National University Polyclinics
A member of the NUHS

LIPIDS

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Contents

OVERVIEW

Introduction & Screening

Blood lipid levels are important risk factors for coronary artery disease (CAD). The relationship between CAD and total cholesterol levels is continuous and curvilinear. Most of the cholesterol in the blood is carried on low density lipoprotein (LDL) particles, and LDL cholesterol (LDL-C) is a well-established risk factor for CAD. **[1]**

Whom to Screen?

- All patients aged 40 years and above **[2]**
- All patients aged 18 years and above with risk factors for coronary artery disease (CAD)*. **[GPP, 1][2]**
- All patients with **established coronary heart disease, cerebrovascular disease, peripheral vascular disease, hypertension and diabetes mellitus, impaired fasting glycaemia or impaired glucose tolerance irrespective of age.**
- Screening of all first degree relatives of diagnosed familial hypercholesterolemia patients is recommended (see section on Familial Hypercholesterolemia). **[GPP, 1]**

Screening for lipids should be performed as part of a global cardiovascular / cardiometabolic risk assessment. Clinician should consider screening for other risk factors such as blood pressure and blood glucose.

* - Risk factors for CAD include:

1. Diabetes mellitus.
2. Multiple CAD risk factors (e.g. tobacco use, hypertension, impaired fasting glycaemia or impaired glucose tolerance).
3. A family history of cardiovascular disease before age 50 years in male relatives or before age 60 years in female relatives.
4. A family history suggestive of familial hypercholesterolemia.

Screening may be done using a fasting or non-fasting Lipid Panel (as part of the Non-Fasting Coronary Risk Screen). **In individuals with a higher risk of lipid disorders or a strong family history (e.g. familial hyperlipidaemia), the fasting lipid profile is preferred*.**

A Fasting Lipid Panel should be performed annually for individuals with diabetes or hypertension.

Screening should be done annually, except for individuals with screening results within the LDL-C target levels (see page 5) and have low triglyceride (TG) levels (< 2.3 mmol/L), when screening should be repeated at 3-yearly intervals unless they are at very high or high risk of CAD, in which case screening should be repeated annually. **[GPP, 1]**

** - sentence in bold drawn from MOH paper*

Screening with Non-Fasting Lipid Panel

Clinicians should note when interpreting non-fasting lipid profiles for screening ~~is~~ that post-meal TG levels can be slightly higher while LDL-C levels can be slightly lower compared to the fasting levels.

Clinicians who use the non-fasting Lipid Panel need to be aware of possible misclassification in test results, as follows:

(a) Over-diagnosis of Hypertriglyceridemia: Individuals with raised TG levels in the non-fasted state, who would have otherwise had normal TG levels in the fasted state

Many of these individuals may still benefit from lifestyle intervention in the first instance. There may also be some cases of spuriously high TG readings that are secondary to very high fat intake prior to sampling. **Clinicians may consider repeating the fasting lipid profile to confirm the level and to guide treatment decisions**, especially when planning to start pharmacological therapy.

(b) Under-diagnosis of Hyperlipidaemia: Individuals with normal/borderline LDL-C levels in the non-fasted state, who would have otherwise have had elevated LDL-C levels in the fasted state

The magnitude of the difference in LDL-C values in these scenarios is small and may not significantly alter the risk of cardiovascular disease over a 3-year period. Furthermore, these individuals should undergo repeat screening in the next 3 years, and there would be opportunities to identify them at subsequent testing if LDL-C levels remain elevated. **Depending on clinical judgment patients with results close to the threshold (based on their risk category) may need to be reviewed earlier with a fasting lipid profile**.

