Treatment of Hyperlipidemia

Yasuhide Nakashima

Abstract

In the treatment of hyperlipidemia, when to begin and end therapy is important. In recent years, potent anti-hyperlipidemia drugs have been widely used, and the results of many intervention trials have shown that combinations of diet, exercise and drug therapies are effective for the primary and secondary prevention of coronary heart disease. The present paper summarizes these trials; introduces the therapy guidelines for adult hyperlipidemia established by Japan Atherosclerosis Society in 1997; and discusses the drugs for hyperlipidemia.

Key words: hyperlipidemia, cholesterol, triglyceride, guideline for treatment of hyperlipidemia

Introduction

The goal of hyperlipidemia therapy is not only to correct elevated blood lipid levels, but also to treat atherosclerosis and reduce the prevalence and mortality of diseases caused by atherosclerosis, following the lowering of the blood lipid level. Recently, the effectiveness of hyperlipidemia therapy utilizing diets and various drugs has been documented by large-scale clinical studies. In particular, HMG-CoA reductase inhibitors (statins) in the 1980's had a great impact on hyperlipidemia therapy. The usefulness of these drugs in primary prevention and secondary prevention of coronary heart disease has been confirmed by many large-scale intervention studies, and at present, they are mainly being used to treat hyperlipidemia (hypercholesterolemia).

The present paper summarizes intervention trials utilizing HMG-CoA reductase inhibitors and briefly discusses the importance of cholesterol-lowering therapy. Furthermore, it introduces the therapy guidelines for adult hyperlipidemia (1) established by Japan Atherosclerosis Society in 1997, and reviews various types of hyperlipidemia drugs.

Lipid Intervention Trials

Based on the results of such large-scale epidemiological studies as the Framingham Heart Study (2), Multiple Risk Factor Intervention Trial (MRFIT) (3) and Seven Country Study (4), an additional large-scale clinical study, the Lipid Research Clinical Coronary Primary Prevention Trial (LRC-CPPT) (5, 6), was conducted before the clinical use of HMG-CoA reductase inhibitors. This trial was the first to show the significance of utilizing drugs in cholesterol-lowering therapy, and suggested a correlation between the level of low-density lipoprotein (LDL)-cholesterol and the risk of coronary heart disease (CHD).

The Scandinavia Simvastatin Survival Study (4S) was published in 1994 (7): On average, simvastatin was administered for 5.4 years to 4,444 hypercholesterolemia patients with coronary heart disease. The mortality rate for patients with coronary heart disease decreased by 42%, and the overall mortality rate was reduced by 30%, thus suggesting that statins lower the overall mortality rate by reducing the mortality rate for patients with coronary heart disease. Furthermore, in the Cholesterol and Recurrent Event (CARE) Study (8), 4,159 myocardial infarction patients with normal cholesterol levels (mean cholesterol: 209 mg/dl) were studied. The results showed that the administration of pravastatin significantly reduced the recurrence of coronary heart disease and myocardial infarction by 24%. The results of the Long-term Intervention with Pravastatin Ischemia Disease (LIPID) Study (9) showed that this statin was useful for the secondary prevention of coronary heart disease in ischemia patients with normal cholesterol levels.

The West of Scotland Coronary Prevention (WOSCOP) Study (10) is one of the well-recognized primary prevention studies. In this study, pravastatin was administered to 6,595 men with moderately elevated cholesterol levels (mean cholesterol: 272 mg/dl) for an average of 4.9 years. The results showed that not only the level of cholesterol decreased, but also the onset of myocardial infarction and the mortality rate for patients with coronary heart disease decreased significantly by 31%, thus confirming that this drug reduces the mortality rate for patients with cardiovascular diseases.

Furthermore, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/Tex AAPS) (11) showed that
the administration of a statin significantly suppressed the onset of cardiovascular events (myocardial infarction and unstable angina) among patients with average cholesterol levels (the level of HDL-cholesterol was below average), suggesting that statins are effective primary prevention agents.

There have been many studies on secondary prevention, and some actively investigated the regression of coronary atherosclerosis: Regression Growth Evaluation Study (REGRESS).

