

Cholesterol and Atherosclerosis: A Contemporary Perspective[†]

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Abstract

Monumental advances in the field of lipid metabolism and its relationship to atherosclerotic cardiovascular disease have been achieved during the last half century. Epidemiologic studies have defined lipid disorders as highly significant independent risk factors for coronary heart disease, along with diabetes mellitus, hypertension and smoking. Primary and secondary prevention studies including the Coronary Primary Prevention Trial, Helsinki Heart Study, and the Coronary Drug Project have shown that lowering the atherogenic low density lipoproteins (LDL) and very low density lipoproteins (VLDL) whilst raising the high density lipoproteins (HDL) significantly decreases the risk for coronary disease. Striking evidence that aggressive therapy (to sharply lower LDL and raise HDL with newer drugs) prevents progression and induces regression of coronary narrowing has been obtained in numerous recent studies using quantitative coronary arteriography. An interesting and unexpected lesson learned from these arteriographic studies was that a highly significant reduction within months in several studies in coronary events was out of proportion to improvements in luminal narrowing.

Recently, three major clinical trials to assess the effects of cholesterol reduction by the newly discovered HMG CoA reductase inhibitors (statins) have been published. Pravastatin significantly reduced coronary events in hypercholesterolemic patients [mean LDL-Chol. = 5.0 mM/L (192 mg/dl)] without a history of myocardial infarction. In a secondary prevention study, simvastatin also reduced coronary complications in hypercholesterolemic patients [mean LDL-Chol. = 4.9 mM/L (190 mg/dl)] with pre-existing coronary disease. Very recently, pravastatin treatment significantly reduced coronary events and stroke in patients with a history of myocardial infarction and average cholesterol levels [mean LDL-Chol. = 3.6 mM/L (139 mg/dl)], representing the majority of patients with coronary disease. In all these studies, reduction in cardiovascular events was approximately one-third. In subgroup analyses, men, women, elderly, smokers and hypertensives benefited from cholesterol lowering. There was no significant increase in non-cardiovascular causes of death.

In the United States of America, the National Cholesterol Education Program (NCEP) Adult Treatment Panel, representing major health organizations, developed national guidelines on the detection, evaluation and treatment of high blood cholesterol in adults. In a given patient, the Panel recognizes the importance of weighing all cardiovascular disease risk factors including age (men >45 years, postmenopausal women >), family history of premature coronary disease, smoking, hypertension, diabetes and HDL-Cholesterol (<35 mg/dl) in determining how aggressive therapy should be. The patient with manifest coronary heart disease (CHD) is given a special position as such patients are at highest risk for recurrent events. Major goals of therapy are to lower the LDL-Cholesterol to 2.6 mM/L (<100 mg/dl) in the CHD patient. In non-CHD patients with two or more risk factors, the LDL-Cholesterol goal is 3.4 mM/L (130 mg/dl). In those with fewer risk factors, the goal is 4.2 mM/L (160 mg/dl). These guidelines should be modified as appropriate for Singapore. Patients with elevated triglycerides usually have low HDL-Cholesterol levels and often represent a heterogeneous group who may have other concurrent abnormalities including the presence of small dense LDL, insulin resistance, hypertension, obesity, overt diabetes and combined hyperlipidemia. Such patients merit individualized treatment. The prevalence of this syndrome may be more common in Singapore and requires further investigation.

Current therapeutic guidelines emphasize the need for weight loss and dietary restriction of total and especially saturated fat (<7% to 10% total calories), cholesterol (<200 to 300 mg/day), and exercise. Pharmacologic therapy should be considered after maximal compliance with diet and exercise and therapeutic goals are not met.

The major drugs include niacin, bile acid sequestering agents, fibrates, and a relatively new class of compounds that

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inhibit HMG-CoA reductase (a key enzyme in cholesterol biosynthesis) i.e. “statins”.

