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Editorial Office Address
Editor
Singapore Medical Journal
Singapore Medical Association
2 College Road
Singapore 169850
Fax: (65) 6224 7827
Email: smj@sma.org.sg
Website: www.sma.org.sg/smj

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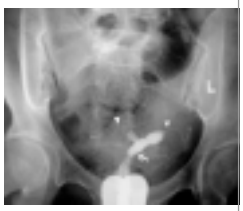

31-year-old woman with TB of the endometrium and fallopian tubes. Hysterosalpingogram shows a contracted uterine cavity (arrow) and strictures of both fallopian tubes (arrowheads). (Courtesy of Dr Juntima Euathrongchit, Chiang Mai University).
(Refer to pages 568-575)

Editorial

High-density lipoprotein cholesterol: ready for prime time?

Y C Kon

INTRODUCTION

Statins reduce the incidence of cardiovascular events by about 25-35% compared with placebos, both in patients with and without clinical atheroslcerotic disease, across a wide range of low-density lipoprotein cholesterol (LDL-C) levels. All the landmark statin mega-trials provide solid evidence for reducing LDL-C as a primary target, yet these studies also show that up to 65-75% of events cannot be prevented by LDL-C lowering with statin therapy. This has led to a more aggressive approach to LDL-C lowering, as well as targeting other lipid targets such as high-density lipoprotein cholesterol (HDL-C).

A low HDL-C has been found in more than 40% of patients experiencing a myocardial infarction (MI)[1]. A low HDL-C level indicates reduced reverse cholesterol transport, reduced anti-inflammatory and anti-oxidative protection, and often indicates high levels of atherogenic remnant lipoproteins. Currently, it is possible to achieve mild to moderate increases in HDL-C levels with non-statin drugs such as fibrates (10-20%) and niacin (15-35%). These drugs can, by and large, be combined safely with statins. Hence, the article by Tavintharan et al in this issue of the Singapore Medical Journal is timely, by drawing attention to low HDL-C as a potent independent cardiovascular risk factor and potential therapeutic target[2].

Given that the cardiovascular benefits of LDL-C reduction and HDL-C improvement may be additive, such a multi-targeted, complementary approach is especially relevant in high-risk individuals[3]. Low HDL-C may occur in isolation, but usually occurs with raised plasma triglyceride levels, in familial combined hyperlipidaemia, or more commonly as part of the atherogenic dyslipid triad (↓ HDL-C, ↑ VLDL-C, and ↑ small dense LDL-C) associated with the metabolic syndrome. Two potentially complementary approaches have emerged regarding the management of dyslipidaemia in patients with the metabolic syndrome: either aggressive statin therapy or combination therapy to achieve therapeutic targets.

EVIDENCE FOR LOW HDL-C AS AN IMPORTANT CARDIOVASCULAR RISK FACTOR

The Framingham Study found that in healthy men and women aged 49 to 82 years, the most potent risk factor for coronary heart disease (CHD) was low HDL-C[4]. Persons with HDL-C below 0.9 mM (35mg/dL) had eight times higher incidence rate than those with HDL levels 1.7 mM (65mg/dL) or above (107/1,000 vs 13/1,000 over 4 years). Moreover, low HDL-C (0.6 mM, 25mg/dL) in the presence of normal LDL-C (2.6 mM, 100mg/dL) was associated with a similar magnitude of

Department of Endocrinology
Tan Tock Seng Hospital
11 Jalan Tan Tock Seng
Singapore 308433

Y C Kon, MBBS, MRCP, FAMS
Consultant

Correspondence to:
Dr Kon Yin Chian
Tel: (65) 6357 7881
Fax: (65) 6357 7871
Email: winston_kon@ttsh.com.sg

cardiovascular risk as normal HDL-C (1.2 mM, 45mg/dL) in the presence of markedly-elevated LDL-C (5.7 mM, 220mg/dL)[5]. A strong relation between baseline HDL-C and subsequent event rates was demonstrated in statin-treated patients in several of the large statin trials[6,7,8]. Among patients with type 2 diabetes mellitus, UKPDS 23 identified low HDL-C as one of the quintet of independent CAD risk factors, the other four being age, high LDL-C, HbA1c and systolic hypertension[9].

