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CME ARTICLE

Beyond low-density lipoprotein cholesterol: why, who and when

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You were reviewing Mr Andy, a 56-year-old Chinese man, on follow-up for hypertension and hyperlipidaemia for the past three years. He was on nifedipine LA 30 mg OM, atenolol 50 mg OM, hydrochlorothiazide 12.5 mg OM and simvastatin 10 mg ON. His blood pressure was 134/84 mmHg, with a body mass index (BMI) of 23.9 kg/m^2. His latest fasting glucose and lipid profile, as of April 2011, was as follows: fasting glucose 6.9 mmol/L (124 mg/dL); total cholesterol 5.03 mmol/L (194 mg/dL); high-density lipoprotein (HDL) cholesterol 0.56 mmol/L (21 mg/dL); triglyceride (TG) 4.19 mmol/L (371 mg/dL); and low-density lipoprotein (LDL) cholesterol 2.56 mmol/L (99 mg/dL). Having explained to him about his impaired fasting glycaemia, you requested for him to do an oral glucose tolerance test to exclude undiagnosed diabetes mellitus. Mr Andy was concerned that some of his medications could have contributed to these abnormalities.

INTRODUCTION

Cardiovascular diseases due to atherosclerosis and thrombosis have been the leading cause of death in the United States and other developed countries. In Singapore, ischaemic heart disease and cerebrovascular disease are the second and fourth most common causes of death after cancers.[1] Current strategies target LDL cholesterol through dietary counselling, lifestyle modifications and pharmacotherapy, namely with statins monotherapy or combination therapy, which is associated with a 20%–40% relative risk reduction in major cardiovascular events.[2-4]

HDL, TG AND CORONARY HEART DISEASE

Current data suggests an independent and inverse relationship between circulating HDL cholesterol levels and coronary heart disease.[5-7] Every 1 mg/dL decrease in HDL cholesterol level is associated with a 2%–3% higher risk of coronary artery disease, independent of LDL cholesterol levels.[7] Apart from HDL cholesterol, a meta-analysis of 17 studies has also demonstrated that with every 1 mmol/L (88.5 mg/dL) increase in serum TG levels, there is a 30% and 75% increased risk of coronary heart disease in men and women, respectively.[8]

CAUSES OF LOW HDL

Low HDL cholesterol is commonly associated with type 2 diabetes mellitus and metabolic syndrome. In these patients, increased insulin resistance together with an increase in the rate of catabolism of HDL, possibly due to TG enrichment of the HDL particles, are important mechanisms that lower HDL. Low HDL levels are also seen with inherited genetic conditions, familial combined hyperlipidaemia and hypertriglyceridaemia. Concomitant drug use, such as medications for prevention and treatment of cardiovascular risk factors, may also adversely affect the lipid profile. Non-selective β-blockers and thiazide diuretics may increase TG levels and lower HDL cholesterol levels without any major impact on LDL cholesterol levels.

TREATMENT GUIDELINES FOR HDL

Evidence from a cohort study in the Honolulu Heart Program has demonstrated that the incidence of thromboembolic stroke was threefold in men with low HDL levels of 1.0 mmol/L (40 mg/dL) as compared to men with high HDL levels of ≥ 1.6 mmol/L (60mg/dL).[9] While low HDL is associated with increased atherosclerotic risks, therapy to raise HDL in those with pre-existing coronary artery disease by every 1% is associated with a 3% reduction in cardiovascular risks and events.[10] International guidelines recommend HDL cholesterol as a secondary lipid target, after LDL cholesterol, with levels above 1.0 mmol/L for males and 1.3 mmol/L for females considered to be desirable in patients with high risk of cardiovascular disease.[11]

LIFESTYLE MODIFICATIONS

Lifestyle modifications, such as weight loss, increasing physical activity and smoking cessation, have been shown to be beneficial in raising HDL cholesterol levels. With every kilogram decrease in body weight, there is a 0.009 mmol/L or 0.35 mg/dL increase in plasma HDL cholesterol levels in people who maintain stable weight reduction. Increasing physical activity has also been

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Table I. Lipid-modifying medications and their estimated efficacy.