In clinical practice, pharmacologic selection should be individualized. In general, niacin should be considered initially and, as indicated earlier, its side effects and contraindications should be assessed. In patients with elevated LDL-Cholesterol, the statins should be considered. In patients with CHD where the LDL-Cholesterol goal of <2.6 mM/L (100 mg/dl) is not achieved, or in other patients with severe elevations, combination with a bile acid resin can have a synergistic effect in further lowering LDL. For patients with moderate or severe hypertriglyceridemia, especially if associated with a history or danger of pancreatitis, low HDL-Cholesterol and diabetes mellitus, fibrates should be considered. Patients with difficult diagnostic or therapeutic problems should be referred to a specialized lipidology centre.

In summary, we live in a new era in the area of preventive cardiology. The fruits of research have led to clinical applications in new diagnostic technology, and effective lipid regulating agents are currently available to control blood lipoproteins to reduce the epidemic of coronary disease in many parts of the world, including Singapore.

Introduction

Considerable evidence obtained during the last half century suggests that cholesterol deposition, which is the hallmark of atherosclerosis and its complications, is influenced by the concentration of the atherogenic lipoproteins consisting of low density lipoproteins (LDL), very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), and Lp(a). During the last two decades or so, we have learned that another class of lipoproteins known as the high density lipoproteins (HDL) are associated with protection for heart disease.¹⁻⁴ Several lines of evidence indicate that HDL participate in the process of reverse cholesterol transport whereby excess cholesterol from tissues is removed.⁵ Evidence also indicates that the ratio of the atherogenic lipoproteins and the anti-atherogenic HDL influences not only the rate of progression of atherosclerosis, but a reduction in this ratio is also associated with significant regression of coronary atherosclerosis and more importantly a significant reduction in coronary events rates. The major aim of this lecture is to review the current clinical evidence on the relationships between cholesterol, its carrier lipoproteins, and their regulation and coronary disease.

Although blood cholesterol is the “final common pathway” for the atherosclerotic process, it is well recognized that this process is also influenced by a number of risk factors. At the present time, according to the USA National Cholesterol Education Program Adult Treatment Panel Guidelines, the following risk factors are considered to be positive: age i.e. men ≥ 45 years, women ≥ 55 years, premature menopause without oestrogen replacement therapy, family history of premature coronary heart disease, smoking, hypertension, HDL cholesterol below 35 mg/dl (0.9 mM/L) and diabetes mellitus.⁶ For the first time in the new guidelines a high HDL cholesterol ≥ 60 mg/dl is now considered to be a negative risk factor indicating the concept that high levels of HDL maybe cardio-protective. Studies from Framingham indicate that for a given level of LDL cholesterol the relative risk of coronary heart disease is directly related to the HDL cholesterol i.e. the higher the HDL cholesterol the lower the risk.

A cholesterol level above 6.2 mM/L (240 mg/dl) is considered to be high risk level. It is interesting to note that in the United States, the prevalence of high risk high blood cholesterol is very high in men and women over the age of 45. The prevalence of cholesterol levels above this concentration are approximately one in three men and one in two women.⁶ Thus, the problem of hypercholesterolemia is not one that is restricted to the rare genetic disorders but it is a major public health problem. This is particularly true in postmenopausal women in whom the risk for coronary disease begins to approximate that of men. Several studies have shown that patients with pre-existing coronary disease have very high risk for recurrence of complications from coronary heart disease. Most of these patients have three or more risk factors, thus underscoring the fact that this risk factor recognition is extremely important in this high risk population.⁷

Undertreatment of Dyslipidemia

The frustrating aspect of treatment is the fact that several studies recently have shown that many patients with elevated cholesterol and coronary disease are patients who are at very high risk and are not treated for this condition. In one study,⁸ before cardiac catheterisation only 16.7% patients were treated although the diagnosis had been established for both hypercholesterolemia and the presence of coronary disease. What was frustrating was that one to two years following cardiac catheterisation only 36% of patients were treated and those that were treated to target were even less than that. Thus, we are treating only the tip of the iceberg of patients who need medical management for this condition.

