LIPID LOWERING EFFECTS ON CARDIOVASCULAR MORBIDITY AND MORTALITY. CLINICAL EVIDENCE AND THERAPEUTIC GUIDELINES

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The leading cause of death in western societies, and possibly worldwide, is cardiovascular disease[1,2]. At the root of most cardiovascular disease is atherosclerosis. Atherosclerosis is a specific type of arteriosclerosis that affects the inner lining of large arteries, primarily the coronaries and the carotids. Any factor which causes or contributes to injury of the endothelium will increase the biochemical and pathophysiologic abnormalities that predispose a person to atherosclerosis. As the normal healing process of this injury progresses atheromatous plaques, containing cholesterol, lipoid and other material, are deposited at the site of the injury. In people whose cholesterol level exceeds the normal range, an excessive amount of cholesterol containing plaque forms at the site. This results in a narrowing of the vessel lumen, thereby leading to decreased blood flow (or even complete occlusion); hence, coronary heart disease (CHD).

Although there are a number of major risk factors contributing to the development of CHD, i.e., hypertension, cigarette smoking, diabetes, genetic predisposition, age and male sex, hyperlipidemia (high blood levels of cholesterol and other lipids) is perhaps one of the most readily controllable. There are five distinct types of hyperlipidemia (Types I-V), all characterized by specific lipoprotein imbalances due to a variety of metabolic defect (Table 1). There are five classes of lipoproteins: high density lipoprotein (HDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), and chylomicrons. Each class of lipoproteins consists of different proportions of lipids and proteins which include cholesterol, triglycerides, phospholipids and proteins. LDL, which contains the highest proportion of cholesterol (50%), and possibly VLDL, are associated with the development of atherosclerotic disease[1]. On the

TABLE I—Characteristics of types of hyperlipoproteinemia

Type of Hyperlipidemia	Lipoprotein Characteristics of **Plasma**	**Metabolic Defect**
Type I Exogenous Hyperlipidemia (Hyperchylomicronemia)	Chylomicrons markedly increased: LDL, VLDL, and HDL usually decreased	Clearance of chylomicrons decreased by lipopro tein lipase deficiency or apo C-II abnormality
Type IIa Hyperbetalipoproteinemia (Hypercholesterolemia)	LDL increased; VLDL normal; chylomicrons absent	LDL synthesis increased and LDL clearance decreased by deficiency in primary LDL receptors or defective LDL receptors
Type IIb Combined Hyperlipidemia (Mixed Hyperlipidemia)	LDL and VLDL increased: chylomicrons absent	Same as Type IIa plus elevated VLDL LDL may contain increased amounts of apo B
Type III Broad Beta Pattern (Dysbetalipoproteinemia)	LDL increased; chylomicrons may be present	Either production of LDL increased or clearance of LDL decreased; total plasma apo-E (as apo E-II isoform) increased plus apo E-III deficiency possi bly deficiency of hepatic lipase
Type IV Endogenous Hyperlipidemia (Hypertriglyceridemia)	VLDL increased; LDL normal (or decreased); chylomicrons absent	Production of VLDL increased and/or clearance of VLDL decreased; possibly abnormal apo A-I/ C-III complex
Type V Mixed Hyperlipidemia	VLDL increased; chylomicrons increased; LDL normal (or decreased)	Either production of chylomicrons and VLDL increased or clearance of both is decreasd; possi bly imbalance between apo C II and C-III; possi bly abnormal apo E (apo E-IV isoform present in E-III deficiency)

Adapted from Drug Evaluations, Sixth Ed, American Medical Association 1986, chapter 50, table II.

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other hand, it is believed that HDL (50% proteins) protects against atherosclerosis, perhaps by removing cholesterol from the tissues and transporting it back to the liver where it is catabolized and eliminated'. The association of triglycerides with CHD risk has not yet been definitively characterized.

For many years, the relationship between cholesterol levels and CHD risk was unknown. Over the past two decades, numerous large scale long term trials were conducted to clarify and define this relationship[3-9]. These studies also evaluated the effectiveness of several hypolipidemic drugs with respect to the ability to lower cholesterol levels and subsequent effect on the development of coronary heart disease and overall mortality.

