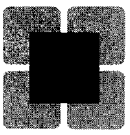

Management of hypercholesterolemia in the hypertensive patient

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■ Measurement of serum total cholesterol (TC) and high-density lipoprotein-cholesterol (HDL-C) is recommended in the comprehensive evaluation of hypertensive patients. The prevalence of hypercholesterolemia is higher in hypertensive compared to normotensive individuals and the cardiovascular risk associated with high blood pressure is increased when hypercholesterolemia is present. Diuretics and/or beta blockers may increase TC, triglyceride (TG), and very low-density lipoprotein-cholesterol (VLDL-C) levels and/or reduce HDL-C levels, but it is not certain if these changes in blood lipids and lipoproteins decrease the benefits of the blood pressure reduction that they produce. Blood pressure and blood cholesterol levels may be reduced through dietary modification and low-fat diets blunt the changes in lipids and lipoproteins induced by diuretics or beta blockers. Despite these changes, many hypertensive patients require lipid-lowering drugs to reduce low-density lipotrotein-cholesterol (LDL-C) levels to an acceptable range. Lipid lowering drugs may produce bothersome side effects and/or increase the cost of medical therapy considerably. However, several lipid lowering drugs have been shown to reduce primary CHD incidence in middle-aged men with hypercholesterolemia.

□ INDEX TERM: HYPERCHOLESTEROLEMIA □ CLEVE CLIN J MED 1989; 56:351–358

HYPERCHOLESTEROLEMIA is common in hypertensive patients and its presence increases the risk of cardiovascular complications.[1] Reduction of blood cholesterol levels decreases the incidence of CHD in middle-aged men with hypercholesterolemia.[2–3] For these reasons, evaluation of the hypertensive patient should include measurement of blood lipid and lipoprotein levels.

As aggressive detection and treatment of hypertension has increased over the past few decades, the cardiovascular mortality rate in the U.S. has declined.[4] The reason for this effect is difficult to determine and is probably multifactorial. Clinical trials in hypertensive patients have generally shown a decreased incidence of pressure-related complications, such as stroke, but no decrease in the incidence of coronary heart disease (CHD) during diuretic-based antihypertensive therapy.[5–7] Although it is not certain why antihypertensive drug treatment has not been shown to reduce CHD incidence, adverse effects of antihypertensive agents on blood lipids may be involved.

This report presents recommendations for the detection and treatment of lipoprotein abnormalities in hypertensive patients. These guidelines are consistent with recent recommendations from the Joint National Com-

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TABLE 1
CLASSIFICATION OF BLOOD PRESSURE (mmHg) IN ADULTS[4]

Systolic (when DBP <90 mmHg)	
<140	normal blood pressure
140–159	borderline isolated systolic hypertension
≥160	isolated systolic hypertension
Diastolic	
<85	normal blood pressure
85–89	high normal blood pressure
90–104	mild hypertension
105–114	moderate hypertension
≥115	severe hypertension

TABLE 3
CLASSIFICATION OF LDL-C LEVELS (mg/dL) IN ADULTS[5]

<130	desirable
130–159	borderline high-risk
≥160	high risk

Measurement of LDL-C requires a fasting blood sample for determination of TC, TG, and HDL-C levels. Treatment decisions are based on LDL-C levels.

mittee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure and the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[8,9]

DEFINITIONS AND PREVALENCE

The cardiovascular risk associated with increased diastolic blood pressure (DBP) and TC is continuous and graded. Therefore, definitions of hypertension and hypercholesterolemia are arbitrary. Martin et al[10] reported that the age-adjusted six-year death rate per 1,000 men screened for the Multiple Risk Factor Intervention Trial (MRFIT) increased as either DBP or TC rose. The risk was accentuated when DBP was greater than 94 mmHg or TC was above 253 mg/dL; these levels were observed in about 15% of the men screened.

Blood pressure and cholesterol levels are classified in *Tables 1* and *2*.[8,9] Based on these classifications, the prevalence of hypertension and hypercholesterolemia increases with age, from about 15% in the third decade to approximately 40% in the fifth decade of life.[11,12] Stamler et al[1] noted that 20% of all men screened in the MRFIT had TC levels of 245 mg/dL or greater; among men who were hypertensive without baseline evidence of myocardial infarction, the prevalence of TC levels in this range increased to 27%. The relative risk of CHD increased more than threefold in hypertensive men whose baseline TC was 245 mg/dL or greater compared to those whose TC was less than 182 mg/dL. Consequently, noted Stamler, "relatively low-risk hypertensive men were rare exceptions. The norm was high blood pressure combined with an elevated serum cholesterol level and, in a sizable proportion of the cohort, cigarette use as well."