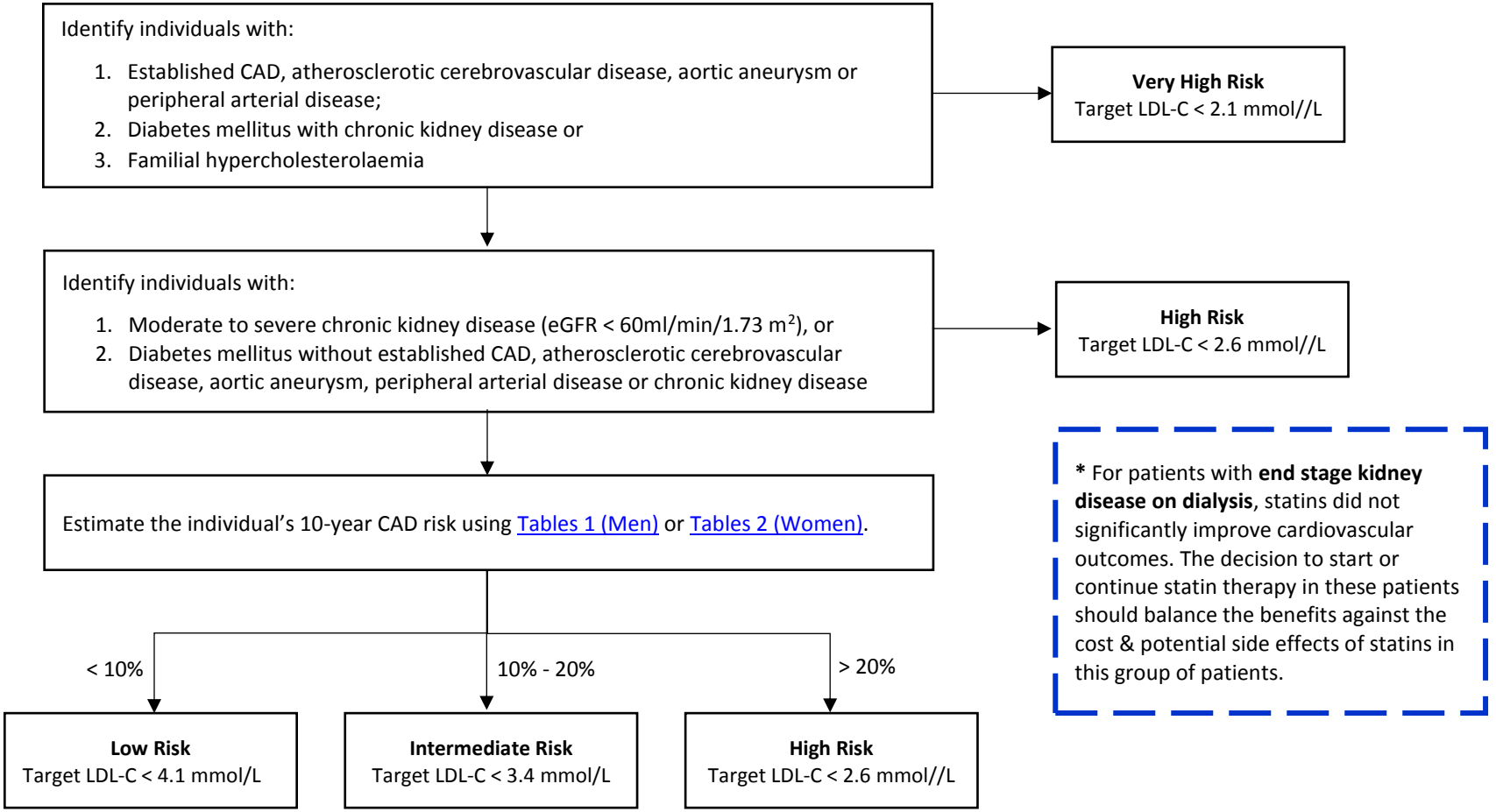
Doctors who prefer to use fasting lipid tests for the initial screening of lipid disorders can continue to do so.

ASSESSMENT

Risk Stratification and Treatment Goals

A basic principle in the prevention of CAD is that the intensity of risk reduction therapy should be adjusted to a person's risk of developing future coronary events. As such, the first step to be taken is the assessment of the individual's risk status and assigning individuals to one of four risk categories as follows **[1]**:

Risk Stratification (adapted from MOH CPG on Lipids Dec 2016)



10-Year Coronary Artery Disease Risk (Men)

Table 1.1 *Estimation of 10-Year Coronary Artery Disease Risk for Men*

Age	Points
20 - 34	-9
35 - 39	-4
40 - 44	0
45 - 49	3
50 - 59	6
55 - 59	8
60 - 64	10
65 - 69	11
70 - 74	12
75 - 79	13

HDL Cholesterol mmol/L (mg/dL)	Points
≥ 1.6 (60)	-1
1.3 - 1.5 (50 - 59)	0
1.0 - 1.2 (40 - 49)	1
< 1.0 (40)	2

Total Cholesterol mmol/L (mg/dL)	Points				
	Age 20 - 39	Age 40 - 49	Age 50 - 59	Age 60 - 69	Age 70 - 79
< 4.1 (160)	0	0	0	0	0
4.1 - 5.1 (160 - 199)	4	3	2	1	0
5.2 - 6.1 (200 - 239)	7	5	3	1	0
6.2 - 7.2 (240 - 279)	9	6	4	2	1
≥ 7.3 (280)	11	8	5	3	1

Systolic BP (mmHg)	Points	
	If untreated	If treated
< 120	0	0
120 - 129	0	1
130 - 139	1	2
140 - 159	1	2
≥ 160	2	3

Smoker	Points				
	Age 20 - 39	Age 40 - 49	Age 50 - 59	Age 60 - 69	Age 70 - 79
No	0	0	0	0	0
Yes	8	5	3	1	0

1. Estimate the individual's 10-year CAD risk by allocating points based on his age, total and HDL cholesterol levels, smoking status and systolic blood pressure (BP).
2. Check the total points against Table 1.2 to estimate that individual's 10-year CAD risk.