Analysis of epidemiological data show that for every 0.025 mM (1mg/dL or about 2-3%) rise in HDL-C, the risk of CHD decreases by 2% in men and 3% in women, independent of LDL-C levels[10]. Thus, raising HDL-C may potentially give equivalent proportional event rate reduction as lowering LDL-C (1% decrease in LDL-C level reduces CHD risk by 1.25%). A small study of familial hypercholesterolaemic heterozygotes found that subjects with CHD were more likely to have low plasma HDL-C or high total/HDL-C ratio than control heterozygotes without CHD[11]. In the Singapore Cardiovascular Cohort Study, males with low HDL-C below 0.9 mM had an adjusted risk of 1.3 for CHD compared with those with HDL-C 0.9 mM or greater[12].

However, a low HDL-C level is not always associated with increased risk for atherosclerosis. For example, subjects with apolipoprotein A-I Milano have low HDL-C levels but yet have reduced coronary risk, while other mutations in cholesterol transfer protein (CETP) cause an increase in HDL-C without conferring the protective effect against atherosclerosis[13]. Some authors contend that the anti-atherogenic effects of reverse cholesterol transport are better assessed by the flow of cholesterol through this pathway than by the mere concentration of HDL-C[14]. To date, the best clinical outcome data to support the benefits of raising HDL-C level comes from the Veterans Affairs HDL Intervention Trial (VA-HIT)[15].

The VA-HIT enrolled 2,531 men with CHD and a mean age of 64 years, body mass index (BMI) 29kg/m^2, HDL-C of 0.8mM (32mg/dL), LDL-C of 2.9 mM (111mg/dL) and triglycerides (TG) of 1.8 mM (160mg/dL)[15]. About one-half had the metabolic syndrome, and 25% were diabetic. As this was a secondary prevention study, the subjects recruited were at high risk, with a placebo event rate for coronary death or non-fatal MI of 22% over five years. This was the first large scale randomised, controlled, double-blind clinical trial to show that improvements in HDL-C levels, 6% increase, 0.8 mM (32mg/dL) to 0.9 mM (34mg/dL) and TG 31% decrease) with gemfibrozil, without any reduction in LDL-C levels, decreased coronary death and non-fatal MI by 22% (95% CI 7-35%), and CHD death, nonfatal MI and stroke by 24% (95% CI 11-36%, $p<0.001$), after a median follow-up of 5.1 years. The beneficial effect of gemfibrozil did not become apparent until two years after randomisation.

Thus, in a population similar to the one in this study, 23 patients would need to be treated for five years to prevent one coronary death or non-fatal MI (5 YR NNT = 23). The magnitude of this benefit from gemfibrozil is similar if not better than that of pravastatin in populations with average to moderately-high LDL-C levels. For example, in the Cholesterol and Recurrent Events (CARE) study (average LDL-C 3.6mM) and the Long Term Intervention with Pravastatin in Ischemic Disease (LIPID) study (average LDL-C

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3.9 mM), the 5-YR NNT to prevent one non-fatal MI or death from CHD were 33 and 28, respectively[16,17].

On multivariate analysis, only HDL-C levels on treatment with gemfibrozil significantly predicted the incidence of CHD. Moreover, the change in HDL-C levels only partially explained the beneficial effect of gemfibrozil. Each 0.125 mM (5mg/dL) increase in HDL-C on gemfibrozil was associated with an 11% reduction in CHD events (or each 1% increase in HDL-C decreased CHD risk by 3%)[18]. This is consistent with the results of the Helsinki Heart Study, a primary prevention trial with gemfibrozil, which suggested that an 8% increase in HDL-C would reduce such events by 23%[19]. This 3:1 ratio of reduced clinical events for each percent increase in HDL-C on fibrates exceeds that of LDL-C reduction (1:1 ratio) on statins. In a subsequent analysis, most of the clinical benefit was seen in patients with diabetes and/or the metabolic syndrome, but not in those without these conditions[20].

RAISE HDL-C OR FURTHER LOWER LDL-C, OR BOTH?

Fibrates correct the typical lipid abnormalities of type 2 diabetes mellitus without worsening diabetic control, thus fibrates are a logical choice of drug treatment for diabetics.

NCEP-ATP III recognises low HDL-C, defined as a level <1 mM (40 mg/dl), as a strong independent predictor of CHD. In the present NCEP-ATP III guidelines, low HDL-C modifies the goal of LDL-lowering therapy and is also used as a risk factor to estimate 10-year CHD risk[21]. Patients with type 2 diabetes mellitus have a two- to four-fold excess risk of cardiovascular disease (CVD), for any given cholesterol level[22]. The American Diabetes Association (ADA) defines low-risk lipid levels in a diabetic as LDL-C <2.6 mM (100mg/dL), TG <1.7 mM (150mg/dL), and HDL-C >1.3 mM (50mg/L). We could ask if a diabetic patient is better protected from CVD if his LDL-C were 2mM and HDL-C 1.0mM, compared to LDL-C of 2.6mM and HDL-C of 1.3mM? Or should our focus be on the ratio of LDL-C to HDL-C, or total cholesterol (TC) to HDL-C? For example, the Canadian guidelines recommend two treatment targets in high-risk patients: LDL-C <2.5, and TC/HDL-C ratio less than 4.0[23]. For diabetic patients with hypertriglyceridaemia (TG >5.0mM), this target TC/HDL-C ratio may be more difficult to achieve than target LDL-C levels with statins alone. Such patients may require fibrates or niacin as additional therapy.

