Management of dyslipidaemia

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Introduction

Dyslipidaemia is one of the major modifiable risk factors in the development and progression of atherosclerosis. Clinical trials have provided conclusive evidence that reducing low density lipoprotein cholesterol (LDL-C) levels can decrease coronary artery disease morbidity and mortality. Reductions of (LDL-C) levels can also reduce the risk of stroke in those patients with high risk of vascular disease[1]. Low high density lipoprotein cholesterol (HDL-C) is identified as a significant risk factor for coronary heart disease but there are still no specific recommendations for a target HDL-C level goal

Recent treatment strategy for patients suffering from dyslipidaemia should be addressing on global risk assessment in determining the intensity of therapy. Identification and treatment of the metabolic syndrome is a secondary target of therapy.

Pathophysiology

Primary dyslipidaemia
Primary dyslipidaemia occur as a result of inherited defects in the degradation, synthesis or removal of lipoprotein particles. Classification systems can be based on the genetic or biochemical abnormality involved[2].

Secondary dyslipidaemia
Dyslipidaemia can also be caused by other medical diseases or drugs. Treatment of the causes is the goal of treatment.

(i) Hypothyroidism, nephrotic syndrome and obstructive jaundice are medical diseases that can cause elevation of LDL-C
(ii) Diabetes.
Type I diabetic patients are generally not dyslipidaemic if the glycaemic control is good. However hypertriglyceridaemia can occur in ketoacidotic state.
Type 2 diabetic patients are usually dyslipidaemic, even when the glycaemic control is good. Elevated plasma triglyceride, dense LDL and decreased HDL-C are common and is due to the high levels of insulin and insulin resistance.
(iii) Drugs : Thiazides, Cyclosporine and Tegretol can cause variable degree of LDL-C elevation
(iv) Obesity is frequently but not invariably accompanied by dyslipidaemia. Weight reduction is often associated with increase of HDL-C

Modification of dyslipidaemia and other associated risk factors

Dyslipidaemia is major modifiable risk factors for the development of atherosclerosis and its complications, namely ischaemic heart disease, ischaemic stroke and peripheral vascular disease. As ischaemic heart disease and ischaemic stroke are the leading cause of morbidity and mortality in Western countries and recently in Asian countries; the costs associated with these diseases are substantial and place a large burden on our society. Our effort will be in the direction of risk reduction of asymptomatic individuals developing cardiovascular disease (primary prevention) or to retard the progression of patients with established cardiovascular disease (secondary prevention). As majority of cardiovascular events occurs in individuals with risk factors for, but without a clinically overt cardiovascular disease[3], the delineation of primary and secondary prevention may be deemphasised, with more on risk identification and reduction.

Hence our goal of therapy is
(i) Global assessment of the patient for risk reduction.
(ii) Achievement of target serum lipid levels.

Patients suffering from cardiovascular disease commonly have multiple risk factors. In one retrospective cohort study, individuals with two risk factors were more common than expected by chance. Those with more than one risk factor were at greater risk for developing other risk factors than those without risk factors [4]. Since the presence of multiple risk factors has a synergistic effect, it is important to identify the presence of other risk factors in those patients with dyslipidaemia so that a global risk reduction therapeutic strategy can be implemented. Smoking cessation, hypertension control, regular exercise, good diabetic control and maintenance of optimal body mass index are important issues to be addressed.

Non-pharmacological measures

Regular exercise with adherence to proper lifestyle and dietary habits are suggested. Physical activity programme should be supervised for high risk patients (those having hypertension, coronary events history or heart failure). For general population, 30 to 60 minutes of moderate intensity aerobic activity, such as brisk walking on most, if not all, days of the week is suggested[5].

Dietary therapy aims at reducing the intake of saturated

fat and cholesterol while maintaining a nutritionally balanced diet. Study has shown that dietary therapy bears a favourable effect on plasma lipid profile even superimposed to pharmacological therapy[6]. However, with good dietary compliance, dietary therapy can only reduce LDL-C by 0.39-0.65 mmol/L[7], therefore most patients require pharmacological therapy for LDL-C lowering. Moreover the timing and threshold of medication initiation also depend on the clinical setting. Early initiation of high dose statins can have significant beneficial effect on composite cardiovascular end point[8] in high risk individuals.

