Dyslipidemia is an important etiologic component to cerebrovascular, peripheral vascular and coronary heart disease worldwide, including Singapore. Most studies have shown that the 10% of the population with the highest LDL levels account for only 20-30% of the CHD events. Conversely, 70-80% of CHD events occur in patients with so-called “normal” or “near-normal” levels. Standard guidelines therapy 5-6 years ago focus treatment only on those with very high cholesterol levels and ignore this large group of the people with “normal” or mildly raised cholesterol levels. New approaches in last few years include more intensive lowering of LDL-cholesterol levels, reducing triglycerides/non-HDL components and raising the high-density lipoprotein (HDL)-cholesterol level. In 2006, a target of <70 mg/dL LDL goal has become a “reasonable goal” in the guidelines for secondary prevention. High triglycerides or too-low HDL-cholesterol, also contribute to CHD risk and these lipid abnormalities often cluster with other risk factors, including obesity, insulin resistance, hyperglycemia, and hypertension (metabolic syndrome). Such patients are considered to have mixed, or atherogenic dyslipidemia, and include those with metabolic syndrome and type 2 diabetes. In patients whose triglyceride levels remain high (>200 mg/dL) or HDL-cholesterol levels low (<40 mg/dL) even after they have achieved their LDL-cholesterol goals, the NCEP ATP III guidelines recommend non–HDL-cholesterol as a secondary target of therapy. Combination therapies using fibrates seemed appealing and two ongoing trials are comparing combination therapy (statin with either niacin or a fibrate) to assess the incremental benefit of combination therapy.

Keywords: High-risk patients, residual cardiovascular risks, statin therapy, fibrate therapy, LDL-cholesterol, non-HDL-cholesterol, combination therapy

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INTRODUCTION
This article reviews the current state of treatment of dyslipidemia in the high-risk patients in light of latest trials and how to reduce the residual cardiovascular risks that frequently remains.
years. In the high-risk group with pre-existing CHD, a 1-mmol/L (or 38 mg/dL) reduction in LDL-cholesterol reduces 14 deaths per 1000 subjects. The benefit is seen regardless of baseline LDL-cholesterol levels i.e. benefit is still obtained when statin is given when the baseline levels were low by previous conventional treatment guidelines i.e. <2.6 mmol/l (or 100 mg/dL). Of note is that greatest benefit was achieved in the high-risk and very-high-risk groups. This group comprised patients with diabetes, known CAD, those with peripheral arterial disease and those older than 75 years. In fact long-term follow-up monitoring has shown that lowering LDL-cholesterol in this high risk group continued to reduce cardiovascular events for 10 years after the study has ended, thus alluding to the long-term salutary effects of statin therapy.

However, how low a level should LDL cholesterol be reduced remains highly contentious. Observational and experimental studies have shown that the relationship between cholesterol and CHD mortality has no apparent lower threshold, and that the physiologic normal level for LDL-cholesterol in some societies especially Asian countries may be lower than that seen in Western countries. In some studies done in urban Chinese population e.g. amongst native Beijing city dwellers and even amongst local population, the mean baseline total cholesterol level was lower compared to western populations, and likewise a lower rate of deaths were attributed to CHD. Nonetheless there is an independent and strongly positive relationship between total cholesterol and risk of CHD death, starting at a level as low as 150-mg/dL total cholesterol level. A similar relationship was seen in LDL-cholesterol level with acute events occurring even at levels of 90-100 mg/dL. Other studies have indicated that the physiologic norm for LDL-cholesterol levels should be in the range of 50 to 65 mg/dL. Serum total cholesterol concentrations of at least 125 mg/dL or less. However, favorable outcomes were more closely related to the baseline LDL-cholesterol levels of at least 125 mg/dL or less. For that reason, the investigators suggested that reducing LDL-cholesterol level of <116 mg/dL to 62 mg/dL in the intensive high dose therapy group and to 95 mg/dL in the standard pravastatin therapy group. At 2 years, the primary end point of cardiovascular events was 16% lower (P= .005) in patients on intensive therapy, and the greatest benefit is seen in those with baseline LDL-cholesterol levels of at least 125 mg/dL or less.

