Current pharmacologic treatment of elevated serum cholesterol

Matti J. Tikkanen, M.D., and Esko A. Nikkilä, M.D.†

ABSTRACT A basic difference between dietary and drug therapy of hypercholesterolemia is that dietary therapy can be used as part of a population strategy, whereas the decision to use drugs is always made on an individual basis. In each case, the decision to treat must be based on the assumption that more good than harm is caused to the patient. This is a difficult situation for the physician. As long as there is no easy way of assessing the state and rate of progression of coronary lesions, the physician must treat the patient on statistical grounds only, i.e., rely on the results of studies showing that lowering serum cholesterol significantly decreases the risk of coronary events. Such evidence has recently been strengthened, which increases motivation for both physician and patients. The current general opinion is that drug therapy must be generally confined to those at high risk, i.e., patients with severe hypercholesterolemia. For individuals with moderately elevated serum cholesterol levels, dietary advice and correction of other risk factors should be adequate.


THE CURRENT intense interest of the medical profession (and pharmaceutical industry) in the lowering of serum cholesterol by pharmacologic agents stems from several recent developments that are related to each other. Discovery of the low-density lipoprotein (LDL) receptor pathway by Brown and Goldstein⁴ provided the basis for a better understanding of the regulation of serum cholesterol. The important therapeutic implication from their studies was the concept that serum cholesterol could be efficiently lowered by enhancing hepatic LDL receptor number and removal of LDL via these receptors. Two clinical trials with cholestyramine, a bile acid sequestrant known to lower serum cholesterol by increasing LDL receptor-dependent removal of LDL, have demonstrated the efficacy of such therapy. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) showed that coronary heart disease could be reduced significantly by treatment with cholestyramine, the reduction being greatest in patients with the greatest decreases in serum cholesterol.²,³ The National Heart, Lung, and Blood Institute Type II Coronary Intervention Study demonstrated a reduction in the angiographic progression of coronary artery disease in subjects treated with this drug.⁴ The emergence of new agents such as the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors raises additional hopes. These drugs inhibit cellular cholesterol synthesis and thereby enhance synthesis of LDL receptors in the liver even more efficiently than do bile acid sequestrants. Altogether, this has prompted the medical profession to try to reevaluate what levels of serum cholesterol should be regarded as elevated, i.e., what the generally accepted “intervention levels” are. Such guidelines have been recommended by the 1984 National Institutes of Health Consensus Development Conference⁵ and the 1986 Study Group of the European Atherosclerosis Society.⁶

**Definition of intervention levels.** Definition of intervention levels for serum cholesterol remains a matter of arbitrary decision. The 1984 NIH Consensus Development Conference recommended drug treatment for patients with serum cholesterol above the 90th percentile of the U.S. population (high risk) if diet alone proved inadequate, and only dietary measures for moderate elevations (75th to 90th percentiles).⁵ According to these guidelines, high-risk serum cholesterol values are ≥220 mg/dl (5.6 mmol/liter) for patients aged 20 to 29 years, ≥240 mg/dl (6.2 mmol/liter) for patients aged 30 to 39, and ≥260 mg/dl (6.7 mmol/liter) for individuals aged ≥40. The European Atherosclerosis Society, on the other hand, has provided a report entitled “Strategy for the Prevention of Coronary Heart Disease” (SPCHD). Unlike the NIH guidelines, the SPCHD Study Group did not base the intervention level

---

From the Third Department of Medicine, University of Helsinki, Helsinki, Finland.

Address for correspondence: Matti J. Tikkanen, M.D., Third Department of Medicine, University Central Hospital, 00290 Helsinki, Finland.

† Dr. Nikkilä died September 21, 1986.
on any population distribution or age, but recommended drug therapy for patients with serum cholesterol remaining above 250 mg/dl (6.5 mmol/liter) despite dietary modification. Similarly, in the Helsinki Heart Study, an ongoing primary prevention trial, the acceptance criterion for participants was 200 mg/dl (5.2 mmol/liter) for “total minus HDL cholesterol,” corresponding to a total serum cholesterol of approximately 250 mg/dl (6.5 mmol/liter). For the present purposes, this has been defined as the level above which drug therapy should be considered (table 1). As a general rule, all intervention levels should be regarded as guidelines only. The individual risk is determined by many risk factors in addition to serum cholesterol.