### Table 1. Diagnostic Criteria for Total Cholesterol and LDL-Cholesterol

<table>
<thead>
<tr>
<th>Range</th>
<th>Total cholesterol (mg/dl)</th>
<th>LDL-cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desirable Range</td>
<td>Less than 200</td>
<td>Less than 120</td>
</tr>
<tr>
<td>Borderline Range</td>
<td>200–219</td>
<td>120–139</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>220 or more</td>
<td>140 or more</td>
</tr>
</tbody>
</table>

1. Even when the level of cholesterol is within the boundary range, the presence of other risk factor may necessitate therapy.
2. Patients with coronary heart disease must be followed carefully, and the therapy initiation standard is established at total serum cholesterol levels of higher than 180 mg/dl (LDL-cholesterol: higher than 100 mg/dl). Therapy may be necessary even if the level of cholesterol is within the normal range.

### Table 2. Criteria for Management of Hypercholesterolemia of Hyper-LDL-Cholesterol

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk factor</th>
<th>Life style change</th>
<th>Drug treatment</th>
<th>Goal level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHD</td>
<td>dietary treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>RF (–)</td>
<td>220 or more</td>
<td>240 or more</td>
<td>Less than 220</td>
</tr>
<tr>
<td></td>
<td>CHD (–)</td>
<td>140 or more</td>
<td>160 or more</td>
<td>Less than 140</td>
</tr>
<tr>
<td>B</td>
<td>RF (+)</td>
<td>200 or more</td>
<td>220 or more</td>
<td>Less than 200</td>
</tr>
<tr>
<td></td>
<td>CHD (–)</td>
<td>120 or more</td>
<td>140 or more</td>
<td>Less than 120</td>
</tr>
<tr>
<td>C</td>
<td>CHD (+)</td>
<td>180 or more</td>
<td>200 or more</td>
<td>Less than 180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 or more</td>
<td>120 or more</td>
<td>Less than 100</td>
</tr>
</tbody>
</table>

1) CHD: Coronary heart disease, RF: risk factors.
(1) myocardial infarction, (2) angina, (3) asymptomatic myocardial ischemia (e.g., ischemic ECG abnormalities, etc.), and (4) significant stenosis confirmed by coronary angiography.
2) Major coronary risk factors other than hypercholesterolemia.
(1) age (men: 45 years and older, women: postmenopausal), (2) family history of coronary heart disease, (3) smoking, (4) hypertension (higher than 140 and/or 90 mmHg), (5) obesity, and (6) glucose tolerance abnormality (Japan Diabetes Society's Criteria, Borderline, Diabetic type).

Note 1: Lifestyle change and diet therapy are the basis of therapy for patients in all three categories (A, B and C). In particular, patients in Category A should undergo lifestyle change and diet therapy and be followed for at least a few months. Patients who are classified as belonging to Category B can be reclassified as belonging to Category A by strictly controlling the other risk factors.
Note 2: When administering drugs, patient’s background and condition need to be analyzed carefully.
Note 3: Patients with arteriosclerotic disease affecting arteries other than the coronary artery (e.g., peripheral arteriosclerotic disease, symptomatic carotid arteriosclerotic disease or cerebral infarction) should be classified as belonging to Category B even when the other risk factors are absent.

(12), Multiple Anti-Atheroma Study (MAAS) (13), and Lipoprotein and Coronary Atherosclerosis Study (LCAS) (14). These studies documented that lowering the level of cholesterol leads to the prevention of progression and/or regression of atherosclerotic lesions in coronary arteries.

### Guidelines for Hyperlipidemia Therapy

Based on the results of the above studies, Japan Atherosclerosis Society introduced guidelines for the treatment of adult hyperlipidemia in 1997 (1). As shown in Table 1, the association proposed that the normal level of total cholesterol is less than 200 mg/dl, and that the level of LDL-cholesterol can be used as an indicator of the severity of hypercholesterolemia. The level of LDL-cholesterol is calculated by the Freedwald's Formula.

Table 2 shows the therapy initiation standards and therapy goals for patients in various categories. Its basic concept is two-fold: 1) Since various coronary risk factors (e.g., hyperlipidemia, aging, smoking, obesity, glucose tolerance disorder, hypertension) can induce and exacerbate coronary heart disease, risk factors, other than hypercholesterolemia, must be properly identified, and 2) therapy must first take into account diet and lifestyle management, and then drugs should be selected while managing the risk factors in addition to the cho-
Treatment of Hyperlipidemia

The patients with CHD are roughly divided into primary and secondary prevention. Further, primary prevention is divided into two subgroups: Group A consists of patients who have hypercholesterolemia, but no other risk factors, while Group B consists of those who have hypercholesterolemia and other risk factors. The therapy initiation standards and therapy goals are least strict for group A, and they become stricter for group B and the secondary prevention group (C group), in this order.