In our own medical centre we studied the prevalence of dyslipidemia in veterans with coronary artery disease and found that in 1743 patients, 51% had type IIA hyperlipidemia, 11% had type IIB, 9% had type IV, 1% had type V and

10% had the low isolated HDL syndrome. Only 18% of patients with coronary disease were found to have normal lipid patterns by today's criteria. Also of interest is the fact that 25% to 30% of patients with so called normal cholesterol i.e. total cholesterol below 5.2 mM/L (200 mg/dl) have an isolated low HDL syndrome which contributes to this disease.

Thus, there are several challenges that we have in the current management of coronary artery disease (CAD). Most patients receive anti-platelet therapy to reduce chance of vessel occlusion (often prescribed after angioplasty, bypass surgery, and acute myocardial infarction), and medical therapy to reduce myocardial ischaemia and coronary artery bypass graft surgery and angioplasty to increase myocardial oxygen delivery. However, fewer patients receive therapy to change the lipid dependent aspects of the atherosclerotic process itself. Thus, in my opinion, managing coronary artery disease today without treating dyslipidemia and other risk factors is akin to managing bacterial pneumonia without antibiotics!

Early Trials to Test the Lipid Hypothesis

The cholesterol hypothesis states the higher the blood cholesterol, the greater the risk of coronary heart disease. Blood cholesterol can be lowered by diet and drugs. The question is whether lowering blood cholesterol reduces the risk of coronary heart disease. This so called hypothesis, in my opinion, is no longer a hypothesis but a fact-i.e. lowering cholesterol prevents heart disease. We will examine the current clinical evidence which supports this conclusion.

The first study to conclusively show that lowering LDL cholesterol prevented heart disease was the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) in which approximately 3500 men between the ages of 35 and 59 were recruited.⁹ All these men had elevated cholesterol levels and no evidence of heart disease. They were all treated with a diet to lower cholesterol and all those who qualified were randomised and given either placebo or cholestyramine to lower the LDL. After seven years of follow up there was an unequivocal reduction in the incidence of primary endpoints of fatal and non-fatal myocardial infarction. The reduction was of the order of 19% and was highly significant, the LDL reduction that was achieved was approximately 11%. A very important relationship between reduction of LDL and reduction in incidence for CHD was noted. The data indicated that for every 10% reduction in LDL there was a corresponding 19% reduction in CHD event rate. This has many public health implications. For example, in a hypercholesterolemic population of patients, reduction of LDL cholesterol by 25% would achieve a reduction in CHD of approximately 35%. This prediction has indeed been borne out by subsequent studies which are discussed below.

The next major clinical study to attest to the lipid hypothesis was the Helsinki Heart Study in which gemfibrozil was used in a large cohort of patients. This agent increases HDL cholesterol and it reduces triglycerides and also LDL cholesterol. In this landmark study published in 1987, a highly significant reduction of 34% in the incidence of coronary event rate was found.¹⁰ It was also found by covariate analysis that the elevation in HDL-cholesterol was independently associated with reduction in risk. This further supports the theory that not only LDL reduction but raising HDL is extremely important in prevention of heart disease. Additional evidence for the role of HDL in the prevention of heart disease has also been recently obtained in very striking experimental studies in transgenic mice which produced high concentrations of human apoprotein AI, major protein of HDL.¹¹ These mice were extremely resistant to atherogenic diets and atherosclerosis was significantly reduced. Also, work by Badimon et al¹² has shown that intravenous injections of HDL in rabbits also prevents atherosclerosis.

