blood sample as an estimate of the lipid profile

(Table continued on next page)

†Risk factors in NCEP guideline include cigarette smoking, hypertension, low HDL cholesterol, family history of premature CHD (CHD in male first-degree relative < 55 years of age; CHD in female first-degree relative < 65 years of age), and age (men ≥ 45 years; women ≥ 55 years).

‡CHD risk equivalents in NCEP guideline include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or > 50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD > 20%.

Table 3. Treatment target levels of lipid (if available) for primary prevention in some of the international guidelines. *(Continued)*

Guideline	Risk Category	Lipid Target (if any)/ treatment strategies	Remarks
NICE (2014)[15]	10-year CVD risk ≥ 10%	Offer atorvastatin 20 mg for the primary prevention of CVD, and aim at > 40% non-HDL-C reduction	Fasting blood is not required for non-HDL-C
ESC/ EAS (2019)[12]	*Low:* • SCORE < 1%	Consider drug treatment if LDL-C ≥ 3.0 mmol/L despite of lifestyle intervention, target LDL-C < 3 mmol/L	
	Moderate: • Young patients (Type 1 DM <35 years; Type 2 DM <50 years) with DM duration <10 years, without other risk factors. • SCORE ≥ 1% to < 5%	LDL-C < 2.6 mmol/L	
	High: • markedly elevated single risk factors (e.g. TC > 8 mmol/L, LDL-C >4.9 mmol/L, BP ≥ 180/110 mmHg) or • Patients with FH without other major risk factors or • Patients with DM without target organ damage (microalbuminuria, retinopathy, or neuropathy), with DM duration≥10 years or another additional risk factor or • moderate CKD (GFR 30–59 mL/min/1.73 m2) or • SCORE ≥ 5% to < 10%	LDL-C < 1.8 mmol/L and ≥ 50% reduction on LDL-C	
	Very high: • documented ASCVD or • DM with target organ damage (microalbuminuria, retinopathy, or neuropathy), or at least three major risk factors, or early onset of Type 1 DM of long duration (>20 years) or • severe CKD (GFR < 30 mL/min/1.73 m2) or • SCORE ≥ 10% • FH with ASCVD or with another major risk factor	LDL-C < 1.4mmol/L (with and without FH) and ≥ 50% reduction on LDL-C Remark For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.	

(Table continued on next page)

Table 3. Treatment target levels of lipid (if available) for primary prevention in some of the international guidelines. *(Continued)*

Guideline	Risk Category	Lipid Target (if any)/ treatment strategies	Remarks
New Zealand (2018)[21]	TC:HDL-C ratio ≥ 8	Recommend drug treatment irrespective of CVD risk	Risk based on new 5-year CVD risk prediction equations from the New Zealand PREDICT study[22] (i.e. NZ Primary Prevention Equations). However, the NZ Primary Prevention equations are currently not yet fully available for clinicians to use in practice. Clinicians can classify patients as low (5-year CVD risk <10%), intermediate (5-year CVD risk 10-20%) or high risk (5-year CVD risk ≥20%) using existing Framingham-based equations, and follow the appropriate management recommendations for the same risk category in the 2018 CVD consensus statement. Non-fasting blood is used to calculate CVD risk
	Low risk: 5-year CVD risk < 5%	Lifestyle advice (diet, weight management, physical activity, smoking cessation)	
	Intermediate risk: 5-year CVD risk 5-15%	Individualised informed decision on drug treatment. ≥ 40% LDL-C reduction is recommended if drug treatment commenced	
	High risk: 5-year CVD risk ≥ 15%	Recommend drug treatment and target LDL-C < 1.8mmol/L	
AHA/ ACC (2018)[19]	*Recommends the use of high or moderate intensity statin in different patient categories*		*Moderate-intensity statin:* 30% to < 50% LDL-C reduction (e.g. atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40mg); *High-intensity statin:* ≥ 50% LDL-C reduction (e.g. atorvastatin 40-80 mg, rosuvastatin 20-40mg)
	Primary LDL-C ≥ 4.9mmol/L	High-intensity statin. Additional therapy (e.g. ezetimibe) for those achieve < 50% reduction of LDL-C and/or LDL-C ≥ 2.6 mmol/L with maximally tolerated statin therapy	
	Age 40-75 years with DM	Moderate-intensity statin. Consider high-intensity statin therapy with the aim to reduce LDL-C levels by ≥ 50% for DM patients with multiple ASCVD risk factors	
	Age 40-75 years without DM and LDL-C ≥ 1.8 to < 4.9 mmol/L		
	• *Low risk:* 10-year ASCVD risk < 5%	Emphasise lifestyle modifications	
	• *Borderline risk:* 10-year ASCVD risk 5% - < 7.5%	If risk enhancers* present, then risk discussion regarding moderate-intensity statin therapy	
	• *Intermediate risk:* 10-year ASCVD risk ≥ 7.5% - < 20%	If risk estimate with risk enhancers* favour statin, initiate moderate- intensity statin to reduce LDL-C by 30-49%	
	• *High risk:* 10-year ASCVD risk ≥ 20%	Initiate statin to reduce LDL-C ≥ 50% (high-intensity statin)	