Table 1.2 ***Estimation of 10-Year Coronary Artery Disease Risk for Men***

Total Points	10 Year Risk (%)		
	Chinese	Malay	Indian
-1	< 1	< 1	1
0	< 1	< 1	1
1	< 1	1	1
2	1	1	1
3	1	1	2
4	1	1	2
5	1	1	3
6	1	2	3
7	2	2	4
8	2	3	5
9	3	4	7
10	4	5	9
11	5	6	11
12	6	8	14
13	8	11	18
14	11	13	> 20
15	13	17	> 20
16	17	> 20	> 20
≥ 17	> 20	> 20	> 20

10-Year Coronary Artery Disease Risk (Women)

Table 1.1 *Estimation of 10-Year Coronary Artery Disease Risk for Women*

Age	Points
20 - 34	-7
35 - 39	-3
40 - 44	0
45 - 49	3
50 - 59	6
55 - 59	8
60 - 64	10
65 - 69	12
70 - 74	14
75 - 79	16

HDL Cholesterol mmol/L (mg/dL)	Points
≥ 1.6 (60)	-1
1.3 - 1.5 (50 - 59)	0
1.0 - 1.2 (40 - 49)	1
< 1.0 (40)	2

Total Cholesterol mmol/L (mg/dL)	Points				
	Age 20 - 39	Age 40 - 49	Age 50 - 59	Age 60 - 69	Age 70 - 79
< 4.1 (160)	0	0	0	0	0
4.1 - 5.1 (160 - 199)	4	3	2	1	0
5.2 - 6.1 (200 - 239)	8	6	4	2	1
6.2 - 7.2 (240 - 279)	11	8	5	3	2
≥ 7.3 (280)	13	10	7	4	2

Systolic BP (mmHg)	Points	
	If untreated	If treated
< 120	0	0
120 - 129	1	3
130 - 139	2	4
140 - 159	3	5
≥ 160	4	6

Smoker	Points				
	Age 20 - 39	Age 40 - 49	Age 50 - 59	Age 60 - 69	Age 70 - 79
No	0	0	0	0	0
Yes	9	7	4	2	1

1. Estimate the individual's 10-year CAD risk by allocating points based on his age, total and HDL cholesterol levels, smoking status and systolic blood pressure (BP).
2. Check the total points against Table 2.2 to estimate that individual's 10-year CAD risk.

Table 2.2 ***Estimation of 10-Year Coronary Artery Disease Risk for Women***

Total Points	10 Year Risk (%)		
	Chinese	Malay	Indian
5	< 1	< 1	1
6	< 1	< 1	1
7	< 1	1	1
8	< 1	1	1
9	1	1	2
10	1	1	2
11	1	2	3
12	1	2	3
13	1	3	4
14	2	4	6
15	3	5	7
16	3	6	10
17	4	8	12
18	5	10	16
19	7	13	20
20	8	16	> 20
21	12	20	> 20
22	15	> 20	> 20
23	19	> 20	> 20
≥ 24	> 20	> 20	> 20

Secondary Dyslipidaemia

Secondary dyslipidaemia may occur in the various conditions listed below. These conditions should be excluded in any patient presenting with dyslipidaemia. **[1]**

Common Causes of Secondary Dyslipidaemia [5]

Causing Increased Total Cholesterol and LDL-C

- Hypothyroidism
- Nephrosis
- Cholestatic diseases of the liver due to abnormal lipoproteins, e.g. Primary Biliary Cirrhosis
- Progestin or anabolic steroid treatment
- Dysgammaglobulinemia (SLE, Multiple myeloma)
- Protease inhibitors for treatment of HIV infection

Causing Increased Triglyceridemia and VLDL-C

- Type 2 Diabetes
- Chronic renal failure
- Excessive Alcohol intake
- Hypothyroidism
- Obesity
- Antihypertensive medications (thiazide diuretics and B-blockers)
- Corticosteroid therapy (or severe stress that increases endogenous corticosteroid)
- Orally administered oestrogens, OCPs, pregnancy
- Protease inhibitors for treatment of HIV infection

Hypertriglyceridaemia

Triglyceride

Several studies suggest that elevated blood TG levels are associated with CAD. However, the associations between TGs are significantly attenuated after adjustment for other blood lipid levels. **[1]**

Individuals with very high levels of TG, i.e. > 4.5 mmol/L or especially > 10 mmol/L, have an increased risk of acute pancreatitis and should be treated to reduce the risk of pancreatitis. In these patients, the first priority is to reduce the TG level to prevent acute pancreatitis. **[1]**

Fibrates (but not gemfibrozil) can be considered as add-on therapy to statins in very high or high risk diabetes patients when TG is between 2.3 mmol/L and 4.5 mmol/L, **in the presence of low HDL-C** (< 1.0mmol/L). **[1]**

Familial Hypercholesterolemia

1. Screening of all first degree relatives of diagnosed familial FH patients is recommended. **[GPP, 1]**
2. Children at risk of FH because of one affected parent can be screened starting from the age of 2 years.
3. Clinical diagnosis of FH can be made by applying any one of several validated sets of criteria, including the Simon Broome Trust diagnostic criteria (see below).
4. Healthcare professionals should offer all people with **possible** or **definite** FH a referral to a specialist to make a recommendation on the need for therapy and to initiate therapy if required.
5. Coronary heart disease risk estimation tools such as those based on the Framingham algorithm should not be used because people with FH are already at a high risk of premature coronary heart disease.