Drug	Effect on LDL	Effect on TG	Effect on HDL
Niacin	Decrease 5%–25%	Decrease 20%–50%	Increase 20%–35%
Fibrates	Decrease 5%–20%	Decrease 20%–50%	Increase 10%–25%
Statins	Decrease 20%–55%	Decrease 15%–35%	Increase 2%–14%
Ezetimibe	Decrease 20%–53%*	Decrease 6%–10%¶	Minimal effect
Resins	Decrease 15%–30%	Increase 3%–7%	Increase 3%–5%
Omega-3 acids	Increase 5%–10%	Decrease 25%–30%	Increase 5%–10%

*Ezetimibe decreases LDL by 20% when used as monotherapy and 40%–53% when combined with statins. ¶Ezetimibe decreases TG by 6% when used as monotherapy and 10% when combined with statins. LDL: low-density lipoprotein; TG: triglycerides; HDL: high-density lipoprotein

shown to increase HDL cholesterol levels by 3%–9%, especially in those with sedentary lifestyles.[12] In overweight or obese patients, aerobic exercise has been showed to raise HDL cholesterol levels by about 3%, with potential for greater rise in levels with increased frequency and intensity of exercise. Smoking has been associated with a reduced HDL cholesterol level and increased cholesteryl ester transfer protein (CETP) activity. Smoking cessation has been shown to increase HDL cholesterol levels by a mean of 0.10 mmol/L or 4 mg/dL, more so in women than in men.[13]

PHARMACOTHERAPY

Patients with pre-existing cardiovascular disease should be considered for pharmacological therapy to raise HDL and lower TG, once LDL target is addressed. There is a limited number of medications that are effective in raising the level of HDL cholesterol. These include nicotinic acid (niacin), fibric acid derivatives (fibrates), and to a smaller extent, statins, resins and omega-3 acids. Niacin is currently the most effective HDL-raising agent in clinical practice. Table I shows the types of lipid-modifying medications and their estimated efficacy.

Nicotinic acid (niacin)

Niacin raises HDL by increasing the synthesis of apolipoprotein A (apo-A, the key protein in HDL) and by reducing the fractional catabolism of apo-A. By reducing lipolysis and increasing apo-B degradation in the liver, niacin also reduces TG and LDL, resulting in an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation) to large buoyant particles. Niacin has been shown to be effective in reducing the rate of progression of atherosclerosis as well as causing plaque regression in angiographic studies. Additionally, it has been shown to reduce and improve carotid intimal thickness in patients already on statin treatment. In the AIM-HIGH study, while the addition of niacin did not result in risk reduction in patients with high cardiovascular risk and low LDL levels < 2.2 mmol/L, the clinical outcome of using niacin in combination with statins in a larger group of patients with average LDL cholesterol levels is unknown and awaits to be seen in future clinical trials.[14]

Side effects such as cutaneous flushing, dyspepsia, and a potential increase in uric acid levels and gouty flares may sometimes limit its use in some patients. Flushing, which is prostaglandin-mediated, may be minimised by using the extended-release formulation of niacin, with concurrent consumption of a low-fat snack at bedtime or 30 minutes after ingestion of aspirin, starting with a low-dose regime (500 mg niacin ON) with gradual increase. Alternatively, a combination of extended-release niacin with laropiprant (Tredaptive®) has been tried, resulting in a reduction in flushing and better adherence to treatment. Niacin may cause hyperglycaemia, and should thus be used with caution in diabetic patients with poor glycaemic control, especially when HbA1C is above 9%. Niacin may also reduce platelet adhesion and is contraindicated in those with active peptic ulcer disease. Its effects, when used in combination with simvastatin in patients with type 2 diabetes mellitus, low HDL and high TG, are currently being studied in the HPS2-THRIVE trial, which will be reporting their results in 2013.