TABLE 2
CLASSIFICATION OF TOTAL BLOOD CHOLESTEROL (mg/dL) IN ADULTS[5]

<200	desirable blood cholesterol
200–239	borderline-high blood cholesterol
≥240	high blood cholesterol

The classification of total cholesterol in adults 20 years of age or older does not depend on age or sex.

DETECTION OF LIPID ABNORMALITIES

Measurement of TC as well as high-density lipoprotein cholesterol (HDL-C) is recommended in the initial evaluation of all hypertensive patients.[8] A fasting blood sample is not needed, and analysis of the TC:HDL ratio is a more reliable predictor of CHD risk than TC alone.[13,14] If the TC level is 200 mg/dL or greater or the HDL-C level is lower than 35 mg/dL, a fasting blood sample should be obtained to estimate low-density (LDL-C).[8] When fasting triglyceride (TG) levels are less than 400 mg/dL, LDL-C levels may be calculated using the formula[15]:

$$\text{LDL-C} = \text{TC} - (\text{TG}/5 + \text{HDL-C})$$

The National Cholesterol Education Program treatment guidelines are based on LDL-C levels,[9] which are classified in *Table 3*.

DEVELOPMENT OF HYPERCHOLESTEROLEMIA

Genetic and environmental factors influence the development of high blood pressure or abnormal blood lipid and lipoprotein levels. Hubert et al[16] noted a strong association between weight gain and increased blood pressure and cholesterol levels among the young adult offspring of the Framingham Heart Study Cohort. Body mass index had a negative correlation with HDL-C levels in adults in the second National Health and Nutrition Examination Survey.

Changes in body weight also may influence blood lipid and lipoprotein levels in patients receiving diuretics.[17] All men in the Special Intervention group of the MRFIT were offered a diet low in saturated fat and cholesterol, and hypertensive patients received diuretic therapy as well.[18] Among participants who lost 10 or more pounds in the Special Intervention group of

MRFIT, the reduction in TC was 62% less in those receiving compared to those not receiving diuretics.[13]

Hypertension and blood lipid abnormalities aggregate in certain families.[19] Williams et al[20] recently proposed that a syndrome characterized by mixed lipid abnormalities is present in about 12% of patients with essential hypertension. They observed concordant abnormalities in fasting serum lipid or lipoprotein levels in two or more siblings of nearly half the individuals with essential hypertension diagnosed before age 60. These investigators suggested that dyslipidemia and essential hypertension represented manifestations of a common familial syndrome. The presence of a variety of lipid and lipoprotein abnormalities (increased TG and LDL-C and low HDL-C) in these families raises the possibility of familial combined hyperlipidemia syndrome. This syndrome is characterized by the presence of multiple lipoprotein phenotypic abnormalities (Type IIA, IIB, IV) that may change over time in affected patients and their first-degree relatives.[21]

Approximately 20% of patients with premature CHD are thought to have familial combined hyperlipidemia syndrome.[22] In addition to increased TC, fasting TG, or LDL-C levels, there may be low HDL-C concentrations or abnormal composition of LDL particles.[21] These LDL particles may be small and dense and contain a high ratio of LDL apoprotein B (apoB) to LDL-C. Their increased atherogenic potential may contribute to a higher incidence of premature atherosclerosis in the affected individuals.

The presence of normal LDL-C levels does not rule out the possibility of abnormalities in LDL composition. Sniderman et al[23] identified a subset of patients with angiographic evidence of coronary artery disease whose LDL-C levels were normal, but whose LDL-apoB levels were similar to those observed in phenotype II hyperlipoproteinemia. They referred to this syndrome as "hyperapobetaliproteinemia." This diagnostic possibility should be considered in the evaluation of hypertensive patients who have a strong family history of premature CHD.