TREATING DYSLIPIDEMIA IN THE HIGH-RISK GROUP PATIENTS- CURRENT MANAGEMENT AND FUTURE APPROACH

Evaluation and Infection Therapy trial and Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, patients who had been hospitalised for acute MI were randomly assigned to atorvastatin 80 mg/day or pravastatin 40 mg/day for 2 years. The patients’ median LDL-cholesterol levels fell from 106 mg/dL at baseline to 62 mg/dL in the intensive high dose therapy group and to 95 mg/dL in the standard pravastatin therapy group. At 2 years, the primary end point of cardiovascular events was 16% lower (P=.005) in patients on intensive therapy, and the greatest benefit is seen in those with baseline LDL-cholesterol levels of at least 125 mg/dL or less. Favorable outcomes were more closely related to the on-treatment levels of LDL-cholesterol and C-reactive protein than to the specific agent used. Hence both trials show that in high-risk patients, a LDL-cholesterol level of very low levels of 60 to 80 mg/dL results in better outcomes than regimens that achieve LDL-cholesterol levels of approximately 100 mg/dL.

Treatment amongst hyperintensive and elderly patients suggest treatment strategy currently used in middled-aged people should equally apply to these groups.

In this era of global and instant connectivity amongst researchers, clinical trials’ findings should rightly be assimilated into guidelines as soon as possible. However since most guidelines are updated only once every 4- 5 years, earlier updating of guidelines or insertion of addendums should be done by the cardiology and advisory societies as needed. In the 2002 NCEP Adult Treatment Panel III (ATP III) guidelines the then recommended LDL-cholesterol goals depend on the patient’s level of risk, with <100 mg/dL as the goal for those in the highest risk category. This is further corroborated by the Heart Protection Study (HPS) where patients achieved a mean LDL-cholesterol level of 89 mg/dL, and a “highly significant” 18% reduction in coronary deaths (P=.0005) was achieved, even in individuals who entered the study with baseline LDL-cholesterol level of <116 mg/dL. No threshold effect was found. For that reason, the investigators suggested that reducing LDL-cholesterol further to very low levels might produce greater reductions in cardiovascular events. Hence in the 2004 NCEP guidelines update, they suggest that for CHD patients in the “very-high-risk” group, a target of <70 mg/dL LDL goal is an “optional target level”. This “very-high-risk” group includes those with established cardiovascular disease and additional risk factors such as diabetes mellitus, continued cigarette smoking, metabolic syndrome, renal failure and acute coronary syndrome.
In 2006, a target of <70 mg/dL LDL goal has become a "reasonable goal" in the guidelines for secondary prevention jointly issued by the American Heart Association and the American College of Cardiology. It states that a goal of <70 mg/dL is "reasonable" for all patients with CHD and other clinical forms of atherosclerotic disease, even for those whose baseline LDL-cholesterol level is between 70 and 100 mg/dL.

Likewise, abundant data from prospective trials have revealed a strong and direct relationship between on-treatment LDL level and rate of atherosclerotic progression. These randomised controlled trials show that whether patients were on statin therapy or placebo, the rate of angiographic progression of atherosclerosis was closely related to the LDL levels and in a few studies inversely related to HDL levels. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trial which used 80 mg/day atorvastatin versus 40 mg/day pravastatin patients with a mean baseline LDL of 150 mg/dL. Atorvastatin reduced LDL by 50% to a mean LDL of 76 mg/dL compared with a 27% drop to a mean of 110 mg/dL on pravastatin. The carotid intima-media thickness regressed 0.038 mm in the atorvastatin group compared with a mean progression of 0.026 mm in the pravastatin group (p = 0.021).

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial compared the effects on atheroma volume, as measured by intracoronary intra-vascular ultrasound, using intensive (atorvastatin 80 mg/day) vs. moderate (pravastatin 40 mg/day). In the intensive treatment group, which a mean LDL-cholesterol level of 79 mg/dL was achieved, a 0.4% reduction in atheroma volume was seen. This indicated no disease progression from baseline and a significantly lower progression rate (P=.02). By contrast, the group on moderate treatment that achieved a mean LDL-cholesterol level of 110 mg/dL had a 2.7% increase in atheroma volume, indicating progression of atheroma / plaque volume. Both of these trials demonstrated the inadequacy of LDL reduction to current goals of <100mg/dL.

In the ASTEROID study, (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden,) the effect of rosuvastatin 40 mg/day on coronary disease progression was again assessed by intracoronary ultrasound at baseline and after 2 years of treatment. The results showed a regression in the mean change in percent atheroma volume (~0.98%, compared with baseline P<.001). The investigators attributed disease regression to intensive statin treatment (a very low mean LDL-cholesterol level together with significantly increased HDL-cholesterol levels up to 49 mg/dL, up 5% from baseline.