Simon Broome Trust Diagnostic Criteria for Familial Hypercholesterolemia

1. Diagnose a person with **Definite** Familial Hypercholesterolemia if they have cholesterol concentrations as defined in Table 3 **and at least one of the following**:
   - tendon xanthomas, or evidence of these signs in first- or second-degree relative, or
   - DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

2. Diagnose a person with **Possible** Familial Hypercholesterolemia if they have cholesterol concentrations as defined in Table 3 **and at least one of the following**:
   - Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative.
   - Family history of raised total cholesterol greater than 7.5 mmol/L in adult first- or second-degree relative or greater than 6.7 mmol/L in child, brother or sister aged younger than 16 years.

Table 3 - *Cholesterol levels to be used as diagnostic criteria for the index individual* *(Levels either pre-treatment or highest on treatment)*

	Total Cholesterol	LDL-C
Child / young person aged under 16 years	> 6.7 mmol/L	> 4.0 mmol/L
Adult	> 7.5 mmol/L	> 4.9 mmol/L

Special Considerations

Children

Children who have a first degree relative diagnosed with familial hypercholesterolemia can be screened starting from the age of 2 years (see section on Familial Hypercholesterolemia). **[1]**

Healthcare professionals should offer all people with **possible** or **definite** FH a referral to a specialist to make a recommendation on the need for therapy and to initiate therapy if required.

Women

Statins are contraindicated in women who are pregnant, likely to be pregnant, or who are still breastfeeding. **[Grade D, Level 4, 1]**

Elderly

In the elderly (age > 75 years), the decision to start treatment should take into account the potential risk-reduction associated with treatment, risk of adverse effects, drug-drug interactions, and patient preferences. **[Grade D, Level 4, 1]**

In very high risk elderly patients, more intensive therapy (achieving LDL-C in the range of 2.1 mmol/L) has not shown benefit over less intensive therapy. Treatment for such patients should be individualised and special precautions need to be taken when instituting pharmacotherapy for hyperlipidaemia.

When used, lipid lowering medications in the elderly should be started at the lowest dose and then titrated to achieve optimal LDL-C levels, in order to avoid statin-associated side effects. For patients on treatment with a statin and LDL-C <2.1 mmol/L or 80 mg/dL when they turn > 75 years of age, there is no need to reduce therapy if the treatment is well-tolerated without any adverse effects. **[GPP, 1]**

Renal Disease

In patients with end stage chronic kidney disease on dialysis, statins did not significantly improve cardiovascular outcomes.

The starting dose of statins in chronic kidney disease should be low. During therapy, serum creatine kinase (CK) and renal function should both be carefully monitored. **[GPP, 1]**

Fibrates can be used in patients with chronic kidney disease in stages 1 to 3, but the dosages should be reduced, with appropriate monitoring for side effects, especially myopathy. **When creatinine clearance is less than 30 ml/min (stage 4 or 5), fibrates are contraindicated. [GPP, 1]**

Liver Disease

In patients with dyslipidaemia and chronic liver disease, if the level of the two transaminases (ALT and AST) is elevated but < 3 times the upper limit of the normal range, statins can be given but the starting dose should be low. Careful monitoring of the serum transaminases and CK after commencement is recommended. **[Grade D, Level 4, 1]**

Fibrates can be given in patients whose transaminase levels are elevated < 3 times the upper limit of the normal range, but at a lower starting dosage. Careful monitoring of the serum transaminases and CK after commencement is recommended. **[GPP,1]**

MANAGEMENT

Lifestyle Changes

Appropriate lifestyle changes are an integral part of dyslipidaemia management. Lifestyle interventions can reduce risk of cardiovascular disease. **[1]**

- Patients who smoke should be advised to stop smoking immediately. **[1]**
- Patients with body mass index above 23 kg/m^2 should achieve weight reduction through diet modification and exercise. **[1]**
- Persons with dyslipidaemia should undertake 150 to 300 minutes per week (~30 to 60 minutes per day) of moderate intensity aerobic activity spread out over 5 to 7 days per week. **[1]**
- A diet rich in wholegrain foods, vegetables, fruit, legumes, nuts, fish and unsaturated oils and low in saturated and trans fat, refined grains and cholesterol should be encouraged. **[1]**
- For good overall health, individuals who do not currently drink alcohol should not start. For individuals who do drink alcohol, a maximum of two standard drink per day for women and three per day for men is recommended. **[1]**