These guidelines were established for patients between the ages of 20 and 65, whereas similar guidelines for patients over 65 years of age or those under 20 years of age have not been established.

Treatment of Dyslipidemia

A detailed analysis of the relationship between autopsy findings and risk factors among men with coronary heart disease who died suddenly in Maryland, USA was carried out. The results showed that increases in total cholesterol and decreases in HDL-cholesterol played an important role in plaque rupture and thrombogenesis, thus confirming the clinical significance of hyperlipidemia therapy (15).

The foundation of hyperlipidemia therapy is diet therapy (16), and patients with hyperlipidemia need to watch their diet for a certain length of time. Diet therapy is one of the three elements of lifestyle improvement, and body weight loss (when necessary) and exercise are also important in the treatment of hyperlipidemia.

The effectiveness of diet therapy differs from one patient to the next, and when the level of lipids does not reach a target level after a certain period of diet therapy, drug therapy is initiated. With diet therapy, it often takes 3 to 6 months before the level of lipids decreases, and thus physicians need to continuously educate and guide patients.

Diet Therapy for Hypercholesterolemia

Having a body mass index (BMI) value of 22.2 as the reference point, calorie intake is set at about 25–30 kcal per 1 kg body weight. When patients are considered obese, their body weight should be lowered.

When the serum total cholesterol and LDL-cholesterol do not reach target values after the first stage of therapy, the intake of cholesterol is reduced to less than 300 mg/day. The composition of fatty acids is an important issue for diet therapy in the treatment of hypercholesterolemia. The saturated fatty acid: monounsaturated fatty acid: polyunsaturated fatty acid ratio should be about 1:1.5:1. During the second stage of therapy, the intake of cholesterol is restricted to below 200 mg/day (17).

When the serum triglyceride is high, the intake of total calorie, alcohol (less than 25 g/day) and sugar (in particular, disaccharides and monosaccharides: about 50% of the overall intake) are restricted. Excessive consumption of alcohol increases the level of VLDL triglyceride. When necessary, the intake of all alcoholic beverages should be prohibited, and the ratio of sugars to the overall intake energy should be maintained at 50%.

Exercise is another element of lifestyle improvement. Exercise not only lowers body weight, but also increases the level of HDL-cholesterol. Ideally, patients should exercise 30 to 60 minutes at least three days a week for a total of 180 minutes per week, because the beneficial effects of exercise disappear in two to three days. Patients should exercise at least over 20 minutes at a time. Since many patients with hyperlipidemia also have coronary heart disease, an exercise test must be performed before starting exercise therapy.

Drug Therapy

If strict diet therapy fails to lower the level of LDL cholesterol below the drug therapy initiation standards (Table 2), then the use of an anti-hyperlipidemia drug should be considered. In general, diet therapy takes about six months to lower cholesterol, but anti-hyperlipidemia drugs can be used sooner if patients have coronary artery disease or the level of cholesterol is too high for diet therapy alone to be effective. Nonetheless, when drug administration is discontinued, the level of LDL-cholesterol quickly returns to pre-therapy levels.

If the use of a drug fails to lower the level of LDL-cholesterol to a target value, the administration of multiple drugs should be considered. The use of a second drug may increase the risk for side effects or drug interaction. However, since lower doses are administered when more than one drug is used, the risk of side effects and therapy costs can be reduced in some cases, thus making it more likely for patients to remain on a particular drug regimen for a longer period of time. At present, drugs such as HMG-CoA reductase inhibitors, bile acid sequestrants, nicotinic acid, fibric-acid derivatives and probucol are being used (18) (Table 3).

HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors are very effective, well-tolerated, easy-to-use drugs, and have greatly contributed to advances in drug therapy for dyslipidemia. In Japan, pravastatin, simvastatin, fluvastatin, cerivastatin and atorvastatin have been approved for clinical usage.