Our research group has conducted considerable research on the mechanism of action of gemfibrozil in order to understand why it reduces coronary disease and how it can prevent atherosclerosis. In brief, two types of studies have been done. The first set of studies was to determine the effect of gemfibrozil on HDL kinetics and also its effects on lipoprotein lipase.¹³ Patients with low HDL and high triglycerides were recruited for this study and were treated with gemfibrozil for two months. At baseline and two months after gemfibrozil therapy, special research studies were done. In the kinetic studies, plasma HDL was isolated from each patient and radio-labelled with ¹²⁵I. The HDL was then purified, sterilised and injected into each subject and blood was drawn at periodic intervals for approximately 12 days. The radio-activity associated with apo AI and AII was measured and the decay curve plotted. The data indicated that gemfibrozil had no effect on the catabolic pathway of apo AI or AII. Gemfibrozil stimulated the production of apo AI and AII. We then went on to study the effect of gemfibrozil on cultured human liver cells as the liver is the major organ for the production and removal of HDL. These studies showed that gemfibrozil directly stimulates the production of apoproteins AI and AII by the human liver.¹⁴ It appears to do so by increasing the messenger RNA for apo AI. Nuclear run-off and transcript half-life studies showed that it stabilises the mRNA for apo AI.

These studies have suggested the concept that any drug or agent that stimulates the production of HDL would

theoretically be anti-atherosclerotic because a drug that blocks the catabolism of HDL would raise plasma levels but would theoretically not have a similar effect on reverse cholesterol transport.” We have recently found that oestrogens also stimulate hepatic production of HDL.

Angiographic Trials

After publication of the two major primary prevention studies i.e. Coronary Primary Prevention Trial (CPPT) and the Helsinki Heart Study, scientists focused on a whole series of studies aimed at the question of whether aggressive lipid regulation could affect progression of atherosclerosis or regression of CAD. The first well-conducted study was the cholesterol lowering atherosclerosis study which was published by Blankenhorn et al.¹⁵ In this study, patients with coronary artery bypass surgery were recruited and treated with a combination of colestipol and niacin and compared to a placebo group. Baseline angiograms were performed and a repeat angiogram was performed approximately two to four years later. The treated group had a very marked reduction in LDL, a significant elevation in HDL and reduction in triglycerides. Such aggressive lipid regulation was associated with 17% regression of atherosclerosis compared to only 3% to 4% in the placebo group. This difference was highly significant and demonstrated for the first time by quantitative angiographic techniques that coronary regression was a distinct possibility. Subsequent to this study, results of a series of angiographic studies were published. There are at least approximately a dozen such reasonably good arteriographic studies that have been done with different interventions and in different populations of patients.¹⁶ The basic design was to identify patients with coronary disease associated with different types of lipid disorders or other risk factor characteristics and to intervene with diet plus lipid regulating drugs. In one study, effects of surgical intervention (partial ileal bypass) were assessed. The earlier studies were done with resins and the more recent studies have been done with the HMG CoA reductase inhibitors (“statins”). Recent monotherapy studies have been with either lovastatin, pravastatin or simvastatin. These studies show very definitely that aggressive lipid regulation and diet and even lifestyle changes (e.g. extremely low fat diet and exercise) can be associated with a significant reduction in the percent stenosis for coronary disease as assessed by quantitative angiography.

Although these studies were focused on the coronary stenosis as the primary endpoint, these patients were also monitored for coronary event rates. Such analysis of the data revealed an unexpected result. Across the board the investigators found that patients treated with aggressive lipid regulation had a striking decrease in coronary event rate compared to the placebo group in virtually every study. In several of these studies which used a larger number of patients, these differences in event reduction were highly significant and ranged between 25% and 89% of the control values. Two of these studies were done on carotid artery disease and the intima-media thickness was measured by B mode ultrasonography. Both of these studies in which pravastatin was used showed a significant reduction in the rate of progression of carotid thickening. These arteriographic studies historically formed the basis for the observations that aggressive lipid regulation that is possible with newer agents today is capable of reducing coronary events in a very significant manner. From a clinical point of view, the reduction of clinical events is more important than the small amount of regression or lack of progression that was observed in the arteriographic studies.