* ASCVD risk enhancers in AHA/ACC guideline: family history of premature ASCVD, persistent elevated LDL-C ≥ 4.1 mmol/L, chronic kidney diseases, metabolic syndrome, condition specific to women (e.g. preeclampsia, premature menopause), inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV), ethnicity (e.g. South Asian ancestry), persistently elevated triglycerides (≥ 2 mmol/L)

Abbreviations:

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

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 [6, 12]

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

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[23,24]. These subjects should receive more meticulous monitoring of their medication-taking behaviour.

(1) Statins (HMG - CoA reductase inhibitors) [25-27]

- ↓ LDL-C ≥50%, if high intensity and 30-50% if moderate intensity, ↓TG 10-20%, ↑ HDL-C 1-10%[12]
- 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 [28]

- ↓ TG 50%, ↑ HDL-C ≤20%, ↓ LDL-C ≤20%[12]
- There is no strong evidence for using fibrate therapy in primary prevention of cardiovascular disease[12,28]. 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)[19,28]. 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.

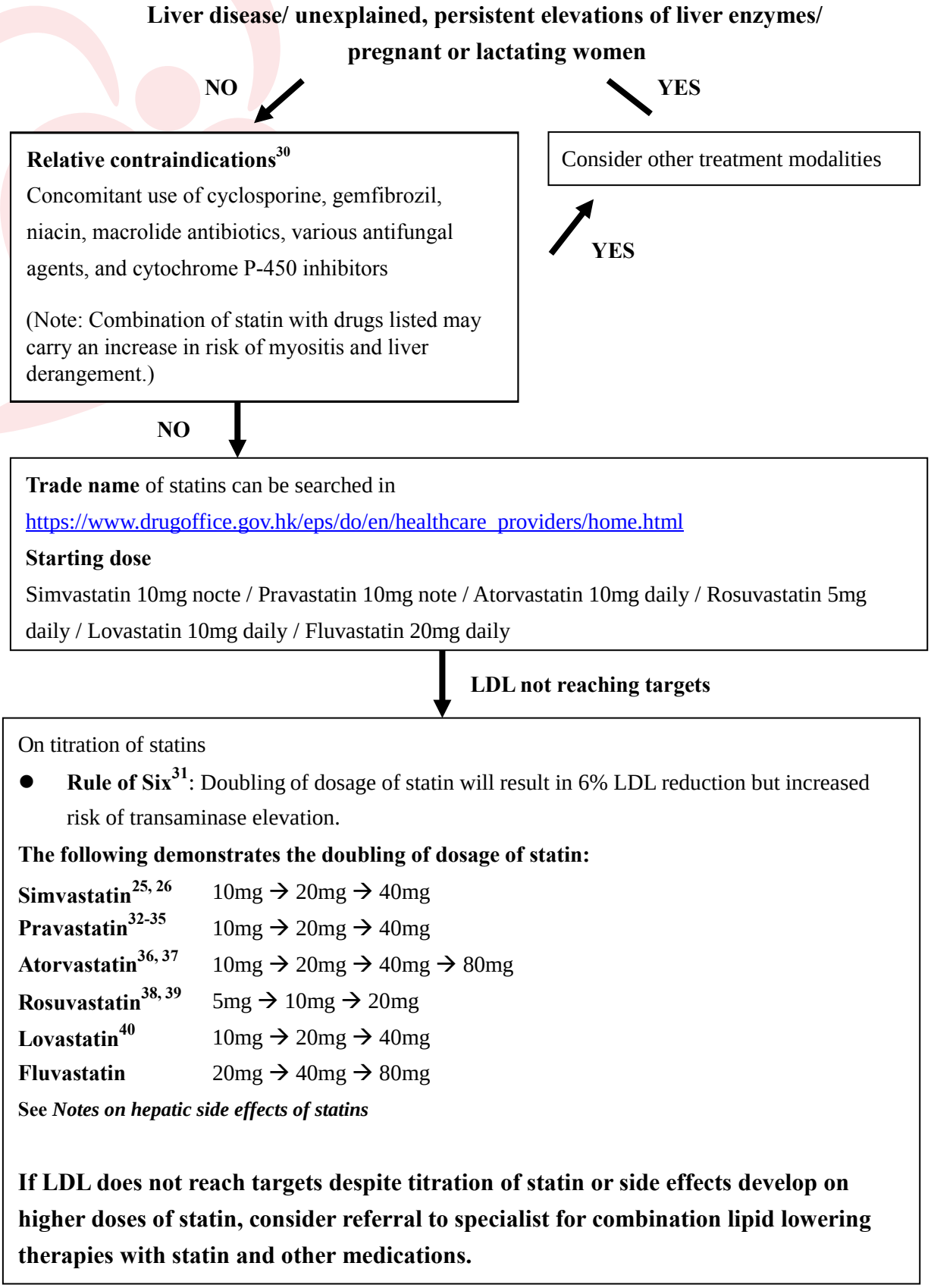
(3) *Ezetimibe*

- ↓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%.[12]
- 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[4,12]
- 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.[12]

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

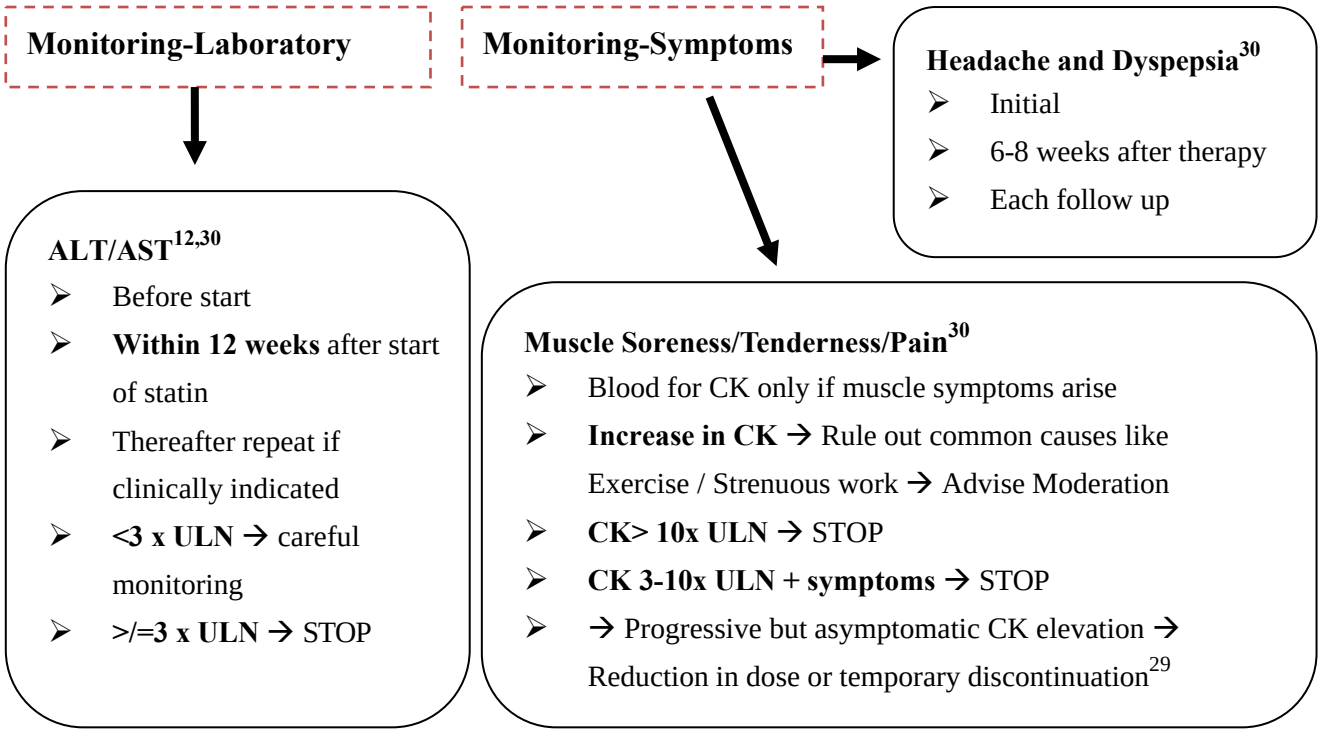
- ↓TG 26%, ↑HDL-C 9%,↓ LDL-C 60%, depending on dose, largely independent of any background therapy[12]
- Have been approved as adjunctive therapy for patients with atherosclerotic cardiovascular disease (ASCVD) or familial hypercholesterolaemia who are receiving maximally tolerated statin therapy but require additional lowering of LDL-C[28].
- Requires subcutaneous injection
- Adverse events were minimal and tolerable[29]. Among the most frequently reported side effects are itching at the site of injection and flu-like symptoms[12].