Despite their structural differences, all HMG-CoA reductase inhibitors appear to have a common mechanism of action. In other words, these drugs partially inhibit the activity of HMG-CoA reductase, a rate-determining enzyme of the biosynthesis of cholesterol. As a result, the level of intracellular cholesterol in the liver decreases, thus elevating the upregulation of LDL receptors and the elimination of lipoproteins, including apoB or apoE, from plasma. HMG-CoA reductase inhibitors reduce the level of LDL-cholesterol by 20–40%, and increase the level of HDL-cholesterol by 5–15%. However, the mechanism has not been clarified. The level of TG decreases by 10–20%, probably due to an increase in the elimination of VLDL via B/E
Table 3. Effect of Drugs on Cholesterol and Triglyceride

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TC</th>
<th>LDL-C</th>
<th>TG</th>
<th>HDL-C</th>
<th>Advantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMGCoA reductase inhibitors</td>
<td>↓15–30%</td>
<td>↓20–40%</td>
<td>↓10–20%</td>
<td>↑5–15%</td>
<td>reduce CHD mortality and morbidity as primary (pravastatin) and secondary (simvastatin, pravastatin) prevention</td>
<td>7, 8, 55–56, 60</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>↓15–25%</td>
<td>↓15–30%</td>
<td></td>
<td>↑3–5%</td>
<td>Use permitted in children and pregnant women</td>
<td>5, 18, 53, 57, 58</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>↓15–25%</td>
<td>↓15–25%</td>
<td>↓20–50%</td>
<td>↑15–35%</td>
<td>Shown to reduce CHD morbidity and total mortality when used alone and with clofibrate</td>
<td>59–62</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓5–15%</td>
<td>↓10–15%</td>
<td>↓20–50%</td>
<td>↑10–15%</td>
<td>Reduce proportion of circulating small, dense, atherogenic LDL particles Decrease fibrinogen Levels and bezafibrate shown to reduce coronary atherosclerosis progression</td>
<td>18, 63–70</td>
</tr>
<tr>
<td>Probulcol</td>
<td>↓11–22%</td>
<td>↓8–17%</td>
<td></td>
<td>↓22–40%</td>
<td>Antioxidant effect</td>
<td>49, 50, 52, 71</td>
</tr>
</tbody>
</table>

CHD: coronary heart disease, HDL=high-density lipoprotein, HDL-C=HDL-cholesterol, LDL=low-density lipoprotein, LDL-C=LDL-cholesterol, TC=total-cholesterol, TG=triglyceride.

receptors (19). The concentration of Lp (a) appears to be unaffected by the use of HMG-CoA reductase inhibitors (20).

Since HMG-CoA reductase inhibitors are highly effective in reducing the level of lipids and are well tolerated by patients, they are sometimes used alone at first.

It is suggested that statins slow progression and induce regression of atherosclerotic lesions in patients with moderately to severely elevated cholesterol levels (12, 13, 21–23) and induce a better outcome of coronary artery grafts (24).

Thus, their antiatherosclerotic effect is probably related not only to their ability to lower LDL-cholesterol but also to some other direct mechanisms. Statins may act to; 1) reduce atherogenic activity of macrophages, thus stabilizing the fibrous cap of the atherosclerotic plaque; 2) improve the natural vasodilating properties of the vessel wall by reducing endothelial dysfunction; and 3) reduce some prothrombotic factors such as platelet aggregation and levels of plasminogen activator inhibitor 1 (PAI-1) (25).

HMG-CoA reductase inhibitors do not cause many side effects. The major problems associated with its clinical usage are hepatotoxicity and myopathy. With regular doses of statins, elevated serum transaminase was seen in about 0.1% of the cases (26), and rhabdomyolysis in about 0.1% of patients on lovastatin. These symptoms are seen at comparable frequencies with other HMG-CoA reductase inhibitors.

During the second year of the Expanded Clinical Evaluation of Lovastatin (EXCEL) Study, various doses of lovastatin were administered. The results showed that increases in creatine kinase above the normal range were seen in 50–67% of patients, but were also seen in 54% of patients in the placebo group (27). The risk of inducing myopathy increases when HMG-CoA reductase inhibitors are coadministered with fibrin acid derivatives (28), nicotinic acid (29), cyclosporine (30) or erythromycin (31). Despite concerns about side effects attributable to the enzymatic inhibition of cholesterol synthesis, increases in the prevalence of lens opacity caused by the use of HMG-CoA reductase inhibitors have not been reported (32).

**Bile-acid Sequestrants**

The action mechanism of two clinically approved bile-acid sequestrants, cholestyramine and cholestimide, are similar. These polyevalent ion exchange resins bind to bile acids in the small intestine to inhibit the enterohepatic circulation of bile acids to increase the excretion of bile acids, decrease the level of cholesterol in the liver, and elevate the activity of LDL receptors (B/E receptors) (33).