EFFECTS OF ANTIHYPERTENSIVE AGENTS ON BLOOD LIPIDS

Lipoprotein changes have been observed with thiazide diuretic and beta blocker therapy, but there is no consensus about the influence of these changes on cardiovascular risk. Newer drugs such as calcium channel blockers or angiotensin converting enzyme inhibitors do not appear to alter lipoprotein metabolism. However, there is no data that clearly documents whether newer drugs are any more effective in reducing cardiovascular mortality than diuretics or beta blockers.

Thiazide diuretics

Grimm et al[24] compared the effects of chlorthalidone and hydrochlorothiazide on blood lipids in a randomized, placebo-controlled, double-blind study of 24 weeks' duration. Men with mild diastolic hypertension received a placebo, 100 mg chlorthalidone, or 100 mg hydrochlorothiazide after a four-week period of observation without medication. In this study, chlorthalidone or hydrochlorothiazide increased plasma TC and TG levels by approximately 15 mg/dL and 25 mg/dL, respectively. Chlorthalidone increased LDL-C as well; HDL-C levels did not change. There were no significant changes in TC, TG, HDL-C, or LDL-C in individuals receiving a placebo. A cholesterol-lowering diet appeared to prevent the diuretic-associated increase in TC but not in TG levels. However, it could be argued that diuretic administration blunted the expected reduction in TC and LDL-C levels associated with the low cholesterol diet.

The long-term effects of diuretics on blood lipid and lipoprotein levels have been evaluated in several large multicenter clinical trials. In the Medical Research Council (MRC) trial, no change in serum cholesterol level was observed in men who received diuretics during a three-year observation period.[25] Since men receiving placebo had a reduction in TC levels during this time, it is possible that the diuretic had an adverse effect on blood cholesterol levels. Similar trends were apparent in women.

Lasser et al[18] reported the effects of diuretics on lipid levels in men receiving a diet low in saturated fat and cholesterol in the Special Intervention Group of the MRFIT. In this study, 1,917 participants received diuretics for six years and 2,537 received no diuretics (*Table 4*). The mean reduction in TC levels was 4.3 mg/dL greater in participants who did not receive diuretics. The primary reason for the difference was that participants receiving diuretics had a 2.8 mg/dL *increase* in very low-density lipoprotein cholesterol (VLDL-C) level while participants receiving no diuretics had a 2.8 mg/dL *decrease* in VLDL-C levels. Reduction in LDL-C levels did not differ in the two groups, which suggests that major changes in LDL-C levels do not occur in patients receiving low-fat diets during long-term diuretic therapy. HDL-C levels increased 0.1 mg/dL in participants not receiving diuretics and fell 0.8 mg/dL in those receiving diuretics—a statistically significant difference ($P<.01$). A summary of the effects of diuretics on the lipid and lipoprotein levels after six years in this group is

TABLE 4
CHANGES IN PLASMA LIPIDS AND LIPOPROTEINS IN SPECIAL INTERVENTION MEN RECEIVING OR NOT RECEIVING DIURETICS SIX-YEAR MRFIT DATA[13]

	Δ TC (mg/dL)	Δ TG (mg/dL)	Δ HDL-C (mg/dL)	Δ LDL-C (mg/dL)
Diuretics (1,917)	- 8.9	20.8	-0.8	-10.8
No diuretics (2,537)	-13.2*	-13.6*	0.1†	-10.4

*P <.001 or † P <.01 for diuretic *v* no diuretic groups.

provided in *Table 4*.

Beta blockers

Beta blockers were recommended as first-step antihypertensive agents by the JNC 1984 and 1988.[8,26] There are a number of reports and studies regarding changes in lipoprotein metabolism during beta blocker monotherapy and during therapy with diuretics plus beta blocker, which have been summarized by Hegeland.[27]

The effect of beta blockers on blood lipids depends on the type of beta blocker used. Beta blockers with intrinsic sympathomimetic activity, such as acebutolol and pindolol, have no effect on blood lipids,[27,28] nor does the combined beta blocker/alpha$_1$ receptor, labetalol appear to affect blood lipid levels.[29]

Tanaka et al[30] evaluated the effects of propranolol on lipoprotein composition in 10 patients with normal pretreatment blood lipid levels. After an eight-week propranolol treatment period, plasma TC and TG levels were unchanged. During the treatment period, post-heparin lipolytic activity was reduced and TG content of VLDL increased while TG content of LDL was decreased. Thus, propranolol administration altered lipoprotein composition without changing blood lipid concentration.