Recent Trials

Three major studies have recently been published which looked at the effect of the HMG CoA reductase inhibitor monotherapy and the reduction of coronary event rates. The first of these was the Scandinavian Simvastatin Survival Study in which 4444 patients with angina pectoris or previous MI were recruited and treated with a lipid lowering diet for eight weeks.¹⁷ All patients had hypercholesterolemia and half of the patients were placed on placebo and half of them were treated with simvastatin. They were followed up for a median of 5.4 years. The primary endpoint was total mortality and secondary endpoints were coronary deaths and non-fatal myocardial infarction. Tertiary endpoints included incidence of angioplasty and coronary artery bypass graft procedures, survival without atherosclerotic event, and any coronary event. This study showed clearly that the mortality rate was significantly reduced in patients treated with simvastatin. There was a 34% reduction in the major events of coronary deaths and non-fatal myocardial infarction. Thus, this study indicated not only a reduction in cardiovascular events but it showed conclusively that total mortality could be reduced with an HMG CoA reductase inhibitor.

The second recent study and the only primary prevention study with a reductase inhibitor has recently been published and known as the West of Scotland Coronary Prevention Study.¹⁸ The objective of this study was to evaluate the effect of pravastatin monotherapy on the rate of non-fatal MI and CHD deaths in patients with elevated cholesterol levels and no prior MI. Males between the ages of 45 and 64 years with a total cholesterol of equal to or more than 6.5 mM/L (252 mg/dl) were recruited. They were prescribed diet therapy for four weeks and if their LDL cholesterol remained elevated, they were then prescribed pravastatin (40 mg daily) or placebo. A total of 6595 patients were recruited for this study. The endpoints were non-fatal MI or CHD deaths and the secondary endpoints were total

mortality over a five-year period of follow-up. Non-fatal MI or CHD death incidence were reduced by 31% in the pravastatin treated group. The divergence of the curves related to events rates occurred after six months of therapy and became highly significant at the end of the study. This was in sharp contrast to the earlier studies with resins which resulted in a 11% reduction in LDL and a divergence of the event rate curves between placebo and treated groups at approximately two years. In other words, the reduction in event rate was evident within a year with pravastatin. The incidence of coronary angiography, coronary angioplasty, stroke, and coronary artery bypass surgery was also significantly reduced. Total mortality was also reduced by 22% and was nearly significant at the $P < 0.05$ level. It should be remembered that in primary prevention studies, the coronary event rate is much lower than in secondary prevention and therefore total mortality requires either an extremely large number of patients or patients that are followed for many more years, something that is not financially feasible always. Like the Scandinavian Study, the Scotland Study also indicated that younger and older patients also had risk reduction for coronary disease which was highly significant.

These two studies and almost all previous angiographic studies were conducted in hypercholesterolemic patients with or without clinical evidence of coronary disease. No study had been conducted in patients with average levels of LDL-Cholesterol. In the most recent study, five years of treatment with pravastatin or placebo in 4159 men and women who had sustained myocardial infarction was reported. Their total cholesterol was less than 6.2 mmol/L (240 mg/dl) and mean LDL-Cholesterol was 3.6 mmol/L (139 mg/dl).¹⁹ The incidence of fatal coronary event or non-fatal myocardial infarction was reduced significantly by 24%. Secondary endpoints including coronary bypass surgery was reduced by 26%, coronary angioplasty decreased 23% and stroke was reduced by 31%. Coronary event rate was decreased more in women than men and the benefit extended to the elderly, hypertensives, smokers, and diabetics.²⁰

Therefore, the clinical trials to date seem to indicate that substantial reductions in cardiovascular events in angiographic trials are out of proportion to the changes in wall diameter changes. Meta-analysis demonstrates decreased non-fatal CHD and CHD mortality with cholesterol lowering in men, women, and the elderly. Thus the ABCs of secondary prevention based on these results would indicate: antiplatelet agents (e.g. aspirin) result in a reduction in vascular events of approximately 25%; beta blockers which are widely used for the prevention of recurrent coronary disease is approximately 27%; cholesterol lowering agents would reduce the vascular event rate by approximately one third or more.²¹