Drug Therapy / Medication

Drug	Common Dose	Maximum Dose	Common ADR	Contraindications / Precautions
HMG CoA Reductase Inhibitors ("Statin")				
Lovastatin (20 mg Tablet)	10 mg to 40 mg ON	80 mg/day	Constipation, flatulence, dyspepsia	The first line drug for both hypercholesterolemia (elevated LDL-C) and mixed hyperlipidaemia when pharmacotherapy is indicated, except when TG > 4.5 mmol/L **[Grade A, Level 1++, 1]** In patients with moderate to severe hypertriglyceridemia initiated on fibrate therapy, if LDL-C remains elevated, a statin can be further added to reduce cardiovascular risk Use with caution in patients with renal impairment, history of liver disease, elderly. Contraindicated in active liver disease; persistent elevations of serum transaminases > 3 times the upper limit of the normal range; pregnancy; breastfeeding. Place patients who do not meet their LDL-C goal on simvastatin 40 mg ON alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering (see Statin Conversion Table). Patients already on simvastatin > 40 mg may be maintained on their dose only if they have been taking that dose for 12 or more months without evidence of muscle toxicity. **[3]** In rare cases where Rosuvastatin at doses higher than 20 mg is indicated, initiation of therapy should be under close specialist supervision. **[1]** Decreasing the statin dose may be considered when 2 consecutive values of LDL-C levels are < 1.03 mmol/L. **[GPP, 1]**
Simvastatin (10 mg and 20 mg Tablets)				
Pravastatin (10 mg and 20 mg Tablet)	10 mg to 80 mg ON	80 mg/day		
Atorvastatin (Lipitor®) (10mg, 20mg, 40mg and 80mg Tablets)	5 mg to 80 mg OD	80 mg/day		
Rosuvastatin (Crestor®) (10mg Tablet)	5 mg to 40 mg OD	40 mg/day		

Drug	Common Dose	Maximum Dose	Common ADR	Contraindications / Precautions
Fibric Acid Derivatives ("Fibrates")				
Gemfibrozil (300 mg capsule)	300 mg to 600 mg BD	1,200 mg/day	Dyspepsia	Gemfibrozil should not be used in combination with statins. Fibrates can be used in patients with chronic kidney disease in stage 1 to 3 but the dosages should be reduced, with appropriate monitoring for side effects, especially myopathy. **When creatinine clearance is less than 30 ml/min (stage 4 or 5), fibrates are contraindicated. [GPP, 1]** Fibrates can be given in patients whose transaminase levels are elevated < 3 times the upper limit of the normal range, but at a lower starting dosage. Careful monitoring of the serum transaminases and CK after commencement is recommended. **[GPP,1]** Contraindicated in primary biliary cirrhosis; pre-existing gallbladder disease.
Fenofibrate (100 mg and 300 mg capsule; Lipanthyl® 160 mg micronized tablet)	Capsule: 100 mg to 300 mg OD Micronized tablet : 160 mg OD	- 300 mg/day - Lipanthyl® Supra 160 mg/day		
Ezetimibe (Ezetrol®) (10 mg tablet)	10 mg OD	10 mg OD	Abdominal discomfort	For secondary prevention in patients with established CAD, ezetimibe, when added to a statin, produces further lowering of LDL-C and cardiovascular events. **[1]** Use with caution in patients with severe renal impairment (creatinine clearance < 30 ml/min) or mild hepatic impairment (Child-Pugh class A). Not recommended for use with moderate or severe hepatic impairment (Child Pugh class B and C). Contraindication: concomitant use with a statin in patients with active hepatic disease or persistent elevations in serum transaminase.

Drug	Common Dose	Maximum Dose	Common ADR	Contraindications / Precautions
Vitamin B_3				
Nicotinic acid (Niaspan®)	375 mg to 2,000 mg OD (daily dosage should not be increased by > 500 mg in any 4 week period after initiation to 1,000 mg)	2,000 mg/day	Flushing episodes, diarrhoea	When a patient's LDL-C remains above target despite being on the maximum tolerated dose of statin, or in cases of severe hypertriglyceridemia (TG ≥ 4.5mmol/L) when statin therapy is not indicated as first line therapy, niacin can be considered. **[Grade A, Level 1+, 1]** In patients with atherosclerotic cardiovascular disease and low levels of LDL-C < 2.1mmol/L (~80 mg/dL), the HPS2-THRIVE and AIM-HIGH studies showed no incremental clinical benefit from addition of niacin to other LDL cholesterol-lowering therapy (statin or statin-ezetimibe combination). **[1]** Use with caution in patients with DM & in patients with hyperuricemia (as per 2008 MIMS). Contraindication: Active liver disease, active peptic ulcer disease, arterial bleeding.
Bile Acid Sequestrants				
Cholestyramine	4 g once to twice daily	24 g/day	Constipation, nausea / vomiting, flatulence, abdominal pain	Contraindicated in patients with complete biliary obstruction. Drug interactions: To space at least 1 hour before or 4 hours after other medications.
Omega-3-Fish Acid Ethyl Esters				
Omega 3 Fish Oils	2 g to 4 g/day in single or 2 divided doses	4 g/day	Fishy aftertaste; Gastrointestinal side effects like abdominal bloating / pain, diarrhoea. May worsen LDL-C	In severe hypertriglyceridemia (e.g. TG > 10 mmol/L), where fibrates alone may not adequately lower the markedly elevated TG levels, omega 3 fish oils should be added in dosages of 3 to 12 gm per day, which contains 1 - 4 gm of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). **[Grade A, Level 1+, 1]** Omega 3 fish oils can lower TC (due to lowering of TG) but has no effect on LDL cholesterol and cardiovascular mortality. Thus, they should not be used as a substitute for statins. **[1]** Use with caution of high dose fish oil (> 3 g/day) in patients at risk of bleeding or high level of LDL-C.