A Veterans Administration multicenter study assessed the effects of one year of propranolol therapy on blood TC and TG levels in more than 100 patients.[31] Although propranolol monotherapy produced no significant change in TC levels, TG levels increased by 42 mg/dL (P<.01). Significant changes in TC or TG levels were not observed in participants who received hydrochlorothiazide for one year. HDL-C levels were not measured in this study. However, Ames[32] reported that increased TG levels and decreased HDL-C levels were generally present in studies with sufficient sample sizes and propranolol treatment periods of at least four weeks.

Effects of combination therapy

The major blood lipid and lipoprotein abnormalities that develop during treatment with diuretics, beta blockers, or both are increased TC, increased TG, and reduced HDL-C levels. Propranolol may exacerbate the tendency of diuretics to increase TG and reduce HDL-C in hypertensive patients receiving a low-fat diet.[18] In the MRFIT, mean HDL-C was reduced 3.2 mg/dL in the group receiving diuretics plus propranolol; the reduction was significantly (P<.01) greater than that observed in the diuretic-only group. Mean TG level increased 52.2 mg/dL with the diuretic plus propranolol combination; there was no difference in the diet-associated LDL-C reduction in participants receiving no drugs, diuretics alone, or diuretics plus propranolol.

NONPHARMACOLOGIC THERAPY IN HYPERTENSIVE PATIENTS WITH HYPERCHOLESTEROLEMIA

An initial trial of nonpharmacologic treatment, including weight control and alcohol and sodium restriction, is recommended for patients with mild to moderate hypertension.[8,26,33] Alcohol intake should be restricted to less than 2 oz of ethanol per day and sodium to less than 2 g per day. These measures, combined with reduced intake of total fat, saturated fat, and cholesterol, are particularly important when hypercholesterolemia is present. The recent emphasis on "heart-healthy" diets may help motivate patients to make recommended dietary changes. Even so, many patients find it difficult to make changes and may benefit from appropriate counseling or referral to facilities where more detailed information can be provided.

Weight reduction may decrease both blood pressure and blood cholesterol levels. Reduced intake of fatty foods and increased consumption of low-fat foods, such as fresh fruits and vegetables, are particularly useful. The caloric density of carbohydrates is only approximately one-half as high as the caloric density of fat; many patients who reduce their fat intake also reduce their caloric intake and lose weight. Since a considerable percentage of the total fat intake is ingested as meat, it is prudent to advise reduced intake of all meats and particularly of red meat.

TABLE 5
MAJOR CONTRIBUTORS OF TOTAL FAT, SATURATED FAT AND CHOLESTEROL IN THE U.S. DIET: NHANES II DATA (1976–1980)[27]

Total fat	Saturated fat	Cholesterol
hamburgers, cheeseburgers, meat loaf	hamburgers, cheeseburgers, meat loaf	eggs
hot dogs, ham, lunch meats	while milk, whole milk beverages	beefsteaks, roasts
whole milk, whole milk beverages	cheese, excluding cottage cheese	hamburgers, cheeseburgers, meat loaf
doughnuts, cookies, cake	beef steaks, roasts	whole milk, whole milk beverages
beef steaks, roasts	hot dogs, ham, lunch meats	hot dogs, ham, lunch meats
white bread, rolls, crackers	doughnuts, cookies, cake	pork, including chops, roast
eggs	eggs	doughnuts, cookies, cake
cheeses, excluding cottage cheese	pork, including chops, roast	cheeses, excluding cottage cheese
margarine	butter	liver
mayonnaise, salad dressing	white bread, rolls, crackers	chicken or turkey, including fried

In their review of data obtained during the second National Health and Nutrition Examination Survey (NHANES II), Block et al[34] assessed the nutritional contribution of specific foods in a population of 11,658 adults. The 10 most important contributors of total fat, saturated fat, and cholesterol are summarized in *Table 5*. Beef products are the major contributors of both saturated fat and cholesterol, but whole milk products, baked goods, and cheeses also make a substantial contribution. At the time of the survey, 35% of dietary cholesterol was ingested as eggs. A single egg yolk contains approximately 250 mg cholesterol, which is close to the maximum recommended daily intake.[9]

Restriction of total fat, saturated fat, and cholesterol intake is recommended for the treatment of high-risk LDL-C levels.[9] The patient should be advised that several dietary saturated fats, in addition to dietary cholesterol, increase blood cholesterol levels. Furthermore, certain vegetable oils, such as palm, palm kernel, or coconut, contain saturated fat but may be labeled "no cholesterol."