According to the NIH and SPCHD guidelines, the goal of therapy is to reduce serum cholesterol to approximately 200 mg/dl (5.2 mmol/liter). Other risk factors may determine how intensively this goal is to be pursued.

**General indications for drug therapy of hypercholesterolemia.** In reaching a decision on how to treat patients with hypercholesterolemia, three laboratory determinations are critical: serum cholesterol, serum triglycerides (fasting), and high-density lipoprotein (HDL) cholesterol. In the absence of grossly abnormal triglyceride levels, elevated serum cholesterol is almost always caused by an increased LDL cholesterol level. For the practicing physician, it is usually enough to classify patients as (probably) having either familial hypercholesterolemia (FH) or nonfamilial hypercholesterolemia (non-FH), which comprises all other forms of hypercholesterolemia. FH heterozygotes can be distinguished from other hypercholesterolemic subjects if they have markedly elevated serum cholesterol (350 to 600 mg/dl), usually normal triglyceride levels (type IIa phenotype), and tendinous xanthomata or if they have one or more first-degree relatives with typical FH.

All patients with FH must be considered for drug therapy, since dietary modification alone is seldom effective (table 1). Mostly it is not necessary (or even possible) to distinguish between different forms of non-FH, such as familial combined hyperlipidemia or polygenic hypercholesterolemia. However, it may be helpful to subdivide non-FH patients into the type IIa phenotype (normal triglycerides) or type IIb phenotype (triglycerides above 200 mg/dl).

**Drugs used for lowering elevated serum cholesterol.** Several classes of drugs are available for serum cholesterol lowering (table 2). Bile acid sequestrants (cholestyramine and colestipol), nicotinic acid, the fibric acid derivatives (clofibrate and gemfibrozil), and probucol have been approved for general use in the United States and many other countries. The HMG CoA reductase inhibitors (the statins) have been tested for several years in clinical trials and may enter the market soon. Most of the currently approved drugs are effective (table 3). The major difficulty, however, is that they have not been well tolerated by all patients (table 4). Even minor side effects can pose major problems when brought about by agents that must be used for decades by asymptomatic patients. Currently established agents and some forthcoming new drugs are discussed below.

**Bile acid sequestrants.** Cholestyramine (14 to 24 g/day) and colestipol (15 to 30 g/day) are nonabsorbable agents that bind bile acids in the intestine. More cholesterol is therefore diverted to bile acid production, resulting in reduced hepatic cholesterol content. This promotes enhanced synthesis of LDL receptors and increased rates of uptake of LDL cholesterol from the blood. However, the synthesis of HMG CoA reductase, the rate-limiting enzyme of cellular cholesterol synthesis, is also activated by reduction of hepatic cholesterol, which blunts the cholesterol-lowering effect of

| TABLE 1 |
| Suggested indications for use of drugs in the treatment of hypercholesterolemia |

| All patients with familial hypercholesterolemia |
| Males with nonfamilial hypercholesterolemia if: Between ages 20 and 65 and |
| Total plasma cholesterol over 250 mg/dl (6.5 mM) despite maximal dietary intervention |
| or |
| Total plasma cholesterol minus HDL cholesterol over 200 mg/dl (5.2 mM) despite maximal dietary intervention |
| Females with nonfamilial hypercholesterolemia if: Between ages 40 and 65 and |
| Cholesterol levels above the same cut-points described above |

| TABLE 2 |
| Drugs available for lowering serum cholesterol |

| Bile acid sequestrants | Cholestyramine |
| Colestipol |
| Nicotinic acid | Rapid-release nicotinic acid |
| Slow-release nicotinic acid |
| Fibrinic acids | Clofibrate |
| Bezaflibrate |
| Fenofibrate |
| Ciprofibrate |
| Gemfibrozil |
| Probucol |
| Neomycin |

| Inhibitors of HMG CoA reductase | Lovastatin |

| *Awaiting FDA approval. |

530

CIRCULATION
TABLE 3
Expected proportion of responders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (g/day)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Neomycin</td>
<td>1.5</td>
<td>60</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>1.5</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>90</td>
</tr>
<tr>
<td>Fibrates</td>
<td>1.5</td>
<td>50</td>
</tr>
</tbody>
</table>