Pharmacological measures

HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors (commonly known as statins) are considered as first line therapy for patients with dyslipidaemia. Depending on the dosage and preparations, statins can reduce LDL-C by 20% - 61%, increase HDL-C by 3-16% and decrease triglycerides by 2-45%. However the dose effect on LDL-C lowering is not linear and its effect decreases at near peak dose. Major clinical trials have shown the beneficial effect of statins in composite cardiovascular endpoints in primary[9,10] and secondary prevention trials[8,11]. Important side effects of statins include myositis and derangement of liver function tests. The former side effect is rare but can progress to fatal rhabdomyolysis. The potential for a statin to produce myositis is dependant on the dose and the extent of lipid lowering. Myositis also occurs more often in patients with concomitant treatment with cyclosporine, macrolide antibiotics, various anti-fungal agents and cytochrome P-450 inhibitors as these agents inhibit the metabolism of statins. Myositis can also occur more often in patients with concomitant treatment with fibric acid derivatives and the exact mechanism is unknown. Patients should be advised to report any unexplained myalgia. Mild assytomatic increase in serum transaminase can be present in 3-5 % of patients and is also dependant on the dose of statin used. Liver function tests should be periodically monitored before and after treatment. Absolute contraindications for statins use include acute or chronic liver disease.

Fibric acid derivatives

Fibric acid derivatives is another main class drug used for treatment of dyslipidaemia, especially for patients with predominant increase in triglyceride as these agents are generally less effective than statins at lowering serum LDL-C. In general fibric acid derivatives can decrease LDL-C by 10-35 %, increase HDL-C by 1-34 % and decrease triglycerides by 20 -50 %. Study has also shown that fibric acid derivative, namely gemfibrozil can reduce the rate of coronary events[12]. Important side effect includes myositis and is also rare. Myositits occurs more often in patients with renal impairment and concomitant treatment with statins. Fibric acid derivatives are contraindicated in severe renal and liver disease patients. Drug interactions with the fibric acid derivatives are due to competition with plasma protein binding and cytochrome P-450 metabolism. Potentiation of warfarin's anticoagulant effect is particularly important through competition with plasma protein binding

Nicotinic acid

Nicotinic acid can reduce LDL-C by 10-25 %; increase HDL-C by 15-35 % and decrease triglycerides by 20-50 %.This is currently the most potent HDL-C raising pharmacological therapy. Trial has shown its effectiveness in reduction of coronary mortality[13]. Its use is mainly limited by its side effect of cutaneous flushing, itching and diarrhea. To overcome this, gradual dose escalation to allow tolerance is the suggested method. Moreover, the newer nicotinic acid preparations have improved tolerability. Rarely, myositis or liver dysfunction can also occur. Absolute contraindications include liver disease and severe gout.

Bile acid sequestrants

Bile acid sequestrants can bind bile acids in the intestine, hence decreasing their absorption and increasing the conversion of cholesterol into bile acids in the liver. This will increase the LDL-C removal from the circulation. Bile acid sequestrants can decrease serum LDL-C by 15-30 %. This class of drug has poor palatability and patients frequently have adverse gastrointestinal side effects. Drug interaction through reducing the absorption of other drugs is another issue when employing this class of medication. As the drug is not absorbed into the body, there is no systemic toxicity.

Ezetimibe

Ezetimibe is a new agent for lipid lowering, it binds to Niemann-Pick C1 like 1 protein on the gastrointestinal tract epithelium. This protein is required to transport cholesterol into the cells, hence ezetimibe blocks absorption of cholesterol. The drug can decrease the LDL-C by 15-17 %. Its major advantage is that it acts synergistically with the statins in loweing the LDL-C. When combined with statins , it can mediate additional 25 % reduction of LDL-C . As previously mentioned, the dose effect on LDL-C lowering of statins is not linear and its effect decreases at near peak dose. The combination of ezetimibe to statins is useful for patients in which the LDL-C reduction is not satisfactory with statin alone. Important issue of using the drug includes drug interaction; its concentration is increased by about 1.5 fold when given together with fenofibrate. The level of ezetimibe can be raised substantially by cyclosporine.

Target of lipid control

According to the Excecutive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection , Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III)[14], patients are categorised into 3 categories, namely,

(i) Highest risk with established coronary heart disease and coronary heart disease equivalents; coronary heart disease equivalents include noncoronary forms of clinical atherosclerotic disease (peripheral artery disease,abdominal aortic aneurysm, symptomatic carotid artery disease) ,diabetes or multiple (>2) risk factors in whom the 10-year risk for coronary heart disease of > 20 %. Risk is estimated from the Framingham risk score in Table 1 and 2 and the major risk factors are listed in Table 3. The LDL-C goal of this category of patients is < 2.6 mmol/L

(ii) multiple (>2) risk factors and the 10 year risk for coronary heart disease < 20 %. The LDL-C goal of this category of patients is < 3.4 mmol/L

(iii) zero to one risk factor and the 10 year risk for coronary heart disease < 10 %. The LDL-C goal of this category of patients is < 4.1 mmol/L

Elevated serum triglycerides.
Recent studies also indicate that elevated triglycerides is an independent risk factor for coronary heart disease. The treatment strategy for elevated serum triglycerides depends on the cause of the elevation and its severity.