The cholesterol-raising potential of different saturated fatty acids is variable. For example, Bonanome and Grundy[35] reported that plasma TC associated with a high stearic acid diet was 14% lower than that associated with a high palmitic acid diet. (Palmitic acid is the major fatty acid in palm oil.) A diet high in oleic acid (a monounsaturated fatty acid) produced a plasma TC 10% lower than that associated with a high palmitic acid diet.

TABLE 6
NUTRITIONAL GUIDELINES FOR MANAGEMENT OF HYPERTENSIVE PATIENTS WITH HYPERCHOLESTEROLEMIA

Nutritional factor	Goal
Total calories	body weight within 15% of desirable weight
Alcohol	less than 2 oz ethanol per day
Sodium	less than 2 g per day
Total fat	less than 30% of total calories
Saturated fat	less than 10% of total calories
Cholesterol	less than 300 mg per day

Possibly, stearic acid (a major saturated fatty acid in beef fat) is converted rapidly to oleic acid by chain elongation and desaturation; this may explain why dietary stearic acid does not raise blood cholesterol to a great extent.

Grundy[36] reported that a diet rich in monounsaturated fatty acids (the type in olive oil) was as effective as a very low-fat, high-carbohydrate diet in reducing blood cholesterol levels. In certain patients, a very high carbohydrate, low-fat diet causes increased blood TC levels and reduced HDL-C levels—changes not observed with diets high in monounsaturated fatty acids. Certain patients respond to very low-cholesterol diets with a marked reduction in HDL-C levels; whether this reduction is detrimental is unknown, but it may be prevented with a diet high in monounsaturated fats.

Finally, there is considerable interest in the cardiovascular effects of the polyunsaturated fats contained in fish oils (omega-3 PUFAs).[37] Diets that are high in omega-3 PUFAs appear to decrease platelet aggregation and reduce blood TG levels. The low cardiovascular mortality in Eskimos may be related to the effects of omega-3 PUFAs on platelet function or lipoprotein metabolism.[38] In large amounts, dietary supplements of fish oil concentrates, packaged in capsules, will produce changes in platelet function or lipoprotein metabolism. Because the doses needed for effect are likely to be high in calories and cholesterol, the use of fish oil supplements is not generally recommended.[39] Fish, on the other hand, is advocated by many as a dietary substitute for red meat.

Nutritional therapy for hypertensive patients with hypercholesterolemia can be complex, since advice about sodium and fiber intake also should be provided. The assistance of a registered dietitian who is trained to counsel these patients can be invaluable. For nutritional therapy to be successful, scientific information must be translated into understandable dietary advice. A summary of nutritional guidelines for managing hyperten-

sive patients with hypercholesterolemia is provided in *Table 6*.[8,9,33]

LIPID-LOWERING DRUG THERAPY

Drug therapy is indicated for treatment of hypercholesterolemia in middle-aged men with LDL-C levels above 190 mg/dL after a 3- to 6-month trial of dietary therapy.[9] Treatment is particularly important for men with hypertension. Nicotinic acid or the bile acid sequestrants (cholestyramine, colestipol) are the agents recommended for initial treatment in the National Cholesterol Education Program (NCEP) guidelines. Selection of one or the other depends on factors such as cost, side effects, and lipoprotein phenotype. Although other drugs are available for treatment of hypercholesterolemia, the scope of this paper is limited to discussion of the classes recommended as first-line agents in the NCEP guidelines.

Cost is a major issue for patients who receive chronic drug therapy, and nicotinic acid is unquestionably the least expensive lipid-altering drug available. Cholestyramine has been shown to reduce primary CHD incidence in middle-aged men with TC levels above 265 mg/dL.[2] Subsequent to the release of the first NCEP guidelines, the Helsinki Heart Study showed gemfibrozil to be effective in primary prevention of fatal and nonfatal myocardial infarction in middle-aged men with hypercholesterolemia[3]; it will likely be considered a first-line drug in the future.