*Response is defined as a sustained reduction of cholesterol or LDL cholesterol of more than 10%.

bile acid sequestrant therapy. During treatment, the serum LDL cholesterol concentration is reduced by 20% to 25%. These agents have a slight triglyceride-elevating effect that may be significant in subjects with initially high serum triglyceride levels (type IIb phenotype). Despite the proven efficacy of bile acid sequestrants, patient compliance remains a problem. Among the carefully supervised participants of the LRC-CPPT study, only a minority took the full prescribed dose of cholestyramine, six packets daily, while a significant number used an average of only zero to one packets daily. Side effects include constipation, flatulence, and abdominal discomfort, which may be alleviated by adding fiber to the diet.

Nicotinic acid. Nicotinic acid (1.5 to 3 g/day) is regarded by many as a first-choice drug for treatment of hypercholesterolemia. Nicotinic acid acts by decreasing the production of very low-density lipoprotein (VLDL), which in turn results in decreased formation of LDL. LDL cholesterol is reduced by 15% to 20% and serum triglycerides by 40% or more, whereas HDL cholesterol levels are moderately elevated. A recent report on the posttreatment follow-up of Coronary Drug Project patients treated with nicotinic acid demonstrated a significant reduction in total mortality as well as in coronary heart disease. Increases in plasma transaminase levels, blood glucose, and urate levels may occur during treatment, and nicotinic acid should be used with caution, if at all, in subjects with diabetes mellitus, gout, or liver disease. The cutaneous flushing sensation is the most usual subjective complaint, which can be alleviated in some patients by using slow-release preparations. When skillfully administered, this drug may ultimately be tolerated by more than half of the patients.

Fibric acid derivatives

Clofibrate. The first drug of this family, clofibrate (1.5 to 2.0 g/day), has been used as a lipid-lowering agent since 1963. However, the use of clofibrate markedly declined or was discontinued in many countries after the publication of the results of a large prospective study in which clofibrate was used for treatment of moderate hypercholesterolemia. In this study, clofibrate treatment decreased coronary heart disease events significantly but was associated with excess noncardiovascular and total mortality.

Gemfibrozil. Gemfibrozil (1.2 g/day) may act both by decreasing the production of VLDL and by increasing its clearance. In hypertriglyceridemic subjects, this results in 50% reduction of the serum triglyceride level. The effect on cholesterol levels is less. In the Helsinki Heart Study, an ongoing primary prevention trial now in its fifth year, 600 mg bid gemfibrozil is being compared with placebo in approximately 4000 middle-aged men with serum cholesterol levels above 250 mg/dl. On the average, serum total cholesterol appears to have been reduced by 13.5% and HDL cholesterol increased by 12% in the treatment group. In their Interim Report, the Helsinki Heart Study Ethical Committee reported that after approximately 4 years of study there had been no significant excess in the incidence of malignant neoplasms, gall bladder disease, or diseases of the liver or intestines. The overall mortality among subjects taking either medication (placebo or gemfibrozil) has been only half that projected for the same age group in Finland. At this stage of the study, the safety estimate seemed to indicate that treatment with gemfibrozil was safer than with clofibrate.

Other fibric acid derivatives. Experience with other members of the fibrate family, such as fenofibrate, bezafibrate, and ciprofibrate, is accumulating. These agents may provide new therapeutic alternatives in the future.

Probucol. The mechanism of action of probucol in humans is not clear. In rabbits, it appears to promote removal of LDL cholesterol through an LDL receptor–independent mechanism. The LDL cholesterol–lowering effect is moderate. HDL cholesterol levels are markedly reduced during treatment because of suppression of apolipoprotein A synthesis. On this basis,
the use of probucol is not recommended unless the patient is resistant to other therapies.