Mechanisms of Event Reduction

Because recent studies have shown that lipid regulation can result in decreased coronary event rates, many ongoing investigations have tried to answer the question of potential mechanisms of action for this clinical benefit. The first hypothesis is based upon the theory that it is the small plaques that result in rupture and thrombosis resulting in the acute, serious and eventually fatal complications of atherosclerosis. It is not the large lesions that rupture and thrombose; small plaques have fresh lipid deposition in them and it has been hypothesised that sharp reductions in atherogenic LDL reduce the influx and increase the efflux of freshly deposited cholesterol, resulting in stabilisation of these plaques and prevention of rupture and thrombosis. The second theory is that lipid reduction restores the abnormal endothelial function that is often observed in patients with coronary heart disease. For example, when acetylcholine is introduced via a catheter in the coronary arteries in normal subjects, coronary dilatation occurs. On the other hand, in patients with severe coronary atherosclerosis, a vasoconstriction results instead. This paradoxical vasoconstriction is thought to be due to an inability of the atherosclerotic coronary artery to produce nitric oxide considered to be a mediator for the vasodilatation.²² Lipid reduction restores the ability of the endothelium to produce nitric oxide, thereby resulting in normalisation of endothelial function.

Current Management

With this background, it is important for us to ask ourselves as to how these data translate into the practical steps in the management of hyperlipidemia. First, it is important to review the current Adult Treatment Plan (ATP) II guidelines of the National Cholesterol Education Program that is used widely in the United States for management and treatment of lipid disorders. The highlights of the major changes to the ATP II guidelines in contrast to the initial guidelines that were published in 1986 are as follows: (a) an increased emphasis on patients with established cardiovascular disease, (b) an increased emphasis on CHD risk status as a guide to type and intensity of lipid altering therapy, including high risk postmenopausal females, high risk elderly patients otherwise in good health, and younger patients with multiple risk factors, and (c) the addition of age to the list of major risk factors. More attention has been paid to HDL cholesterol as a CHD risk factor and increased emphasis on the step II diet plus incorporation of weight loss and physical activity as components of dietary therapy. Low LDL target levels for patients with pre-existing atherosclerotic vascular disease have been recommended. Specifically, LDL target value of 2.6 mM/L (100 mg/dl) or

below is recommended for patients with pre-existing evidence of atherosclerotic cardiovascular disease.

Thus, it is very clear that there is a need for us to be highly alert to the fact that the natural history of coronary artery disease can be changed by lipid lowering. Clinical benefits can often be seen in a relatively short time i.e. less than a year and patients who are at high risk should be treated aggressively.

The initial treatment for hypercholesterolemia is of course, diet and exercise. Basic principles are to reduce the content of total fat in the diet to less than 30% and cholesterol content to less than 300 mg daily. It is recommended that the step II diet be prescribed as soon as possible and this diet has less than 7% of total caloric intake from saturated fat with the rest from monounsaturated fatty acids and up to 10% from polyunsaturated fatty acids. Carbohydrate content should be at least 55% of caloric intake and protein approximately 15%. The cholesterol intake should be reduced from an average intake of 450 mg per day to less than 200 mg per day. It is emphasised that the patient should take sufficient exercise and the caloric content should be to maintain a desirable body weight. Such a diet really means reducing the intake of meat since that is the major source of saturated fat and cholesterol. Also, dietary dairy intake should be reduced to reduce saturated fat intake. Once it is decided that the patient is on maximum compliance to diet therapy, drugs should be considered. The goal for therapy should be to achieve an ideal cholesterol equal to or below 2.6 mM/L (100 mg/dl) in patients with definite CHD or other atherosclerotic disease, 3.4 mM/L (130 mg/dl) or lower in patients with no CHD but with two or more other risk factors and less than 4.2 mM/L (160 mg/dl) in patients with no CHD and with fewer than two other CHD risk factors. The LDL-cholesterol goal of less than 2.6 mM/L for secondary prevention is based upon epidemiologic evidence, primary and secondary trials which have been summarised above, and meta-analysis of angiographic trials.