On average, the level of LDL cholesterol is reduced by 15–30%, and the level of HDL cholesterol is increased by 3–5%. However, it is not clear whether bile acid sequestrants bring about changes in the synthesis and catabolism of HDL.

Major side effects include gastrointestinal disorders such as constipation, reflux esophagitis and nausea. Given that these drugs are not absorbed by circulating blood, systemic side effects are rare. As a result of the non-specific binding of bile-acid sequestrants to bile acids, the absorption of drugs such as warfarin (34), digitalis (35), thiazide diuretics (36) and β-blocker (37), is reduced.
Nicotinic Acid

Nicotinic acid is a form of vitamin B that affects lipids when administered in large quantities.

Nicotinic acid decreases the production and release of VLDL in the liver, and lowers the concentration of intermediate density lipoprotein (IDL) and low density lipoprotein in the circulating blood by reducing the production of their precursors (38). Also, it decreases the release of free fatty acids from fat-cells, thus reducing the usefulness of the substrates of triglyceride (TG) synthesis to lower the production of TG in the liver. However, its long-term effectiveness in the periphery is still in question.

Nicotinic acid decreases the level of LDL cholesterol by 10–25%, and that of TG by 20–50%. Also, it increases the level of HDL cholesterol by 15–35% (39). In general, nicotinic acid lowers the concentration of Lp (a), which is generally unaffected by anti-hyperlipidemia drugs (40).

Flushing, a side effect of nicotinic acid, was seen in every patient. This condition is caused since nicotinic acid acts as a vasodilator to release prostaglandin from the endothelial cell. The preadministration of prostaglandin inhibitors, such as aspirin, alleviates flushing. Furthermore, nicotinic acid worsens glucose intolerance, precipitates gout and glaucoma, and causes ophthalmologic side effects (e.g., cystic maculopathy caused by an increase in pooled fluid in the retina). When nicotinic acid is administered alone, myositis is rare (41). However, when it is coadministered with HMG-CoA reductase inhibitors, its incidence increases slightly (42). Thus, caution should be taken when nicotinic acid is coadministered with other drugs.

Fibric-acid Derivatives

Fibric-acid derivatives are used clinically to treat various types of hyperlipidemia, and their effectiveness and safety have been established. Bezafibrate and fenofibrate are two of the well-known fibric-acid derivatives.

The major pharmacological action of fibric-acid derivatives is to accelerate the catabolism of VLDL by elevating the activities of lipoprotein lipase and hepatic lipase. Also, these derivatives are known to suppress the synthesis of triglyceride in the liver, and decrease the plasma concentration of free fatty acids (43).

The results of a secondary prevention study using bezafibrate (Bezafibrate Coronary Atherosclerosis Intervention Trial: BECAIT) showed that the administration of this drug suppressed the progression of coronary atherosclerosis and significantly prevented the coronary events (44).

Fibric-acid derivatives decrease the level of TG by 20–50%, and increase the level of HDL cholesterol by 10–15%. Typically, the level of LDL cholesterol is decreased by 10–15%. However, among patients with hypertriglyceridemia, probably due to the acceleration of VLDL catabolism, the level of LDL cholesterol may increase since LDL particles cannot be eliminated by B/E receptors.

Side effects associated with the administration of fibric-acid derivatives are generally mild, and many are non-specific gastrointestinal symptoms such as flatulence and bloating. The administration of clofibrate increased the onset of cholecystitis in one study (45), but this side effect has not been confirmed with the other fibrates. When administered alone, fibrates are only weakly muscle toxicity (46), but they can mildly elevate the level of creatine kinase. Nevertheless, as mentioned above, the risk of muscle toxicity increases when a fibrate and an HMG-CoA reductase inhibitor are coadministered. Although, recent studies have shown that this combination does not cause severe muscle toxicity (47), it is necessary to be cautious when coadministering these drugs, and to educate and monitor patients.

Probucol

Probucol is believed to accelerate cholesterol metabolism by affecting pathways other than LDL receptors, and its also reduces the level of cholesterol in familial homozygote hypercholesterolemia (FH). Probucol strongly brings about the regression of xanthoma. This drug is a potent antioxidant, and decreases the progression of atherosclerotic lesions by suppressing the oxidation of LDL (48). It has been reported that, in FH patients, the use of probucol causes the regression of tendonous xanthoma (49).