Neomycin. Neomycin is an almost-nonabsorbable antibiotic that blocks absorption of dietary and biliary cholesterol, probably by interfering with micelle formation. This, in turn, may reduce hepatic cholesterol content and thus increase LDL receptor synthesis and rate of uptake of LDL from the blood. Neomycin is not approved for general use as a hypocholesterolemic agent but is a useful adjunct in selected individuals and may lower LDL cholesterol by 20% to 25%. The drug is well tolerated (table 4) despite a transient loosening of stools.

HMG CoA reductase inhibitors (statin group). Lovastatin (formerly mevinolin) and synvinolin belong to the new group of statins, which lower serum cholesterol by stimulating removal of LDL via the LDL-receptor pathway. They competitively inhibit HMG CoA reductase, the rate-limiting enzyme of cholesterol synthesis, and are effective in both heterozygous FH and non-FH. Therapy with 80 mg/day lovastatin reduces LDL cholesterol by 40% in FH and non-FH (figure 1). Concomitantly, HDL cholesterol levels start to increase through an unknown mechanism, the rise being slower in FH than in non-FH (figure 2). Serum triglyceride concentrations fall by 20% on the average. These alterations in lipid levels persist during prolonged therapy. Lovastatin or its analogs are not yet available for general use in any country. At the time of this writing, serious side effects have not been reported. If this continues to be true, HMG CoA reductase inhibitors may become first-choice agents for cholesterol lowering.

Other agents. Natural estrogens (estradiol valerate 2 mg/day or conjugated estrogens 0.625 mg/day) are powerful cholesterol-lowering agents in postmenopausal women with elevated serum cholesterol levels. LDL cholesterol can be reduced by 20% and HDL cholesterol increased by 30% with estrogens. Cyclic progestogen can be added to the treatment regimen without impairing LDL reduction. Patient compliance is excellent. Dextrothyroxine, an agent believed to stimulate hepatic LDL receptor synthesis, and \( \beta \)-sitosterol, a cholesterol absorption-inhibiting agent, may be used for cholesterol lowering in selected patients.

Recommended therapy for hypercholesterolemia

Familial hypercholesterolemia. Bile acid sequestrants are the first choice among drugs currently approved for general use in FH. If single-drug therapy is not adequate, combination regimens can be used. Impressive results have been reported from combined use of colestipol and nicotinic acid. In subjects who do not tolerate these drugs, neomycin and fibric acid derivatives may be tried. Bile acid sequestrants can be combined with almost any other agent. On theoretical grounds, it was expected that combination of bile acid sequestrants with lovastatin or its analogs would be particularly effective, since the compensatory activation of HMG CoA reductase could be neutralized. The postulated additive effect of these drugs has, in fact, been demonstrated in clinical trials.

Nonfamilial hypercholesterolemia. Nicotinic acid and

![FIGURE 1. Effect of 80 mg/day lovastatin on LDL cholesterol levels in patients with familial (FH) and nonfamilial (non-FH) hypercholesterolemia.](image1)

![FIGURE 2. Effect of 80 mg/day lovastatin on HDL cholesterol levels in patients with familial (FH) and nonfamilial (non-FH) hypercholesterolemia.](image2)
gemfibrozil (or other fibrate) are usually effective in non-FH. If not, bile acid sequestrants or neomycin may be tried. Combination regimens, if accepted by the patient, are highly effective.

Conclusions
Currently established drugs provide effective means for controlling elevated serum cholesterol levels. However, problems with patient compliance have limited the use of these drugs. The growing experience with the expanding families of fibric acid derivatives and HMG CoA reductase inhibitors have raised hopes that effective therapy with minimal side effects may be within reach. At the same time, words of caution are being voiced by experts; one should not forget that a significant proportion of patients can obtain a satisfactory response by dietary modification alone, and that adverse drug effects may become manifest only after large numbers of patients have been treated for several years.

References
Current pharmacologic treatment of elevated serum cholesterol.
M J Tikkanen and E A Nikkilä

Circulation. 1987;76:529-533
doi: 10.1161/01.CIR.76.3.529

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/76/3/529

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/