Lovastatin Dose Limitations
Contraindicated with: • Itraconazole • Ketoconazole • Posaconazole • Erythromycin • Clarithromycin • Telithromycin • HIV protease inhibitors • Boceprevir • Telaprevir • Nefazodone
Avoid with lovastatin: • Cyclosporine • Gemfibrozil
Do not exceed 20 mg lovastatin daily with: • Danazol • Diltiazem • Verapamil
Do not exceed 40 mg lovastatin daily with: • Amiodarone
Avoid large quantities of grapefruit juice (> 1 litre daily)

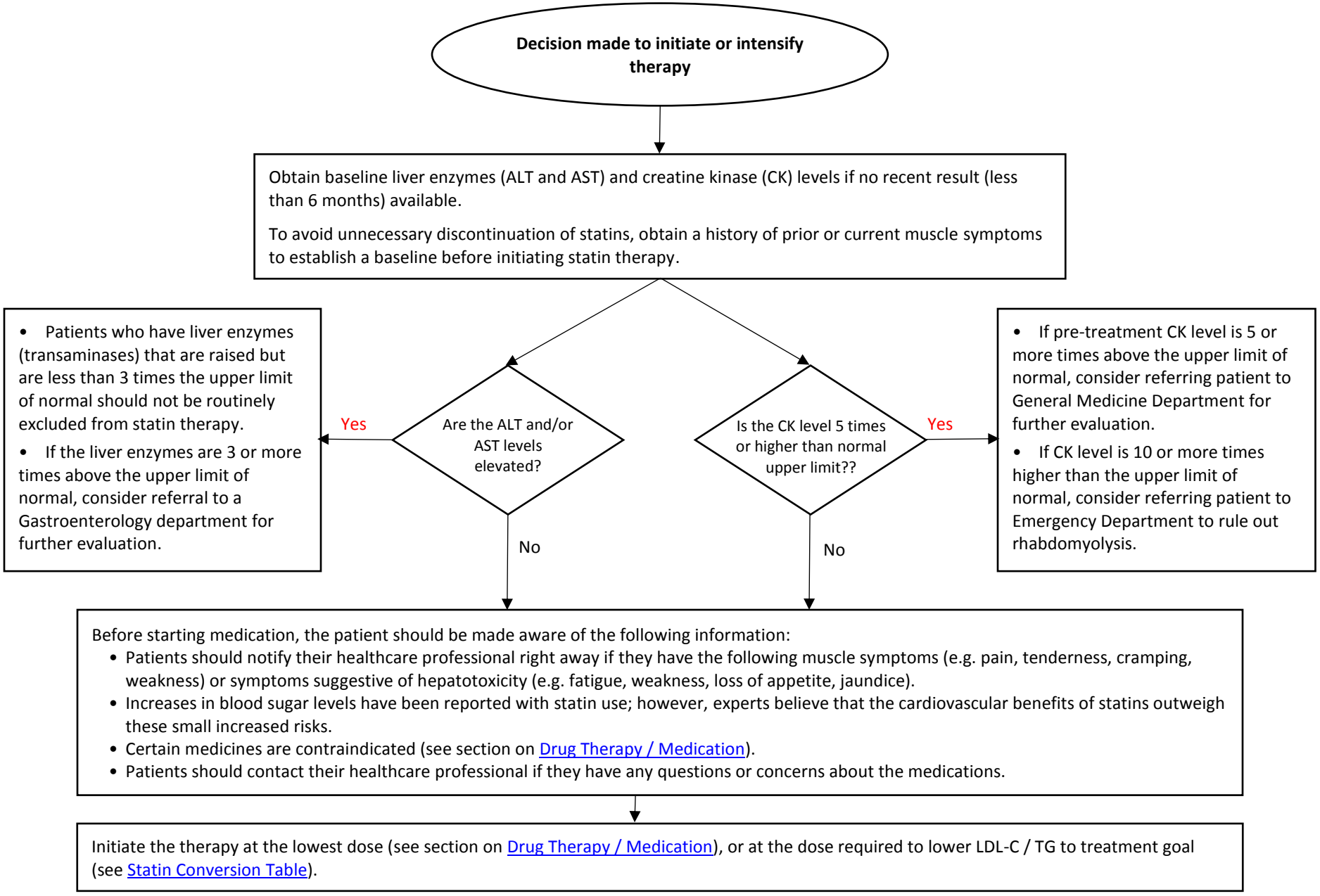
Simvastatin Dose Limitations
Contraindicated with: • Itraconazole • Ketoconazole • Posaconazole (New) • Erythromycin • Clarithromycin * • Telithromycin • HIV protease inhibitors • Nefazodone • Gemfibrozil • Cyclosporine • Danazol
Do not exceed 20 mg simvastatin daily with: • Verapamil • Diltiazem • Amiodarone • Ranolazine (New)
Do not exceed 40 mg simvastatin daily with: • Amlodipine (New)
Avoid large quantities of grapefruit juice (> 1 litre daily)