Probucol decreases the level of LDL cholesterol by 5–15% and that of HDL cholesterol by 20–30%. In general, the level of TG is not affected. This drug increases the level of TG within the HDL fraction, and decreases the level of cholesterol-ester because of elevated cholesterol-ester transfer protein (CETP) activity (50). The clinical effect of probucol-induced decreases in HDL cholesterol is being debated, but it is clear that the administration of probucol increases the reverse cholesterol transport by elevating CETP activity and HDL intake by the liver (51).

Probucol does not cause many side effects, but arrhythmia, attributable to long repolarization (long QT), is one of the side effects. The results of animal experiments showed that the incidence of sudden death caused by arrhythmia was increased by the use of probucol (52). The relationship between the use of probucol and sudden cardiac death in humans has not been clarified. In any case, the QT interval must be monitored when administering probucol to patients with long QT interval or to those on drugs such as satalol, quinidine, procainamide, tricyclic anti-depressants or phenothiazines, which may lengthen the QT interval.

Therapy for Low HDL Cholesterol Levels

According to the above-mentioned guidelines, low HDL cholesterol is defined as levels below 40 mg/dl. The first treatment option for this condition is to improve life-style. In other words, patients are instructed to increase the level of HDL cholesterol by improving their diet, exercising regularly, quitting tobacco smoking, and reducing body weight. Hence, hyper-
tension and diabetes must be controlled strictly. At present, there are no drugs that specifically increase the level of HDL cholesterol. Fibric-acid derivatives and nicotinic acid are being used to increase the level of HDL cholesterol since these drugs are effective in lowering the level of neutral fat. In USA, the use of nicotinic acid is recommended to increase the level of HDL cholesterol even in patients with LDL cholesterol levels below the therapy initiation standards (53). Recently, simvastatin is accepted to use as a drug to increase the HDL-cholesterol in USA.

**Hypertriglyceridemia**

The first treatment option for hypertriglyceridemia is to improve life-style. In other words, patients are instructed to lower their body weight, eat diets low in saturated fat and cholesterol, exercise regularly, and stop smoking. Also, the consumption of alcohol is restricted in many patients with this condition. The use of drug therapy must be considered for patients with hereditary hypertriglyceridemia (juvenile coronary artery disease, hypercholesterolemia accompanied by a low level of HDL cholesterol, dysbetalipoproteinemia or familial combined hyperlipidemia) since these conditions can increase the risk for coronary artery disease. Nicotinic acid or fibric acid derivatives are useful in the treatment of hyper-triglyceridemia.

Among patients with hypertriglyceridemia, in particular among those with a past history of acute pancreatitis, drug therapy should be administered so that the level of triglyceride will be low enough to avoid pancreatitis. In these patients, the level of triglyceride is less likely to return to a normal level, thus a therapy target should be established at 500 mg/dl or less. At present, there is no drug for the treatment of chylomicronemia.

**Conclusions**

Due to the introduction of HMG-CoA reductase inhibitors, hypercholesterolemia can now be treated easily and effectively. The results of large-scale clinical trials have clarified that reducing the level of cholesterol prevents the progression of coronary atherosclerosis, and in some cases, brings about the regression of coronary atherosclerosis. Hence, hyperlipidemia therapy reduces the level of lipids in the blood to improve atherosclerosis and lower the prevalence and mortality of diseases caused by atherosclerosis.

At present, drugs are available that satisfy most of these conditions, thus enabling physicians to administer hyperlipidemia therapy with ease. It is reported that an ideal lipid-lowering drug should; 1) be effective in a broad range of patients; 2) substantially reduce LDL-cholesterol and triglycerides (if used for mixed hyperlipidemia), and significantly elevate HDL-cholesterol; 3) achieve LDL-cholesterol treatment goals at the initial dosage; 4) elicit a maximal response within a short period of time; 5) reduce the risk of CHD morbidity and mortality, and total mortality; 6) be safe and well tolerated with long-term use; 7) have a simple dose regimen; 8) and require minimal patient monitoring of its use (54).

**References**

20) Kostner GM, Gavish D, Leopold B, et al. HMG CoA reductase inhibitors lower LDL cholesterol without resucing Lp (a) levels. Circulation 80:
Treatment of Hyperlipidemia


67) Balfour JA, McTavish D, Heel RC, Fenoibrate. A review of its pharma-