Fibrates correct the typical lipid abnormalities of type 2 diabetes mellitus without worsening diabetic control, thus fibrates are a logical choice of drug treatment for diabetics. Long-term use of fenofibrate produces a fall of 15% or more in TC, mediated through a reduction in LDL-C, while raising HDL-C by 10-15%, and reducing plasma triglycerides by 30-40%. However, no study to date has specifically set out to evaluate the role of fibrate therapy in preventing cardiovascular events in type 2 diabetics (the results of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study are awaited). Similarly, although much epidemiological and experimental, and some clinical outcome data indicate that HDL-C produces significant cardiovascular protective effects, clinical outcome data for raising HDL-C is not as overwhelmingly robust as that for LDL-C reduction[24].

In contrast, there is an abundance of data from clinical trials to show the cardiovascular benefit of LDL-C lowering, including patients with diabetes. Hence, both NCEP-ATP III and the ADA continue to

focus on LDL-C reduction as the primary target for lipid modifying therapy[21,22,25]. These mega-trials show that the relationship between LDL-C levels and CHD risk is curvilinear or log-linear, i.e. risk rises more steeply with increasing LDL-C concentrations[25]. Thus, when LDL-C levels are plotted against a log scale of CHD risk, the relationship becomes linear. This means that the proportional reduction in risk for a given absolute change in LDL-C level is similar at any LDL-C level. Clinical trial data show that for every 1mM reduction in LDL-C level, the risk for cardiovascular events is reduced in proportion by about 25-30% of the absolute risk, regardless of the cholesterol level or the source of cardiovascular risk[25]. This relationship has been shown to apply to patients with baseline LDL-C levels as low as 2 to 3mM with stable coronary disease[26], acute coronary syndromes[27], high-risk patients with or without clinically evident atherosclerotic disease[28-30], diabetic patients[29,30] and hypertensive patients[31].

A reduction in mean LDL-C from 3mM to 2mM with simvastatin 40mg was shown to reduce major vascular events by about 25% in diabetics both with occlusive vascular disease and in those without[29]. Of course, the absolute risk reduction was higher in diabetic patients with clinically evident vascular disease (5-YR NNT = 11) compared to those without (5-YR NNT = 33). Such compelling data from the recent trials noted above has led NCEP-ATP III to support the optional reduction of LDL-C levels to below 1.8mM in very high risk patients, namely those with established CVD plus (1) multiple risk factors, especially diabetes; (2) severe and poorly-controlled risk factors, especially continued cigarette smoking; (3) those with the metabolic syndrome; and (4) patients with acute coronary syndromes[25].

In general, patients with high or very high estimated CVD risk should receive more aggressive therapy targeted at all lipid risk factors.

In general, patients with high or very high estimated CVD risk should receive more aggressive therapy targeted at all lipid risk factors. In patients with elevated triglycerides ≥2.3mM (200 mg/dL) associated with the metabolic syndrome, and in those with low HDL-C, NCEP-ATP III identifies non-HDL-C (LDL + VLDL-C) as a secondary target (after LDL-C goal achieved), reserving treatment of isolated low HDL-C for persons with CHD and CHD risk equivalents[21]. ADA guidelines recommend that in diabetic patients with HDL-C <1 mM and LDL-C between 2.6mM and 3.4mM, fibrates or niacin might be used[22]. This might increase HDL-C (to above 1mM in men and 1.3mM in women), and reduce LDL-C and non-HDL-C to target goals. In patients with very high CVD risk, residual CVD risk after LDL-C lowering therapy using statin alone, statin-ezetimibe or statin-resin may remain unacceptably high when target LDL-C levels are not achieved, either because the baseline LDL-C level was too high (>4mM), the patient is a poor statin-responder, is unable to tolerate statin, is unable to afford the prescribed medications, or develops adverse reactions because of the high statin doses employed.