CLINICAL TRIAL ANALYSIS

The Coronary Drug Project (CDP)studied 8341 men with a previous history of documented myocardial infarction who were randomized to six treatment groups and followed for seven years[3]. Three treatment regimens, high and low dose estrogen and dextrothyroxin were terminated prematurely due to unacceptable adverse reaction trends. Clofibrate, nicotinic acid and placebo groups were analyzed at the conclusion of the study. Clofibrate had no definite beneficial effect on mortality and increased the incidence of non-fatal cardiovascular events compared to placebo, despite sustained reductions in cholesterol and triglyceride levels of about 6% and 22%, respectively. Nicotinic acid had no beneficial effect on mortality (at the time of the 7-year analysis), but decreased the incidence of nonfatal cardiovascular events compared to placebo, and produced sustained reductions in cholesterol and triglyceride levels of 10% and 26%, respectively. A 15-year follow-up of these patients was conducted which demonstrated that mortality from all causes in each of the drug groups was similar to that of placebo, with the exception of the nicotinic acid group, in which mortality was 11% lower ($p = 0.0004$) than in the placebo group[4].

The NHLBI Type II Coronary Intervention Study evaluated the effect of cholesterol level reduction on progression of coronary artery disease (CAD) in 143 hyperlipidemic men[5]. The data indicated that decreases in LDL and total cholesterol (TC), and increases in HDL/TC and HDL/LDL ratios result in delaying progression of CAD; and that diet therapy and cholestyramine are effective in achieving these lipid changes and hence, these treatments can delay the progression of CAD.

Perhaps the most well known of these trials is the LRC-CPPT (Lipid Research Clinics—Coronary Primary Prevention Trial), in which 3806 hypercholesterolemic men were randomized to receive placebo or cholestyramine and followed for an average of 7-10 years[6-7]. This study provided conclusive evidence that lowering cholesterol reduces the risk of CHD, and that each 1% reduction in cholesterol results in a to reduction in the risk of CHD. The study also demonstrated that cholestyramine is effective in reducing cholesterol and hence, mortality from CHD.

More recently, the results of the Cholesterol Lowering Atherosclerosis Study (CLAS) contributed important information to the understanding of the relationship between lipid levels and atheromatous lesions[8]. In this study 162 non-smoking men with previous coro-nary bypass surgery were randomized to receive either placebo or nicotinic acid plus colestipol. The results demonstrated that aggressive lowering of LDL cholesterol levels with concomitant increase in HDL cholesterol levels produces significat benefit to both native coronary arteries and venous bypass grafts; i. e., beneficially affects the formation, progression and regression of lesions. In addition, it was concluded that colestipol and nicotinic acid, when given concomitantly, produce a sufficient effect on HDL and LDL cholesterol to cause a beneficial effect on lesions. This is the first study to show that drug therapy can have a beneficial effect on atheromatous lesions.

The recently published Helsinki Heart Study was conducted to evaluate the effect of gemfibrozil on the incidence of CHD[9]. Because of the unfavorable results seen with clofibrate in the CUP and WHO studies[3,9], gemfibrozil, also a fibrate, was suspect. This trial served to definitively assess the safety and efficacy of gemfibrozil, particularly with respect to CHD morbidity and mortality. The Helsinki Heart Study was a randomized, double-blind, placebo controlled, five-year trial of 4081 asymptomatic men at high risk for CHD because of abnormal concentrations of blood lipids. The gemfibrozil group evidenced an average of 8.5% decrease in total and LDL cholesterol, 11% in-crease in HDL cholesterol and 38% decrease in bigly cerides over the five year treatment period. These results were associated with a 34% reduction in the incidence of CHD in the gemfibrozil group versus the placebo group. However, there was no significant difference between the groups in total mortality.

The Helsinki Heart Study is important not only for the answers it provides, but also for the questions it raises. This trial demonstrated that, firstly, not all fibrates by definition will have safety and efficacy profiles similar to clofibrate, and secondly, that gemfibrozil is a reasonably safe drug that reduces CHD morbidity. However, it questions the need for significant reductions (i. e., > 30% as with HMG Co A reductase inhibitors, see below) in total and LDL cholesterol to beneficially affect CHD morbidity if one can simultaneously raise HDL cholesterol, and it again questions the role of triglycerides in the total lipid profile and of triglyceride reduction in CHD morbidity and rnortality.