However in a very controversial study in patients with familial hypercholesterolemia utilising ultrasound measurements of carotid intima-media thickness, lowered LDL-cholesterol levels did not result in regression of atherosclerosis in contrast to the ARBITER study. In this Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, groups using simvastatin 80 mg plus ezetimibe 10 mg compared with simvastatin 80 mg alone did not demonstrate any difference of carotid intima-media thickness. Despite significant 16.5% greater lowering of LDL-cholesterol with combination therapy (P<.01), no difference was observed in both groups. This negative study was attributed to a different study population disease profile by some experts.

However in recent years, some experts have cautioned against a severe reduction of cholesterol levels to very low levels. As cholesterol is an essential component of the cell membrane/ tissue regeneration process and an obligate precursor for bile acid, steroid hormone, and vitamin D synthesis. It is likely that a physiologically ideal range of blood cholesterol exists above and below which adverse health consequences might be expected. Although individuals with chronic illnesses and malignancies, often develop depressed LDL levels as a result of malnutrition or hypermetabolism, epidemiologic studies show that people with naturally low LDL levels are associated with improved longevity. This is seen in some Asian countries and closed communities. Needless to say, having a naturally low cholesterol level in a healthy person and artificially inducing a low cholesterol level using drugs in a diseased state is two different pathophysiologic process. Thus given the physiologic importance of cholesterol, the very low cholesterol levels artificially achieved with intensive statin therapy in some trials has raised certain issues about the safety of high dose regimens. So far, the cumulative experience with statin therapy shows impressive cardiovascular benefits that are directly proportional to LDL lowering with no increase in adverse events such as malignancy or non-cardiovascular mortality. The incidence of the two principal adverse effects commonly attributed to statins — liver and muscle toxicity — rise modestly as a function of dose and type of statin utilised but not in relationship to the on-treatment LDL level. In the PROVE IT-TIMI 22 trial where patients whose LDL-cholesterol levels had dropped to 40 mg/dL or lower, there were fewer cardiovascular events in this group compared with the patients with LDL-cholesterol levels between 80 and 100 mg/dL, and no relationship was found between this low level and adverse events over 24 months. Similarly, the TNT study group found that the lowest quintile (LDL-64 mg/dL, mean 54 mg/dL) had the lowest event rate, without a difference in adverse events over 5 years. However, some cholesterol expert maintain that little is known about the side effects of taking statins at higher doses for long periods as most trials follow-up patients for less than 5 years and use of intensive regimens has only been instituted in western countries only recently and in relatively small numbers. Animal studies 10 years ago have already shown that the equivalent of high dose statins in humans in the long term does induce a degenerative myopathy and neuropathy state. Recent findings have prompted the Food and Drug Administration to recommend that the use
simvastatin 80 mg / highest approved dose be sharply curtailed because of the risk of myopathy. Moreover a lot of trials do not address issues of “non-quantifiable” or “subtle” side effects like aches and pains, mental and neurological derangements such as depression, sleep disturbance, severe irritability and memory loss.

**NON-HDL-CHOLESTEROL AS SECONDARY TARGET OF THERAPY**

It is also clear from the statin clinical trials that cardiovascular events occur even after LDL-cholesterol is optimally treated. In fact current treatment regimens reduces only about 25-35% of all cardiovascular events over an average of 5 years. Unmet risks of 60-70% still exist despite statin therapy. Other lipid components e.g. high triglycerides or too-low HDL-cholesterol, also contribute to CHD risk. These lipid abnormalities often cluster with other risk factors, including obesity, insulin resistance, hyperglycemia, and hypertension (metabolic syndrome). Such patients are considered to have mixed, or atherogenic dyslipidemia, and include those with metabolic syndrome and type 2 diabetes. In patients whose triglyceride levels remain high (>200 mg/dL) or HDL-cholesterol levels low (<40 mg/dL) even after they have achieved their LDL-cholesterol goals, the NCEP ATP III guidelines recommend non-HDL-cholesterol as a secondary target of therapy. Non-HDL-cholesterol (calculated as total cholesterol minus HDL-cholesterol) is a measure of all the atherogenic lipids i.e. apolipoprotein B-containing lipoproteins (LDL), intermediate-density lipoprotein (IDL), and very-low-density lipoprotein (VLDL).