The drugs that are available for lipid lowering are the bile acid binding resins, nicotinic acid (niacin), fibric acid derivatives, and HMG CoA reductase inhibitors. The bile acid sequestrants primarily lower LDL cholesterol and do not affect HDL significantly. They may increase triglycerides modestly in some patients. Nicotinic acid is extremely useful except that many patients are unable to tolerate it. It can also be referred to as the "broad spectrum" lipid regulating agent because it does all that is desired in a lipid regulating drug including LDL lowering and raising HDL, and lowering triglycerides. It also lowers Lp(a). The fibric acid derivatives, of which gemfibrozil is the major drug used in the United States, lower triglycerides and raise HDL significantly. They also lower LDL modestly and significantly in many patients. The HMG CoA reductase inhibitors reduce LDL-cholesterol by up-regulating LDL receptors; they also modestly raise HDL and decrease triglycerides. Oestrogens can be used in postmenopausal females and they also result in lowering of LDL and raising of HDL.

The selection of these agents should be highly individualised. In general, niacin should be considered as the first line drug because of its effectiveness as well as cost. However, it has been shown in many studies that niacin has several contraindications including peptic ulcer disease, gouty arthritis, and diabetes mellitus.²³ It also has several nuisance side effects like flushing and itching and increased incidence of hepatic dysfunction which prevents its widespread use. If niacin is contraindicated or cannot be used, the decision to use the next drug depends on the nature of the lipid problem. In patients with a predominantly triglyceride problem, gemfibrozil is the drug to be used next in addition or in lieu of niacin. On the other hand, if the patient has a predominantly LDL elevation, the initial drug of choice after niacin is an HMG CoA reductase inhibitor. If the LDL objective cannot be met with the reductase inhibitor with or without combination with niacin, the patient should be prescribed a bile acid binding resin in addition to the reductase inhibitor. This combination is extremely effective in lowering LDL and one can achieve a reduction of as much as 50% or greater on LDL reduction by this combined synergistic therapy. Oestrogen should be considered in postmenopausal women for raising HDL as well as lowering LDL. However in some females, hypertriglyceridemia can result and therefore such patients need to be monitored closely for such complications.

Several clinical studies are being undertaken in the United States at the present time, and these studies address questions that have not been addressed in previous studies. The most important of these are the HDL Intervention Trial, which is a trial to determine whether patients with coronary disease, normal LDL and who have the isolated HDL syndrome (hypoalphalipoproteinemia) can benefit from intervention with gemfibrozil.²⁴ This study will be completed in 1999 and the results should indicate very clearly whether patients with the isolated HDL deficiency and coronary disease should be treated with a pharmacologic agent to raise HDL e.g. gemfibrozil or niacin which is the most potent agent for raising HDL.

Conclusion

In summary, we have considerable data now to suggest that lowering atherogenic lipoproteins (especially LDL) and increasing HDL can reduce the acceleration of the atherosclerotic process and in some cases even affect regression. We also have powerful laboratory methodology to measure these lipids, lipoproteins and their subfractions. We also have

excellent pharmacologic agents that can achieve this objective. It is most important for the clinician to identify patients at risk for coronary disease and to use these agents in the light of current knowledge to reduce the epidemic of coronary disease.