THERAPEUTIC APPROACH

Not only has this tremendous boom in information greatly increased the understanding of certain aspects of atherosclerotic disease, it has also had a significant impact on treatment trended. In 1984, the National Institutes of Health convened a Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Diseased. This meeting was convened in response to the increasing body of pathological, genetic, metabolic, epidemiologic and clinical trial evidence which linked blood cholesterol levels to coronary heart disease. The conference addressed who should- be treated and how. Specifically, the major recommendations were that individuals with total cholesterol levels above 240 mg/dl were at risk of developing CHD and should be treated intensively by diet, or diet and drugs when diet alone is inadequate to achieve a target level of 200 mg/dl. In addition, it was recommended that widespread educational programs be adopted to increase physician, health professional and public awareness of the significance of elevated blood cholesterol and the importance of treating it. Subsequent to this NIH Conference, the National Cho-lesterol Education Program (NCEP) was established to formulate a plan for the education of both health care professionals and the public about hyperlipidemia, its association with CHD and its treatment. In October, 1987, the Adult Treatment Panel presented its final report to the NCEP Coordinating commitee[12]. In summary, the panel recommends (Fig. 1).

1. Initial patient screening should be based on TC levels; TC levels below 200 mg/dl are desirable, 200-239 mg/dl are borderline high and above 240 mg/dl are high.

2. Treatment decisions should be based on LDL levels; LDL levels below 130 mg/dl correspond to low risk, 130-159 mg/dl to moderate risk and above 160 mg/dl to high risk.

3. Patients falling into the moderate and high risk groups should be treated intensively with diet for six months. If diet does not achieve acceptable LDL levels, then drugs should be initiated.

4. First line choice of drug therapy should be bile acid sequestrants and/or nicotinic acid; second line choice would be HMG Co A reductase inhibitors; and third choice would be other drugs such as gemfibrozil, probucol and clofibrate.

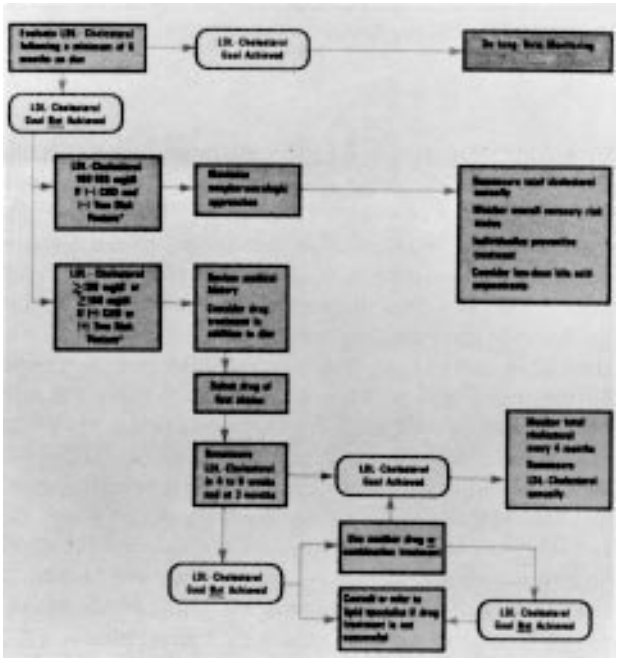

Fig. 1—* One of which can be male sex. From: Highights of the Report of the Expert Panel on Detection. Evaluation and Treatment of High Blood Cholesterol in Adults, October 1987.

The adult Treatment Panel made very strong and specific recommendations with respect to Diet, perhaps for two reasons; the average diet in western societies is far too high in total fat, cholesterol and calories; and currently available drugs for the most part are far from ideal in combining proven safety, efficacy, tolerability, palatability and convenience in a single product. The food industry in the United States has responded positively to the changing, health conscious, American diet by breeding animals which produce leaner meats, by developing low fat and free dairy products and by offering special menus in restaurants which abide by American Heart Association diet guidelines.

Currently available drugs are limited to those which lower lipids through affecting bile acid disposition, cholesterol synthesis or lipoprotein metabolism, and are classified as bile acid sequestrants, fibrates, nicotinic acid/derivatives, HMG Co A reductase inhibitors, thyroid hormones or other (e. g. probucol). (Table II).

Bile acid sequestrants such as cholestyramine and colestipol are non-absorbable anion exchange resins which exert their hypolipidemic effect by preventing absorption of bile acids in the gut and thereby increasing their fecal excretion. They are used primarily in treating Type II hyperlipidemia and have been proven to be extremely safe, and effective in reducing lipids and CHD morbidity and mortality (LRC-CPPT, NHLBI Type II and CLAS studies)[5-8]. However, their widespread use has been severely hampered by poor tolerability, palatability and convenience. They are very gritty powders which must be mixed with liquid and taken in large quantities (gins/dose) up to six times a day. Tolerability problems are understandably focused on GI disturbances, primarily constipation.