Figure 1. Practical algorithm of statin usage



(Figure continued on next page)

Figure 1. Practical algorithm of statin usage (Continued)



Abbreviations:

ALT: Alanine transaminase
AST: Aspartate aminotransferase
CK: Creatine kinase
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[41, 42], 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[43]
- 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[44, 45]

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.

Reference:

1. Hong Kong Reference Framework for Hypertension Care for Adults in Primary Care Settings [document on the Internet]. HKSAR: Food and Health Bureau. 2010 [updated 2021]. Available from: https://www.healthbureau.gov.hk/pho/rfs/src/pdfviewer/web/pdf/hypertensioncareforadults/en/13_en_RF_HT_full.pdf.
2. U.S. Department of Health and Human Services. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[Internet]. Bethesda, MD: U.S. Department of Health and Human Services; c2004. Available from: http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf [cited 2015 Jun 1].
3. World Health Organization. Prevention of cardiovascular disease. Guidelines for assessment and management of cardiovascular risk. [Internet]. Geneva: WHO; 2007. Available from: http://www.who.int/cardiovascular_diseases/guidelines/Full%20text.pdf [cited 2017 Feb 27].
4. Ministry of Health, Singapore. MOH Clinical Practice Guidelines. Lipid. [Internet]. Singapore: MOH; Feb 2016. Available from: http://www.moh.gov.sg/cpg [cited 2017 Feb 27].
5. Framingham Heart Study [Internet]. US: MA; [cited 26 May 2015]. Available from: http://www.framinghamheartstudy.org.
6. Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation. 2002 Dec 17; 106(25): 3143-421.
7. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart. 2005 Dec;91 Suppl 5:v1-52.
8. Asia Pacific Cohort Studies Collaboration, Barzi F, Patel A, Gu D, Sritara P, Lam TH, et al. Cardiovascular risk prediction tools for populations in Asia. J Epidemiol Community Health. 2007 Feb;61(2):115-21.
9. Liu J, Hong Y, D'Agostino RB Sr, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA. 2004 Jun 2;291(21):2591-9.
10. Lee CH, Woo YC, Lam JK, et al. Validation of the Pooled Cohort equations in a long-term cohort study of Hong Kong Chinese. J Clin Lipidol. 2015 Sep-Oct;9(5):640-6.e2.
11. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003 Jun;24(11):987-1003.

12. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111-188.
13. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016 Aug 1;37(29):2315-81.
14. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008 Jun 28;336(7659):1475-82.
15. National Institute of Clinical Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181) [Internet]. London (UK): NICE; Jul 2014 [updated Sept 2016; cited 8 Apr 2021]. Available from: https://www.nice.org.uk/guidance/cg181/.
16. Risk Calculator. JBS3. Joint British Societies for the prevention of cardiovascular disease. [Internet] London: British Cardiovascular Society. Available from: https://www.jbs3risk.co.uk/pages/risk_calculator.htm [cited 2019 Jan 21].
17. JBS3 Board, Deanfield J, Sattar N, et al. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. 2014 Apr;100 Suppl 2:ii1-ii67.
18. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S49-73. Epub 2013 Nov 12.
19. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. Circulation. 2019;139:e1082–e1143.
20. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004 Jul 13;110(2):227-39.
21. Ministry of Health. Cardiovascular Disease Risk Assessment and Management for Primary Care. 2018 [cited 2019 Jan 21]. Wellington: Ministry of Health. Available

from: https://www.health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care.

22. Pylypchuk R, Wells S, Kerr A, et al. Cardiovascular disease risk prediction equations in 400,000 primary care patients in New Zealand: a derivation and validation study. Lancet. 2018 May 12;391(10133):1897-1907.
23. Wong MCS, Jiang JY, Yan BP, Griffiths SM. Subjects at risk of discontinuation of lipid-lowering agents: a 6-month cohort study among 12,875 patients in a Chinese population. Clin Ther. 2011 May;33(5):617-28.
24. Wong MCS, Jiang JY, Griffiths SM. Adherence to lipid-lowering agents among 11,042 patients in clinical practice. Int J Clin Pract. 2011 Jul;65(7):741-8.
25. The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344(8934):1383-9.
26. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002; 360(9326): 7-22.
27. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004: 364(9435): 685-96.
28. American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes - 2021. Diabetes Care. 2021;44(Suppl.1):S125–S150.
29. Choi J, Khan AM, Jarmin M, Goldenberg N, Glueck CJ, Wang P. Efficacy and safety of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, alirocumab and evolocumab, a post-commercialization study. Lipids Health Dis. 2017 Jul 24;16(1):141.
30. Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. J Am Coll Cardiol. 2002; 40(3):567-72.
31. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy of Atorvastatin versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in patients with hypercholesterolemia (The CURVES study). Am J Cardiol. 1998; 81(5):582-7.
32. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with Pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995; 333(20):1301-7.

33. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al, for the Cholesterol and Recurrent Events Trial Investigators. The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels. N Engl J Med. 1996; 335(14):1001-9.
34. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of Cardiovascular Events and Death with Pravastatin in Patients with Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels. N Engl J Med. 1998; 339(19):1349-57.
35. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized control trial. Lancet. 2002; 360(9346):1623-30.
36. Sever PS, Dahlöf B, Poulter NR, Wedeal H, Beevers G, Caulfield M, et al. . Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial- Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. Lancet. 2003; 361(9364):1149-58.
37. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004; 350(15):1495-504.
38. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006; 295(13):1556-65.
39. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008; 359(21):2195-207.
40. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998; 279(20):1615-22.
41. Hsu I, Spinler SA, Johnson NE. Comparative evaluation of the safety and efficacy of HMG-CoA reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia. Ann Pharmacother. 1995; 29(7-8):743-59.
42. Bradford RH, Shear CL, Chremos AN, Dujovne C, Downton M, Franklin FA, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Arch Intern Med. 1991; 151(1):43-9.

43. Pedersen TR and Tobert JA. Benefits and risks of HMG-CoA reductase inhibitors in the prevention of coronary heart disease: a reappraisal. Drug Saf. 1996; 14(1):11-24.
44. Cressman MD, Hoogwerf BJ, Moodie DS, Olin JW, Weinstein CE. HMG-CoA reductase inhibitors. A new approach to the management of hypercholesterolemia. Cleve Clin J Med. 1988; 55(1):93-100.
45. Hunninghake DB. Drug treatment of dyslipoproteinemia. Endocrinol Metab Clin North Am. 1990; 19(2):345-60.