Statin non-compliance may entail loss or diminution of its protective effect against first or subsequent cardiovascular events[28,29]. Even when targeted LDL-C goal is achieved, CVD risk may remain unacceptably high because other risk factors, for example hypertension, may be difficult to control. In such patients, it would seem prudent to institute other therapies aimed at lowering global CVD risk, and one way of achieving this is to raise HDL-C levels. VA-HIT provides some evidence for such an approach at least in patients with the metabolic syndrome[20].

MAXIMISING ABSOLUTE RISK REDUCTION WITH COMBINATION THERAPY

The HDL Atheroclerosis Treatment Study(HATS) illustrates that combination therapy may provide independent and additive benefits for patients with CHD and low HDL-C[32]. This small study enrolled 160 patients with clinical CHD, coronary stenosis, low HDL-C (≤0.91mM in men and ≤1.03mM in women), LDL ≤3.75mM, and TG <4.42mM. Patients were stratified according to gender, TG level and risk level and randomised within their risk stratum to one of four treatment groups: niacin plus simvastatin, antioxidant vitamins alone, all three drugs, or placebo. Patients were initially prescribed sustained-release niacin twice daily and switched to immediate-release niacin twice daily if HDL-C increases were insufficient. Placebo tablets containing niacin 50mg were also taken twice daily, and provoked flushing without affecting lipid levels. Combination lipid therapy alone reduced LDL-C levels by 42% and TG levels by 36%, increased HDL-C levels by 26% and reduced the TC/HDL-C ratio from 6.5 to 3.5. The average degree of coronary stenosis progressed by 3.9% in individuals taking placebo, but regressed 0.4% in those treated with simvastatin/niacin alone. At the end of three years, the frequency of composite clinical end-point of coronary death, MI, stroke or revascularisation was 24% with placebo, compared to 3% with simvastatin/niacin, i.e. a 90% reduction (P=0.03) in first cardiovascular event. This magnitude of event reduction was consistent with the estimate of 68% (42% plus 26%), assuming that each percentage increase in HDL-C level and each 1% decrease in LDL-C level independently accrues a 1% reduction in CVD risk.

Once thought to be contraindicated because of a possible hyperglycaemic effect, the use of niacin in diabetic patients has been shown to be safe and effective in recent studies.

If confirmed in larger trials, such large reductions in major CVD events achieved with combination statin/niacin therapy would represent a substantial advance over current practice for the 40% of patients with CHD who have low HDL-C levels, typical of diabetic patients. Such patients seldom receive therapy directed at both HDL-C and LDL-C. Once thought to be contraindicated because of a possible hyperglycaemic effect, the use of niacin in diabetic patients has been shown to be safe and effective in recent studies[33,34]. The ADVENT study showed that niacin ER at a dose of 1g/day has little effect on glucose control, while some patients treated with doses >1.5g/day required some adjustment in hypoglycaemic therapy so that HbA1c increased only 0.3% from baseline in the group taking higher doses[33]. Due to the high CVD risk of patients with diabetes, the benefits of broad spectrum lipid improvement [↓ LDL-C, ↓ VLDL-C, ↑ HDL-C, ↓ small dense LDL-C, ↓ LDL-Lp(a)] with combination statin-niacin therapy may outweigh any adjustment in diabetes therapy that is needed.

Clinical outcome studies using statin-fibrate combination therapy have not been published. The Action to Control Cardiovascular Risk in Diabetes Trial (ACCORD) using statin-fibrate therapy in 5,800 patients with diabetes is underway, and expected to be completed by 2009. This trial will attempt to establish whether or not therapy with this combination therapy reduces cardiovascular morbidity and mortality more than therapy with statin alone.

CONCLUSION

Clinical mega-trials to confirm the benefit of improving HDL-C levels, especially in high-risk patients, are awaited. These trials would probably

have to be add-on trials, since it would now seem to be unethical to withhold statin therapy in high-risk patients. It is envisaged that the use of combination therapy or novel potent HDL-C raising drugs such as torcetrapib, a cholesterol exchange transfer protein (CETP) inhibitor, in such trials will help provide irrefutable evidence that raising HDL-C should be as important as lowering LDL-C for cardiovascular risk reduction. Preliminary evidence is promising, by indicating that the additional proportional CVD risk reduction that results from combined HDL-C raising and LDL-C lowering may be of the same or greater order of magnitude as that seen when statins were compared with placebo. SMJ

It is envisaged that the use of combination therapy or novel potent HDL-C raising drugs such as torcetrapib, a cholesterol exchange transfer protein (CETP) inhibitor, in such trials will help provide irrefutable evidence that raising HDL-C should be as important as lowering LDL-C for cardiovascular risk reduction.

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Level 2, Alumni Medical Centre
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Tel: (65) 6223 1264
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