Lipid Control for Heart Disease

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Coronary artery disease is the largest cause of premature death in industrialised nations and is a growing threat in developing countries as well. The central role of cholesterol in the pathophysiology of coronary artery disease leads to lipid-lowering therapy for the medical management of this condition.

Clinical research with trials using statins have demonstrated the benefits of serum cholesterol lowering in cardiovascular outcome of our population, ranging from healthy subjects to patients with overt cardiovascular risk and patients suffering from acute coronary syndrome. Our threshold of serum cholesterol lowering has been decreased as compared with the past, especially for patients with higher cardiovascular risk. Below will be a review of some of the trials that can help us to look into the extent of cholesterol lowering that will be beneficial to our patients.

In the Heart Protection study¹, patients with a history of coronary artery disease and low-to-average total or LDL cholesterol (LDL-C) levels, persons at risk for coronary artery disease due to a history of other vascular disease (peripheral vascular disease or stroke); those who had a history of diabetes, and individuals who had been inadequately studied in the past (patients > 70 years of age, females) are studied. Between July 1994 and April 1997, 20,536 individuals were assigned to simvastatin (40 mg/day), against placebo tablets, or to a cocktail of antioxidant vitamins (600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene) against placebo capsules, for a mean duration of at least 5 years. It was shown that subjects with LDL-C < 2.56mmol/L did benefit from further LDL-C level lowering and the risk of cardiovascular events decreased significantly in all subgroups, irrespective of baseline LDL-C.

The Asian population, a group that has been traditionally considered to be at much lower risk than Western counterparts; will we benefit from primary prevention with cholesterol lowering? The management of elevated cholesterol in the primary prevention of adult Japanese (MEGA) trial² was the first large randomised trial of statins therapy in an Asian Population. The aim of the MEGA study was to evaluate the effect of cholesterol reduction with pravastatin on the incidence of cardiovascular disease in subjects with mildly elevated total cholesterol and no evidence of atherosclerotic disease and to evaluate the long-term safety of pravastatin in Japanese patients. A total of 8214 patients were randomised to diet or diet plus pravastatin 10-20 mg/day. All patients were advised to follow the National Cholesterol Education Program (NCEP) step 1 diet, which is low in cholesterol and saturated fats. The primary endpoint of the trial, the first occurrence of the CHD endpoint (fatal and nonfatal myocardial infarction [MI], angina, cardiac or sudden death, or cardiac or vascular intervention) was significantly reduced by 33% in the pravastatin group compared with the diet-alone group (P < .010). The effect of pravastatin on the primary endpoint was observed early, and reached significance at 4 years. Patients having higher risks will have more benefits, including subgroups such as man > 60 years of age and baseline LDL > 4.01 mmol/L.

Coronary intervention has an important role in the treatment of ischaemic heart disease, especially for patients suffering from acute coronary syndrome or acute myocardial infarction. However statins therapy is also very important as part of the medical management of this group of patients.

In the PROVE IT-TIMI 22 study³, 4162 patients with an acute coronary syndrome (ACS) within the preceding 10 days were randomly assigned in a 1:1 fashion to pravastatin 40 mg or atorvastatin 80 mg daily. All patients had a total cholesterol level ≤ 6.21 mmol/L but patients who were receiving long-term lipid-lowering therapy at the time of their index ACS had to have a total cholesterol level ≤ 5.18 mmol/L. The primary end-point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring re-hospitalisation, revascularisation (performed at least 30 days after randomisation) and stroke. The median LDL-C achieved during treatment 2.46 mmol/L in the standard therapy group and 1.60 mmol/L in the high-dose group (p < 0.001). Primary end-point at 2 years was 26.3% for standard therapy and 22.4% for intensive therapy, showing the benefit of intensive therapy (p = 0.005; 95% CI: 0.74-0.95). Muscle-related side effects were low and not significantly different between groups. There were no cases of rhabdomyolysis.

The Treat to New Targets/treat to new targets (TNT)⁴ has compared standard dose (10mg) and high dose (80mg) of atorvastatin in patients with stable coronary artery disease. It has shown that LDL-C lowering down to 2 mmol /L has further risk reduction compared with a LDL level of 2.6 mmol /L in the primary endpoint of coronary heart disease death, myocardial infarction, resuscitated cardiac arrest and stroke.
Role of Trans Fatty Acids

Consumption of dietary Trans fatty acids is associated with a deleterious increase in small, dense low-density lipoprotein (LDL) cholesterol particles. Dietary Trans fatty acids are formed during the process of hydrogenating vegetable oil and should be reduced in our dietary component.

Beyond LDL-C Reduction

The main atheroprotective mechanism of HDL is related to its ability to facilitate the reverse cholesterol transport pathway, by which excess cholesterol from peripheral cells, such as macrophages, in the vessel wall is transported to the liver for excretion. HDL has been shown to prevent endothelial dysfunction; it inhibits the expression of adhesion proteins by endothelial cells, which mediate the initial attachment and infiltration of monocytes into early plaques. HDL also has favourable effects on the vasomotor tone of vessels, by promoting the nitric oxide production of endothelial cells, which increases vasodilatation and suppresses smooth muscle cell proliferation in plaques. HDL reduces platelet activation and promotes fibrinolysis and thus may inhibit the formation of a thrombus over ruptured plaques. A combined approach of simultaneously lowering LDL-C and raising HDL may be more effective in reducing cardiovascular events than only lowering LDL-C.

Other than pharmacological therapy, exercise is useful for increasing the HDL level. Currently, the most effective drug for increasing HDL is niacin but its use has been limited because of side effects. Cholesterol ester transfer protein inhibitors are effective to elevate HDL but in the Investigation of lipid Level management to understand its impact in atherosclerotic events trial (ILLUMINATE) has demonstrated its negative effect. The trial is terminated early because it had recorded 82 deaths in the patients taking torcetrapib-atorvastatin against 51 in patients taking atorvastatin alone. In addition to the increase in mortality, the rates of myocardial infarction (MI), revascularisation, angina, and heart failure were higher in the torcetrapib-atorvastatin arm.

Other HDL Replacement Therapy

Apo-lipoprotein A-I is one of the protein components of HDL and is a natural choice for therapeutic HDL replacement. APOA-I Milano (ETC-216), a synthetic Apo-lipoprotein A-I has been developed as a therapeutic agent for HDL replacement. The first clinical study of the effect of ETC-216 in humans was assessed by intravascular ultrasound on patients with acute coronary syndrome. In this trial, 57 patients were given weekly infusions of ETC-216 at 15 and 45 mg/kg or placebo for 5 weeks and were assessed by intravascular ultrasound at baseline and after the 5-week treatment period. The average decrease in plaque volume for the ETC-216 treatment group was 4.2% compared with baseline, whereas there was a slight increase in plaque volume of 0.14% in the placebo group, which was statistically significantly different from the treatment group. Other secondary measures, such as absolute change in plaque volume and maximum atheroma thickness, also showed a favourable statistically significant improvement. Based on the analysis of the position of the external elastic membrane, atheroma volume in the most diseased segments was reduced by 10.9% on average after treatment with ETC-216. However HDL replacement is still not available for our daily management of patients.

In summary among those at risk of cardiovascular disease, lipid lowering with statins confers similar cardiovascular risk reduction across all ranges of baseline LDL-C and clinical benefit is related to the absolute reduction in LDL-C. Level of < 2.0 mmol/L should be the target in patients having cardiovascular risk. Exercise as a means for HDL raising should be advocated to our patients.

References