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 hypercholesterolemia
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)*

1. *Framingham-based*
   - The original Framingham risk score (published in 1998) derived from Framingham Heart Study[5], a prospective cohort of largely Caucasian population, were widely adapted worldwide, such as in National Cholesterol Education Program (NCEP)[6], Joint British Societies 2 (JBS2)[7] and the New Zealand Cardiovascular Risk Charts[8]; 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[9]: adjusted for Chinese, Malay and Indian populations in Singapore
     - Asia Pacific Cohort Studies Collaboration[10]: cohorts from Japan, Korea, Singapore and China
     - The Chinese Multi-Provincial Cohort Study[11]: 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[12]. There is currently no recalibrated tool available for local use

2. *Systemic Coronary Risk Evaluation (SCORE)*[13]
   - Based on European cohorts
   - Recommended by European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS)[14, 15]

3. *QRISK2*[16]
   - 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)[17]

4. *Pooled Cohort Studies 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[12]

Table 1. Examples of the cardiovascular risk assessment tools (information as at Feb 2017)

Risk estimation system	Recommending guideline	Variables	Endpoint	Remarks
Framingham-based	● NCEP guidelines[6] ● JBS2 guidelines[7] ● New Zealand guidelines[8] ● Singapore guideline[9]	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[13]	● ESC/EAS Guidelines for the management of dyslipidaemias[14] ● European Guidelines on cardiovascular disease prevention in clinical practice[15]	Sex, age, total cholesterol or total cholesterol/HDL-C ratio, SBP, smoking status	10-year risk of CVD mortality	
QRISK2[16]	● NICE guidelines on lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease[17]	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	
Pooled Cohort Studies Equations[18]	● ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk[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[12]

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)

Guideline	Risk Category	Lipid Target (if any)/ treatment strategies	Remarks
NCEP (2004)[20]	*Low*: 0-1 risk factor	LDL-C < 4.1mmol/L	Lipid targets are commonly used as reference in public sectors
	Moderate: ≥ 2 risk factors and 10-year CHD risk < 10%	LDL-C < 3.4mmol/L	
	Moderately high: ≥ 2 risk factors and 10-year CHD risk 10 to ≤ 20%	LDL-C < 3.4mmol/L (optional goal: < 2.6mmol/L)	
	High: CHD equivalent or 10-year CHD risk > 20%	LDL-C < 2.6mmol/L (optional goal: < 1.8mmol/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
New Zealand (2012 and 2013)[21, 22]	*For original recommendation[21], optimal targets were recommended.*		
	5-year CVD risk ≥ 15%	LDL-C < 2.0mmol/L, TC < 4.0mmol/L, HDL-C ≥ 1.0mmol/L, TG <1.7mmol/L	
	Subsequent update[22] does not recommended specific targets.		
	TC ≥ 8mmol/L or TC:HDL-C ratio ≥ 8	Recommend drug treatment irrespective of CVD risk	
	Combined CVD risk > 20%	Recommend drug treatment	
	Combined CVD risk 10-20%	Shared decision-making approach on drug treatment	
ACC/ AHA (2013)[19]	*Recommends the use of high or moderate intensity statin in different risk. No recommendations on specific treatment targets.*		
	Primary LDL-C ≥ 4.9mmol/L	High intensity statin	
	Age 40-75 years without diabetes and 10-year ASCVD risk ≥ 7.5%	Moderate to high intensity statin	
	Remarks: Moderate-intensity statin: 30% to < 50% LDL-C reduction. High-intensity statin: ≥ 50% LDL-C reduction		

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Table 2. 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)[17]	*High:* 10-year CVD risk ≥ 10%	> 40% non-HDL-C reduction	Fasting blood is not required for non-HDL-C
ESC/ EAS (2016)[14]	*Moderate:* • SCORE ≥ 1% to < 5%	LDL-C < 3.0mmol/L	
	High: • markedly elevated single risk factors (e.g. familial dyslipidaemia, severe HT) or • most other people with DM (some young people with type I diabetes may be at low or moderate risk) or • moderate CKD or • SCORE ≥ 5% to < 10%	LDL-C < 2.6mmol/L. ≥ 50% reduction on LDL-C if baseline is between 2.6 and 5.1mmol/L	
	Very high: • documented CVD or • DM with target organ damage or • severe CKD or • SCORE ≥ 10%	LDL-C < 1.8mmol/L. ≥ 50% reduction on LDL-C if baseline is between 1.8 and 3.5 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

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

(1) Statins (HMG - CoA reductase inhibitors) [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 [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[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[4]
- No major adverse effects have been reported; the most frequent adverse effects are moderate elevations of liver enzymes and muscle pain[14]