REFERENCES

1. Miller G J, Miller N E. Plasma high density lipoprotein concentration of ischemic heart disease. *Lancet* 1975; 1:16-9.
2. Castelli W I, Doyle J T, Gordon T, Hames C G, Hjortland M C, Hully S B. HDL cholesterol and other lipids in coronary heart disease. The cooperative lipoprotein phenotyping study. *Circulation* 1977; 55:767-72.
3. Kannel W B, Castelli W P, Gordon T. Cholesterol in the prediction of atherosclerotic disease. New perspective based on the Framingham Heart Study. *Ann Intern Med* 1979; 90:85-91.
4. Gordon T, Castelli W P, Hjortland M C, Kannel W B, Dawber T R. High density lipoprotein as a protective factor against heart disease. The Framingham Heart Study. *Am J Med* 1977; 62:707-14.
5. Kashyap M L. Basic considerations in the reversal of atherosclerosis-significance of high density lipoproteins in stimulating reverse cholesterol transport. *Am J Cardiol* 1989; 63:56H-9H.
6. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993; 269:3015-23.
7. Genest J J, McNamara J R, Salem D N, Schaefer E J. Prevalence of risk factors in men with premature coronary artery disease. *Am J Cardiol* 1991; 67:1185-9.
8. Cohen M V, Byrne M J, Levine B, Gutowski T, Adelson R. Low rate of treatment of hypercholesterolemia by cardiologists in patients with suspected and proven coronary artery disease. *Circulation* 1991; 83:1294-304.
9. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial Results, I: reduction in incidence of coronary heart disease. *JAMA* 1984; 251:351-64.
10. Frick M H, Elo O, Kaapa K, Heinonen O P, Heinsalmi I, Helo P, et al. Helsinki Heart Study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; 317:1237-45.
11. Rubin E M, Krauss R M, Spangler E A, Verstuyft J G, Clift S M. Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. *Nature* 1991; 353:265-7.
12. Badimon J J, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein fraction in the cholesterol fed rabbit. *J Clin Invest* 1990; 85:1234-41.
13. Saku K, Gartside P S, Hynd B, Kashyap M L. Mechanism of action of gemfibrozil on lipoprotein metabolism. *J Clin Invest* 1985; 75:1702-12.
14. Jin F Y, Kamanna V S, Chuang M Y, Morgan K, Kashyap M L. Gemfibrozil stimulates apolipoprotein AI synthesis and secretion by stabilization of mRNA transcripts in human hepatoblastoma cell line (Hep G2). *Arterioscler Thromb Vasc Biol* 1996; 16:1052-62.
15. Blankenhorn D H, Nessim S A, Johnson R L, Sanmarco M E, Azen S P, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987; 257:3233-40.
16. Gotto A M. Lipid lowering, regression and coronary events. *Circulation* 1995; 92:646-56.
17. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344:1383-9.
18. Shepherd J, Cobbe S M, Ford I, Isles C G, Lorimer A R, MacFartane P W, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; 333:1301-7.
19. Sacks F M, Pfeffer M A, Moye L A, Rouleau J L, Rutherford J D, Cole T G, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; 335:1001-9.
20. Sacks F M, Pfeffer M A, Moye L, Brown L E, Hamm P, Cole T G, et al. Rationale and design of a secondary prevention trial of lowering after acute myocardial infarction: The Cholesterol and Recurrent Events Trial (CARE). *Am J Cardiol* 1991; 68:1436-46.
21. Yusuf S, Lessem J, Jha P, Lonn E. Primary and secondary prevention of myocardial infarction and strokes: an update of randomly allocated controlled trials. *J Hypertens* 1993; 11(suppl 4):S61-73.
22. Pearson T A, Marx H J. The rapid reduction in cardiac events with lipid-lowering therapy; mechanisms and implications. *Am J Cardiol* 1993; 72:1072-3.
23. Gray D R, Morgan T, Chretien S D, Kashyap M L. Efficacy and safety of controlled release niacin in dyslipoproteinemic veterans. *Ann Intern Med* 1994; 121:252-8.
24. Bloomfield-Rubins H, Robins S J, Iwane M K, Boden W E, Elam M B, Fye C L, et al. For the Department of Veterans Affairs HIT Study Group. Rationale and design of the Department of Veterans Affairs high-density lipoprotein cholesterol intervention trial (HIT) for secondary prevention of coronary artery disease in men with low high-density lipoprotein cholesterol and desirable low-density lipoprotein cholesterol. *Am J Cardiol* 1993; 71:45-52.