Nicotinic acid

Nicotinic acid has been used for more than three decades to treat patients with lipoprotein abnormalities. It reduces TC, TG, and LDL-C levels,[40] and increases HDL-C levels. Although cutaneous and gastrointestinal side effects may occur, nicotinic acid is a good first choice drug for most hypercholesterolemic patients. Exceptions include patients with poorly controlled diabetes, peptic ulcer disease, chronic liver disease, and recurrent gouty arthritis.

Cutaneous flushing is common with nicotinic acid, particularly early in the course of therapy. To reduce the effect, the patient can increase the dose slowly, take the drug with meals, or precede the dose with aspirin or a nonsteroidal anti-inflammatory drug. A slow release preparation also is helpful in this regard; several are available without prescription and are relatively inexpensive; i.e., a 2,000 mg/dL dosage regimen costs about $6 a month. The regular release formulations are even less expensive. Although slow-release nicotinic acid helps prevent flushing, these preparations cause a higher incidence of hepatitis than regular release nicotinic acid.[41]

The low cost of nicotinic acid, its documented prevention of secondary CHD, and its favorable effects on lipid and lipoprotein levels support is use in the initial treatment of lipid and lipoprotein abnormalities. Hypertensive patients who are taking diuretics or beta blockers or both are particularly likely to benefit from treatment with nicotinic acid because of the tendency of nicotinic acid to reduce TG levels and reduce HDL-C levels.

Bile acid sequestrants

Cholestyramine and colestipol selectively lower LDL-C levels by increasing the clearance of LDL. The agents bind bile acid in the gut, which leads to increased conversion of hepatic cholesterol to bile acids. Stimulation of LDL receptor synthesis leads to enhanced clearance of LDL from the blood.

The bile acid binding resins produce bothersome gastrointestinal side effects (bloating, abdominal pain, and constipation), but because they are not absorbed, serious side effects are infrequent.[2] Constipation can be a major problem for older adults, particularly if they are taking other drugs that cause constipation. The gastrointestinal side effects can be minimized by mixing the resin with a pulpy noncarbonated beverage, increasing fluid and dietary fiber intake, and increasing the dose slowly. The bile acid sequestrants should be administered with meals or before bedtime.

Because bile acid sequestrants may increase triglyceride levels, they should be avoided in patients with TG levels above 500 mg/dL. It is uncertain whether diuretics or beta blockers increase the hypertriglyceridemic tendency of the resins. Bile acid binding resins may reduce the absorption of either of several drugs; therefore, other drugs should be administered at least one hour before or several hours after the ingestion of the resins. Cholestyramine is available in 4-g packets and bulk containers; colestipol is available in 5-g packets and bulk containers. The bulk containers are less expensive than the individual packets. The dosage of cholestyramine ranges from 4 to 24 g/d, and that of colestipol from 5 to 30 g/d.

CONCLUSION

Because of the prevalence of hypercholesterolemia among hypertensive patients, clinicians who treat hypertensive patients are well advised to develop a system-

atic approach to the evaluation and treatment of lipid abnormalities.

The evaluation of hypertensive patients should include measurement of TC and HDL-C levels to predict CHD risk. The prevalence of hypercholesterolemia is higher in hypertensive patients than in normal individuals, and CHD risk increases in these patients as blood cholesterol rises. Weight gain increases the risk of hypertension and hypercholesterolemia while weight loss may lower blood pressure, TC, TG, and LDL-C levels. A trial of nutritional therapy with a diet low in sodium, saturated fat, and cholesterol is indicated for patients with mild to moderate hypertension and hypercholesterolemia. Diuretics and beta blockers may elevate TG levels and reduce HDL-C levels, but they do not appear to increase LDL-C levels. Whether these drug-induced changes in lipoprotein metabolism blunt the beneficial effects of blood pressure reduction is uncertain; a large clinical trial and years of observation are needed to resolve this question and, in the current economic climate, the cost of such a study may be prohibitive.

Nicotinic acid is widely accepted as a first choice agent for treatment of high LDL-C levels; its low cost and ability to reduce TC, TG, LDL-C, and VLDL-C levels while increasing HDL-C levels are major advantages. The bile acid sequestrants effectively reduce LDL-C levels, have no serious side effects, and decrease CHD incidence in middle-aged men with hypercholesterolemia.

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