Fibric acid derivatives (fibrates)

This group of drugs causes reductions in total cholesterol, LDL cholesterol, apo-B, total TG and TG-rich lipoprotein (VLDL) in treated patients. In addition, an increase in HDL cholesterol is also observed, with the increase more pronounced in patients with higher fasting TG levels. Fibrates activate the peroxisome proliferator activated receptor (PPAR-α), which results in increased formation of apo-AI. Fibrates also increase the activity of lipoprotein lipase and lead to the elimination of TG-rich particles from plasma, resulting in a fall in TG and a reduction in small, dense LDL particles. In patients with type 2 diabetes mellitus, fenofibrate has been shown to cause a 40% reduction in the rate of progression of localised coronary artery disease, when compared with placebo.[15] In patients with high cardiovascular risks, combination therapy with statin and fibrate produces synergistic effects and greater risk reductions compared to monotherapy with either drug, and this has been shown to be effective in a subgroup of patients with high TG and low HDL.[16]

Cholesteryl ester transfer protein inhibitors

CETP inhibitors are potent HDL-raising agents. The drugs in this class include anacetrapib, evacetrapib, dalcetrapib and torcetrapib. CETP inhibitors work by blocking the transfer of cholesteryl ester from HDL to LDL and very low-density lipoprotein (VLDL), hence increasing HDL cholesterol levels by 40%–60%.[17] The termination of the ILLUMINATE trial was due to a relative increase of 60% in mortality among patients randomised to torcetrapib plus atorvastatin compared to those

Table II. The patient's lipid profile from April 2011–2012.

Lipid profile	Reading mmol/L (mg/dL)		
	April 2011	October 2011	April 2012
Total cholesterol	5.03 (194)	4.52 (174)	4.84 (187)
HDL cholesterol	0.56 (21.5)	0.64 (24.7)	0.86 (33.5)
TG	4.19 (371)	3.55 (314)	2.71 (240)
LDL cholesterol	2.56 (99)	2.27 (87)	2.27 (87)

HDL: high-density lipoprotein; TG: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein

taking atorvastatin alone. The development of dalcetrapib was halted in May 2012 when the Phase 3 clinical trials did not show important clinical benefits. Anacetrapib and evacetrapib are still undergoing clinical trials, as it is likely that the off-target effects seen with torcetrapib are due to drug effect rather than due to CETP inhibitors as a class. It remains to be seen if CETP inhibitors will prove the HDL hypothesis true and contribute to profound reductions in cardiovascular risks and future cardiovascular events.

Mr Andy, already on simvastatin once daily, was started on fenofibrate 300 mg OM, but a repeat lipid panel still showed elevated TG levels. During a subsequent visit, apart from re-enforcing lifestyle measures, atenolol and hydrochlorothiazide were stopped and he was maintained on nifedipine for blood pressure control. A repeat lipid panel six months later showed optimally controlled LDL, and improvement in HDL and TG levels (Table II). He was encouraged to increase on his exercise routine to further improve his overall lipid profile.

TAKE HOME MESSAGES

1. Low HDL cholesterol level is associated with increased risk of coronary heart disease.
2. Low HDL cholesterol may be associated with metabolic syndrome and diabetes mellitus, and such patients should thus be specifically screened for conditions that are associated with increased cardiovascular risks. Addressing these conditions could also contribute to improvement of HDL and TG elevation, which may co-exist.
3. Patients with low risk of cardiovascular disease and low HDL cholesterol levels should be managed by non-pharmacological measures first. These include weight loss, exercise and smoking cessation.
4. Drug causes of low HDL should be considered. β-blockers and thiazide diuretic should be changed, if possible.
5. Patients with pre-existing cardiovascular disease should be considered for pharmacological therapy to raise HDL and lower TG, once LDL target is addressed.
6. Choice of pharmacological therapy (namely nicotinic acid or fibrates) should be individualised and supported by clinical data, where possible, and should also be based on patient tolerability, safety and cost-effectiveness.