** If treatment with clarithromycin cannot be avoided, statin therapy with lovastatin or simvastatin must be suspended during the course of treatment.* ***[3]***

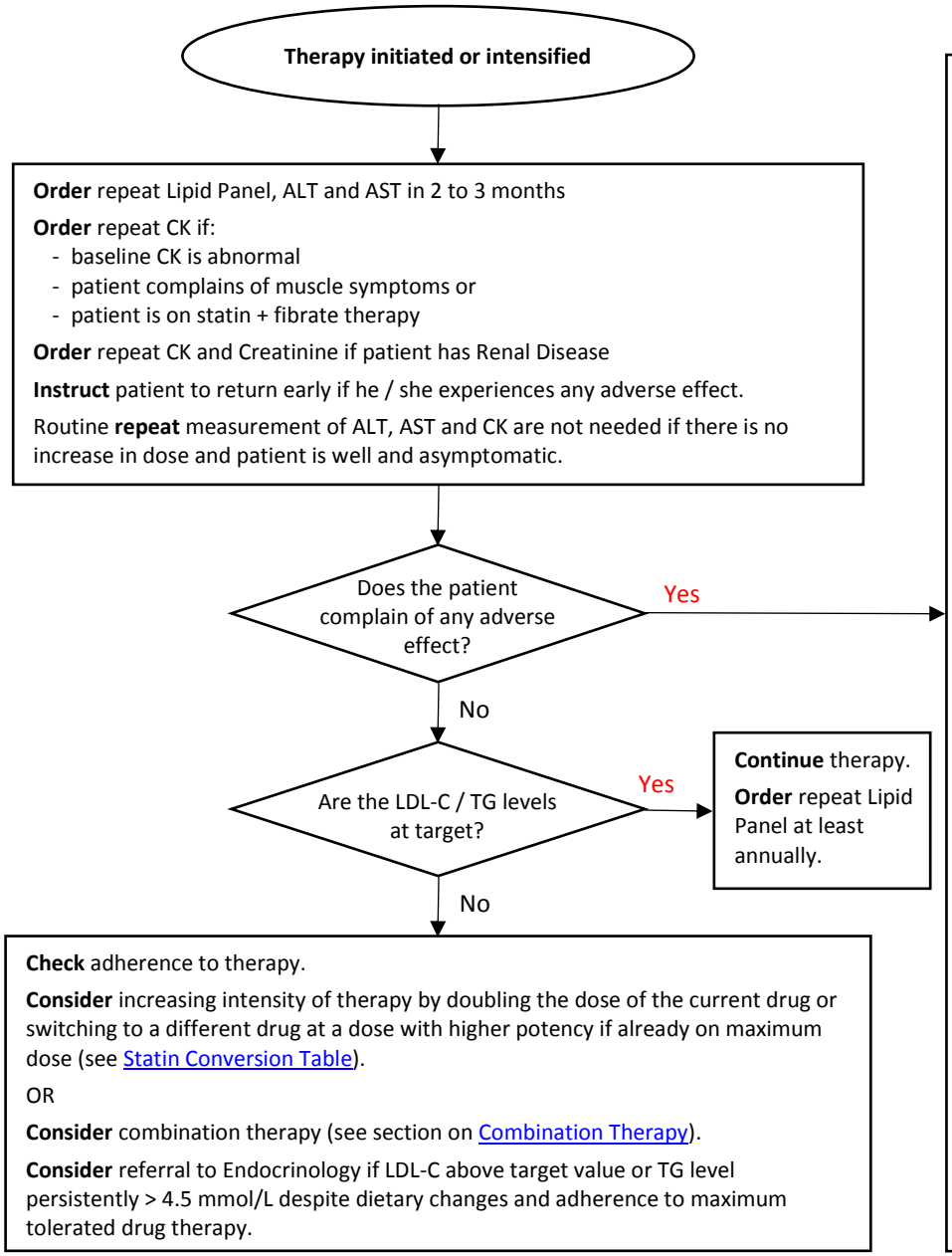
Statin Conversion Table

Statin	Dose / Day	Effect on LDL (%)	Effect on HDL (%)	Effect on TG (%)
Lovastatin	10 mg	-21	+5	-10
	20 mg	-27	+6	-8
	40 mg	-31	+5	-8
	80 mg	-40	+9.5	-19
Simvastatin	5 mg	-26	+10	-12
	10 mg	-30	+12	-15
	20 mg	-38	+8	-19
	40 mg	-41	+13	-28
	80 mg	-47	+16	-33
Pravastatin	10 mg	-22	+7	-15
	20 mg	-32	+2	-11
	40 mg	-34	+12	-24
	80 mg	-37	+3	-19
Atorvastatin	10 mg	-39	+6	-19
	20 mg	-40	+9	-26
	40 mg	-50	+6	-29
	80 mg	-60	+5	-37
Rosuvastatin	5 mg	-45	+13	-35
	10 mg	-52	+14	-10
	20 mg	-55	+8	-23
	40 mg	-63	+10	-28

Initiating Therapy



Monitoring of Side-Effects of Therapy



Abnormal liver enzymes:

Stop therapy if transaminases exceed 3 times upper limit of normal range.

Statin therapy may be re-started at lower doses if the levels returned to normal.

Stop statin therapy if serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment. If an alternate aetiology is not found, the statin should not be restarted.

Muscle symptoms or elevated CK:

- If mild to moderate muscle symptoms develop during therapy and/or CK is elevated 5 to 10 times above the upper limit of the normal range:

- Discontinue therapy.
- Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases).
- If muscle symptoms resolve with discontinuation of statin therapy, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. If a causal relationship exists, discontinue the original statin; once muscle symptoms resolve, use a low dose of a different hydrophilic statin (e.g. Rosuvastatin or Pravastatin).
- Once a low dose of a statin is tolerated, gradually increase the dose as tolerated.
- If, after 2 months without statin treatment, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms listed above.
- If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose.

- If unexplained severe muscle symptoms or fatigue develop during statin therapy, and/or if creatine kinase is more than 10 times upper limit of normal range, promptly discontinue the statin and refer patient to the Emergency Department.

Others:

Stop statin therapy if patient reports cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These reported symptoms are generally not serious and are reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Combination Therapy