In mixed dyslipidemia, the LDL particles are usually smaller and the calculated LDL-cholesterol content does not reflect the increased particle number. Several observational studies suggest that non-HDL-cholesterol is a better predictor of risk than LDL-cholesterol level and higher and denser LDL particle numbers may reflect the pathogenicity of cholesterol better than the absolute LDL-cholesterol levels.

In the TNT and IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) trials, where LDL-cholesterol levels were positively associated with cardiovascular outcome, that relationship turned out to be less significant than the relationship with non-HDL-cholesterol and apolipoprotein B. The ratio of total cholesterol to HDL (Total/HDL) and the ratio of apolipoprotein B to apolipoprotein A-I were each more strongly associated with outcome than any of the individual lipoprotein parameters.

TNT data also shows that HDL-cholesterol levels in patients receiving statins does predict major cardiovascular events. Among subjects with LDL-cholesterol levels <70 mg/dL, those in the higher HDL-cholesterol levels were at less risk for major cardiovascular events. These analyses support the concept that there is residual CHD risk after optimal statin treatment and that the easily obtained non-HDL-cholesterol and HDL-cholesterol levels per se are predictive of that risk.

The ATP III recommended goal for non-HDL-cholesterol is 30 mg/dL above the LDL goal. Thus, a high-risk person whose LDL-cholesterol goal is <100 mg/dL would have a non-HDL-cholesterol goal of <130 mg/dL. ATP III recommends lowering non-HDL-cholesterol by intensifying statin therapy to further reduce LDL as well as considering the addition of niacin or a fibrate to further decrease VLDL and triglycerides. Fish oil supplements with Omega-3 fatty acids at a sufficient dose (3-4 g/d of eicosapentanoic acid and docosahexaenoic acid) can reduce triglycerides as monotherapy, or when added to statins. Likewise the 2008 consensus conference report from the American Diabetes Association and the American College of Cardiology states that in patients with high cardiometabolic risk, measurements of total atherogenic particles are better. These measurements include non-HDL-cholesterol, apolipoprotein B, and the number of LDL particles identified by nuclear magnetic resonance. In individuals in the highest-risk category (known cardiovascular disease or diabetes plus one or more CHD risk factors in addition to dyslipidemia), they recommend a non-HDL-cholesterol goal of <100 mg/dL and an apolipoprotein B goal of <80 mg/dL.

**RAISING HDL-CHOLESTEROL LEVELS**

Another approach widely pursued by investigators nowadays is to raise HDL cholesterol levels. The validity of raising HDL-cholesterol is supported by epidemiological evidence showing an inverse relationship between HDL-cholesterol levels and cardiovascular risk: an increase of 1 mg/dL in HDL-cholesterol is associated with a 2% to 3% decrease in risk of cardiovascular disease. An analysis of data from the Framingham study, the Coronary Primary Prevention Trial, and Multiple Risk Factor Intervention Trial indicates that for every 0.025 mmol/L rise in HDL, the risk of CHD decreases 2% in men and 3% in women. This compares favourably with LDL where a decrease of 1 mg/dL in LDL-cholesterol is associated with only a 1% decrease in risk of cardiovascular disease.

Findings from INTERHEART, a global case control study of heart attack involving 52 countries, imply that even in patients with low levels of LDL cholesterol, if the level of HDL cholesterol is not sufficiently high, there remains an increased risk of further cardiovascular events. Therapeutic lifestyle changes, such as weight loss, exercise, and smoking cessation are effective at increasing HDL-cholesterol and these interventions are always encouraged. Most statins increase HDL-cholesterol only modestly (5-10%), with rosuvastatin generally producing the largest increases. Currently, the most efficacious HDL-raising drug is niacin. As monotherapy, niacin can increase HDL-cholesterol by 15% to 35%. Increases as high as 40-50% have been reported when used in combination with statins. The problem with niacin is that it often causes flushing and other unpleasant side effects especially GI side effects. This cause some...
20% of patients to discontinue therapy especially when high doses are used. Extended-release formulations cause less flushing than immediate-release forms of niacin, and specific flush-reducing agents (laropiprant) are used in combination pills to improve tolerance.