Figure 1. Practical algorithm of statin usage

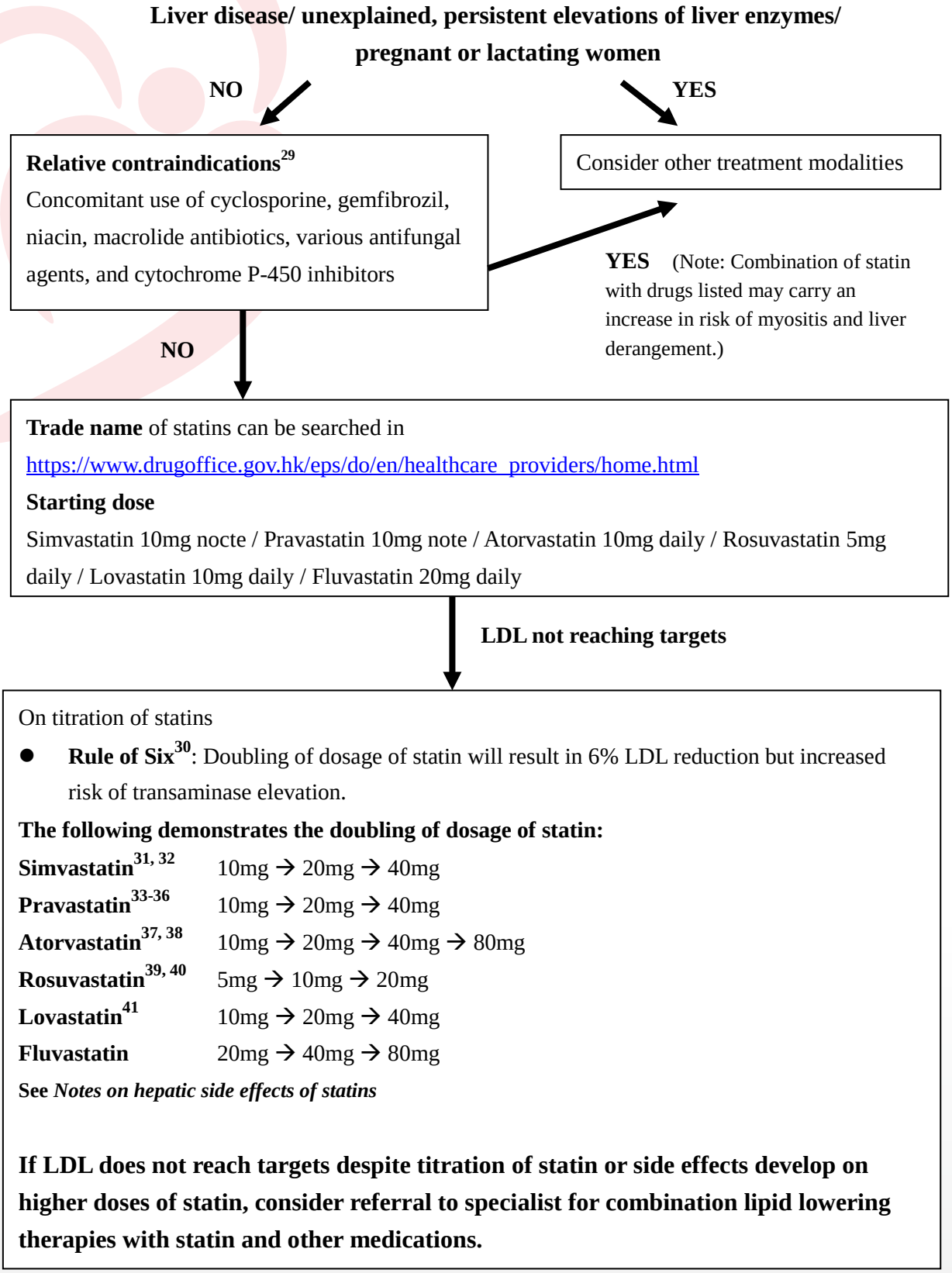

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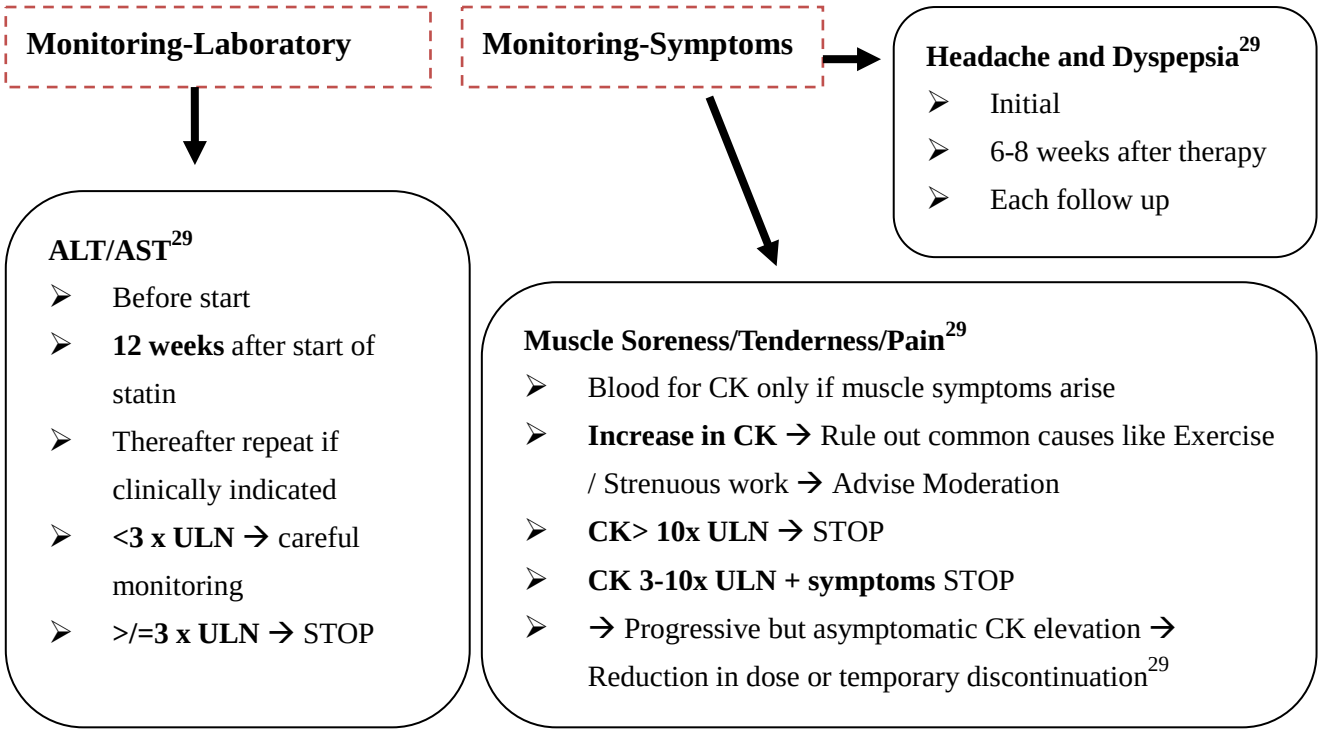
Figure 1. Practical algorithm of statin usage (Continued)



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[42, 43], 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[44]
- 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[45, 46]

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 2013. HKSAR: Department of Health. 2013. Available from: http://www.pco.gov.hk/english/resource/files/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]. Available from: http://www.framinghamheartstudy.org [cited 2015 May 26].
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. Dyslipidaemia Advisory Group on behalf of the Scientific Committee of the National Heart Foundation of New Zealand. 1996 National Heart Foundation clinical guidelines for the assessment and management of dyslipidaemia. NZ Med J. 1996: 109: 224-31.
9. Ministry of Health, Singapore. MOH Clinical Practice Guidelines. Screening for cardiovascular disease and risk factors. [Internet]. Singapore: MOH; Jan 2011. Available from: http://www.moh.gov.sg/cpg [cited 2017 Feb 27].
10. 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.
11. Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, 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.
12. Lee CH, Woo YC, Lam JK, Fong CH, Cheung BM, 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.

13. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, 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.
14. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016 Oct 14;37(39):2999-3058. Epub 2016 Aug 27.
15. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, 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. 0Epub 2016 May 23.
16. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008 Jun 28;336(7659):1475-82.
17. National Institute of Clinical Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 181 [Internet]. London: National Institute of Clinical Excellence; 2014. Available from: https://www.nice.org.uk/guidance/cg181/ [cited 2015 Jun 1]
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. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45. Epub 2013 Nov 12.
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. New Zealand Guidelines Group. New Zealand Primary Care Handbook 2012. 3rd ed. Wellington: New Zealand Guidelines Group; 2012.
22. Cardiovascular disease risk assessment (updated 2013). New Zealand Primary Care Handbook 2012: Wellington: Ministry of Health. December 2013.

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. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. New Engl J Med. 1999; 341(6):410-8.
29. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C, et al. ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. J Am Coll Cardiol. 2002; 40(3):567-72.
30. 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.
31. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: Scandinavian Simvastatin Survival Study (4S). Lancet. 1994; 344(8934):1383-9.
32. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with Simvastatin in 20536 high-risk individuals: a randomized placebo-controlled trial. Lancet. 2002; 30(9326):7-22.
33. 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.
34. 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.

35. 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.
36. 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.
37. 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.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.
46. Hunninghake DB. Drug treatment of dyslipoproteinemia. Endocrinol Metab Clin North Am. 1990; 19(2):345-60.