- The decision to combine a statin and another lipid-lowering agent must be individualised and should be initiated only when it is strongly indicated. When statin therapy fails to achieve LDL-C target on the maximum tolerated dose, consideration should be given to use other therapies such as an add-on drug to achieve the LDL-C target level for the patient. **[Grade D, Level 4, 1]**
- In patients with established coronary artery disease, ezetimibe, when added to a statin, produces further lowering of LDL-C and cardiovascular events. **[1]**
- In patients with atherosclerotic cardiovascular disease and low levels of LDL-C < 2.1 mmol/L (~ 80 mg/dL), the HPS2-THRIVE and AIM-HIGH studies showed no incremental clinical benefit from addition of niacin to other LDL cholesterol-lowering therapy (statin or statin-ezetimibe combination). **[1]**
- Addition of fenofibrate to a statin may benefit certain patients with Type 2 diabetes with both high TG and low HDL-C dyslipidaemia pattern, particularly those with microvascular complications. **[Grade C, Level 2+, 1]**
- Gemfibrozil should not be used in combination with statins.

REFERRAL

When to Refer

- Healthcare professionals should offer all people with possible or definite FH a referral to a specialist to make a recommendation on the need for therapy and to initiate therapy if required.
- If the patient's pre-treatment ALT / AST are 3 or more times above the upper limit of normal, consider referral to a Gastroenterology department for further evaluation.
- If the patient's pre-treatment CK level is 5 or more times above the upper limit of normal, consider referral patient to General Medicine Department for further evaluation.
- If the patient's CK level is 10 times or higher than normal upper limit, refer patient to Emergency Department to rule out rhabdomyolysis.
- Consider referral to Endocrinology if LDL-C above target value or TG level persistently > 4.5 mmol/L despite dietary changes and adherence to maximum tolerated drug therapy.

ABBREVIATIONS

ALT	Alanine transaminase
ApoB	Apolipoprotein B
AST	Aspartate transaminase
BP	Blood pressure
CAD	Coronary artery disease
CK	Creatine kinase
DHA	Docosahexaenoic acid
eGFR	Estimated glomerular filtration rate
EPA	Eicosapentaenoic acid
FH	Familial Hypercholesterolemia
HDL	High density lipoprotein
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
LDL	Low density lipoprotein
PCSK9	Proprotein convertase subtilisin/kexin type 9
TC	Total cholesterol
TG	Triglyceride

REFERENCES

1. Ministry of Health Clinical Practice Guidelines on Lipids, Dec 2016.
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