Fibrates can also increase HDL-cholesterol by 8% to 35% by activating the nuclear transcription factor peroxisome proliferator-activated receptor-α (PPAR-α). The Veterans Affairs HDL Intervention Trial (VA-HIT) studied the effects of gemfibrozil in men with CHD and HDL-cholesterol <40 mg/dL. After a median follow-up of 5 years, gemfibrozil raised HDL-cholesterol by 6% more than placebo and lowered triglycerides by 31% more (P<.001 for both), but did not affect levels of LDL-cholesterol. Compared to placebo, gemfibrozil treatment reduced the risk of CHD death and nonfatal myocardial infarction by 22% (P=.006). In post hoc analysis, each 5-mg/dL increase in HDL-cholesterol was associated with an 11% decrease in the risk of these CHD events. The Helsinki Heart Study reported similar results with gemfibrozil in population without CHD. Small studies using rosuvastatin and fenofibrate and atorvastatin and fenofibrate have shown positive effects on dyslipidemia. Gemfibrozil may be associated with increased risks of myositis, whereas fenofibrate combined with statins has not shown this effect.

**COMBINATION THERAPIES**

Hence combination therapies using fibrates seemed appealing and two ongoing trials are comparing combination therapy (statin with either niacin or a fibrate) with statin therapy to assess the incremental benefit of combination therapy. AIM-HIGH (Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides and Impact on Global Health outcomes) is a 5-year study in 3300 patients with vascular disease and low HDL-cholesterol. This study is designed to find out whether lowering LDL to <80 mg/dL with simvastatin plus niacin can delay the time to a first major cardiovascular event compared to simvastatin therapy alone.

The 6-year ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) randomises patients with type 2 diabetes into 2 groups, 1 receiving statin-fibrate combination therapy and the other statin monotherapy. ACCORD is designed to find out whether raising HDL-cholesterol and lowering triglycerides with targeted reductions in LDL-cholesterol will improve CHD outcomes more than LDL-lowering alone. These trials are not completed and findings are highly anticipated.

Omega-3 fatty acids are also sometimes used in conjunction with simvastatin and dietary counselling to improve non-HDL-C and other lipoprotein parameters to a greater extent than simvastatin alone. Their effect on HDL-C is minimal.

Other HDL cholesterol raisers have initially proved disappointing. The first CETP inhibitor, Torcetrapib, which had been shown to increase HDL-cholesterol by >50% in early clinical trials. However, a clinical outcomes trial comparing torcetrapib and atorvastatin with atorvastatin alone was stopped early because the combination therapy was associated with a higher incidence of adverse events including strokes and total mortality. Significant increases in average systolic blood pressure with torcetrapib were reported. Further, substantial HDL-cholesterol increases of 54% to 61% achieved with torcetrapib in 2 surrogate outcomes trials did not have a beneficial effect on atherosclerosis. Other CETP inhibitors are currently in development that, investigators hope, will not have the adverse effects associated with torcetrapib. Additional investigative approaches for increasing HDL-cholesterol levels such as apolipoprotein A1-Milano, apolipoprotein A1-mimetic peptides, and phospholipid-directed therapies are in development.

**CONCLUSIONS**

Most studies have shown that the 10% of the population with the highest LDL levels account for only 20-30% of the CHD events. Conversely 70-80% of CHD events occur in patients with so-called “normal” or “near-normal” levels. In patients whose triglyceride levels remain high (>200 mg/dL) or HDL-cholesterol levels low (<40 mg/dL) even after they have achieved their LDL-cholesterol goals, the NCEP ATP III guidelines recommend non–HDL-cholesterol as a secondary target of therapy. Combination therapies using fibrates seemed appealing and two ongoing trials are comparing combination therapy (statin with either niacin or a fibrate) with statin therapy to assess the incremental benefit of combination therapy.

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LEARNING POINTS

• Some 70-80% of CHD events occur in patients with so-called “normal” or “near-normal” levels.

• High triglycerides or too-low HDL-cholesterol, also contribute to CHD risk and these lipid abnormalities often cluster with other risk factors, including obesity, insulin resistance, hyperglycemia, and hypertension (metabolic syndrome).

• In patients whose triglyceride levels remain high (>200 mg/dL) or HDL-cholesterol levels low (<40 mg/dL) even after they have achieved their LDL-cholesterol goals, the NCEP ATP III guidelines recommend non-HDL-cholesterol as a secondary target of therapy.

• Combination therapies using fibrates seemed appealing and two ongoing trials are comparing combination therapy (statin with either niacin or a fibrate) to assess the incremental benefit of combination therapy.