ABSTRACT Cardiovascular disease due to atherosclerosis is a leading cause of death around the world, including Singapore. Current treatment strategies primarily target low-density lipoprotein (LDL) cholesterol levels. Low levels of high-density lipoprotein (HDL) cholesterol and high triglyceride (TG) levels have been shown to increase the risk of coronary heart disease, but the clinical benefits of raising low HDL cholesterol have only been proven in a limited number of studies. This guide provides an approach on managing low HDL cholesterol levels in terms of lifestyle modifications and pharmacotherapy.

Keywords: high-density lipoprotein, management, pharmacotherapy
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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201209A)

	True	False
1. Current data suggests that high-density lipoprotein (HDL) cholesterol is an independent risk factor for coronary heart disease, even after adjustments for low-density lipoprotein (LDL) cholesterol levels.	☐	☐
2. A rise in serum triglyceride (TG) levels is associated with an increased risk of pancreatitis but not coronary heart disease.	☐	☐
3. Type 2 diabetes mellitus and metabolic syndrome are commonly associated with low HDL cholesterol.	☐	☐
4. Atenolol and other non-selective β-blockers may increase TG levels and lower HDL cholesterol levels without major impact on LDL cholesterol levels.	☐	☐
5. Higher doses of hydrochlorothiazide diuretics may increase TG levels and lower HDL cholesterol levels without major impact on LDL cholesterol levels.	☐	☐
6. Evidence suggests that the incidence of thromboembolic stroke is threefold in men with low HDL levels of 1.0 mmol/L or 40 mg/dL as compared to men with high HDL levels of ≥ 1.6 mmol/L or 60 mg/dL.	☐	☐
7. Therapy to raise HDL in those with pre-existing coronary artery disease by every 1% is associated with a 3% reduction in cardiovascular risks and events.	☐	☐
8. International guidelines recommend HDL cholesterol as a secondary lipid target, after LDL cholesterol, with levels above 1.0 mmol/L (for males) and 1.3 mmol/L (for females) considered to be desirable in patients with pre-existing cardiovascular disease.	☐	☐
9. Weight loss and increasing physical activity are not beneficial in raising HDL cholesterol levels.	☐	☐
10. In overweight or obese patients, aerobic exercise has been shown to raise HDL cholesterol levels by about 3%, with a potential for greater rise with increased frequency and intensity of exercise.	☐	☐
11. Smoking cessation is not beneficial in raising HDL cholesterol levels.	☐	☐
12. Smoking has been associated with reduced HDL cholesterol level and increased cholesteryl ester transfer protein (CETP) activity.	☐	☐
13. Niacin is currently the most effective HDL-raising agent in clinical practice.	☐	☐
14. Niacin has been shown to be effective in reducing the rate of progression of atherosclerosis and in causing plaque regression in angiographic studies.	☐	☐
15. The side effects of niacin, such as cutaneous flushing, dyspepsia and potential increase in gouty flares, may be minimised by using the extended-release formulation of niacin taken with a low-fat snack at bedtime or 30 minutes after ingestion of aspirin.	☐	☐
16. Niacin should be used with caution in diabetic patients with poor glycaemic control, and it may reduce platelet adhesion and is contraindicated in those with active peptic ulcer disease.	☐	☐
17. In patients with type 2 diabetes mellitus, fenofibrate in combination with statin and fibrate produces synergistic effects in patients with pre-existing cardiovascular disease as well as in the subgroup with high TG and low HDL cholesterol.	☐	☐
18. CETP inhibitors work by blocking the transfer of cholesteryl ester from HDL to LDL and very low-density lipoprotein, hence increasing HDL cholesterol levels.	☐	☐
19. It is unclear if CETP inhibitors would contribute to a reduction in cardiovascular risks and future cardiovascular events.	☐	☐
20. In the management of hyperlipidaemia, LDL, HDL and TG are all important treatment targets to be considered in optimising the patient's cardiovascular risk profile.	☐	☐

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Deadline for submission: (September 2012 SMJ 3B CME programme): 12 noon, 25 October 2012.