ATP III classify the serum triglycerides into

Normal triglycerides	<1.7 mmol/L
Borderline-high triglycerides	1.7- 2.2mmol/L
High triglycerides	>2.2- =5.6mmol/L
Very high triglycerides	>5.6mmol/L

For patients with borderline high or high triglycerides, the primary aim of therapy is to achieve the target goal for LDL-C. When triglycerides are borderline high, emphasis should be placed on weight reduction and increased physical activity and pharmacological therapy needs to be considered for high triglycerides.

HDL-C
ATP III does not specify a goal for HDL-C raising. However, as low HDL-C is a significant risk factor for coronary heart disease and weight loss as well as exercise can raise HDL-C. These non-pharmacological means of HDL-C raising should be recommended.

Beyond the ATP III

Since the publication of the ATP III, several major clinical trials with statin therapy and clinical end points have been published[1,8,10,15]. These trials bring into consideration the treatment thresholds as well as target of the ATP III.

In Heart Protection Study[1], patient subgroup with LDL-C at baseline < 2.6 mmol/L exhibited significant risk reduction after statin therapy is started. In PROVE IT[8], treatment with atorvastatin lowered the LDL-C to a median of 1.6mmol/L as compared with pravastatin to a median of 2.5 mmol/L. This results in reduction of the major cardiovascular events in the atorvastatin arm. This is the reason why some would advocate a LDL-C target of 1.8 mmol/L for high risk individuals.

The PROSPER[15] showed beneficial effect of pravastatin on coronary heart disease of elderly ages 70-82. There is a significant reduction of major coronary events and coronary mortality for those treated elderly.

Conclusion

Global assessment of our patients having dyslipidaemia should be our treatment plan, with emphasis on risk identification and reduction. The ATP III guideline gives us a platform to formulate the treatment strategy. However, target for the LDL-C for high risk individuals is still unknown. Also the role of therapeutic HDL-C raising is still unclear. These probably can be answered by the results of future clinical trials. As lipid lowering agents are commonly used nowadays, their side effects and potential drug interactions should not be overlooked.

Table 1

Estimate of 10-Year Risk for Women (Framingham Point Scores)

Age, year	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Non-smoker	0	0	0	0	0
Smoker	9	7	4	2	1

Total Cholesterol,

mmol/L	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
< 4.1	0	0	0	0	0
>4.1-5.1	4	3	2	1	1
>5.1-6.2	8	6	4	2	1
>6.2-7.2	11	8	5	3	2
>=7.2	13	10	7	4	2

Systolic Blood pressure, mmHg	Untreated	Treated
< 120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
> 160	4	6

HDL-C mmol/L	Points
>= 1.5	-1
< 1.3-1.5	0
< 1.0-1.3	1
< 1.0	2

Estimate of 10- year risk for Women (Framingham Point Scores)

Point Total	10-Year risk
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
> =25	>=30

Table 2

Estimate of 10-Year Risk for Men (Framingham Point Scores)

Age, year	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Non-smoker	0	0	0	0	0
Smoker	8	5	3	1	1

Total Cholesterol,

mmol/L	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
< 4.1	0	0	0	0	0
>4.1-5.1	4	3	2	1	0
>5.1-6.2	7	5	3	1	0
>6.2-7.2	9	6	4	2	1
>7.2	11	8	5	3	1

Systolic Blood pressure, mmHg	Untreated	Treated
< 120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
>= 160	2	3

HDL-C mmol/L	Points
>= 1.5	-1
< 1.3-1.5	0
< 1.0-1.3	1
< 1.0	2

Estimate of 10- year risk for Men (Framingham Point Scores)

Point Total	10-Year risk
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
> =17	>=30

Table 3

Major Risk Factors (Exclusive of LDL-C) that modify LDL-C goals

- Cigarette smoking
- Hypertension (treated or not treated)
- Low HDL-C (<1.0mmol/L)
- Family history of premature coronary heart disease (coronary heart disease in male first degree relative <55 years; coronary heart disease in female first degree relative <65 years)
- Age (men > 45 years; women > 55 years)

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