In addition, these negative attributes have led to significant compliance problems. To address these issues, some companies are developing resins which are presumably more potent than cholestyramine, such as DEAE-Dextran and ET-504. These products theoretically would decrease the amount of drug needed to be taken per day thereby improving convenience and hopefully tolerability. Other companies are putting

TABLE II—Lipid lowering agents available in U.S.

Drug	Class	Mechanism of Action	Effects on Lipids*				Dose/Regimen	Undesirable side Effects
cholestyramine	bile acid sequestrant	Prevents absorption of bile acids and promotes their fecal excretion	↓	↓	↑	↑(?)	12-24 gm/day BID-QID	↑ GI disturbances; constipation; transaminases; interferes with vitamin A, K and D absorption; may bind other drugs in the intestine.
colestipol	bile acid sequestrant	Prevents absorption of bile acids and promotes their fecal excretion	↓	↓	↑	↑(?)	15-30gm/day BID-QID	↑ GI disturbances; constipation; transaminases; interferes with vitamin A, K and D absorption; may bind other drugs in the intestine.
nicotinic acid	nicotinic acid May ↓ VLDL production		↓	↓	↑	↑	2-8 gm/day TID	Intense cutaneous flush; pruritis; GI disturbances. ↑ transaminases, ↓glucose tolerance.
clofibrate	fibrate	↓ hepatic VLDL synthesis, ↑ release of neutral sterols in bile →	↓(?)	↓↑	↑(?)	↓	1 gm/day TID QID	GI disturbances; rash; impotence; myalgia; flu-like syndrome; ↑ transaminases; gall bladder problems; malignancies.
gemfibrozil	fibrate	↓ peripheral lipolysis; ↓ hepatic extraction of FFA; ↓VLDL synthesis	↓(?)	↓↑	↑	↓	900-1500mg/day BID	GI disturbances; hyperglycemia; ↑ benign liver nodules; ↑ tumor formation; ↑ transaminases; ↑gall bladder problems.
lovastatin	HMG Co A reductase inhibitor	Inhibits HMG Co A reductase, ↓ synthesis of cholesterol	↓	↓	↑	↓	20 40 gm/day BID	↑ Transaminases; myalgia; ↑ lens opacities; ↑ CPK
dextrothyroxine	thyroid hormone	↑catabolism and excretion of cholesterol	↓	↓	?	↓(?)	4-8 mg/day OD	Hypermetabolic effects; angina; arrhythmias; ↑ severity of ischemia; nervousness; GI disturbances; changes in libido; potentiation of anticoagulants; hyperglycemia.
probucol	other	May ↑ rate of LDL catabolism	↓	↓	↓	↓	? 1 gm/day BID	GI disturbances; Arrhythmias; QT prolongation; ↑ uric acid, ↑ blood glucose; ↑ liver and kidney abnormalities.

* Adapted from "Table 4. Changes Induced by Administration of Hypolipidemic Drugs" in Chapter 50/Agents Used to Treat Hyperlipidemia, **Drug Evaluations** Sixth Edition, American Medical Association, 1986.

efforts into reformulating cholestyramine to make it more convenient and more palatable. These reformulations will include tablets, capsules, semi-solids and chewable bars. Any and all of these products will have the opportunity to capitalize on the renewed popularity of the non-absorbables in treating hyperlipidemia. Use of these agents in the U.S. is expected to continue to increase dramatically in response to the NCEP recommendations.

Nicotinic acid is an old drug[13]. Its actual use in hyperlipidemia has been difficult to track as it is also a vitamin, niacin, and available without prescription. It has been shown to be relatively safe and is effective in reducing lipids, all-cause mortality and, in combi nation with colestipol, having a favorable effect on atherom atous lesions (C D P and C LAS studies)3 8 , Nicotinic acid lowers lipids through affecting lipoprotein metabolism and is effective therapy for Types II-V hyperlipidemia. However, its use has been significantly restricted also due to tolerability problems, primarily intense cutaneous flushing and GI disturbances.

However, slow titration to the optimal dose has been used to alleviate these symptoms. Although it does not appear that any companies are working to overcome these problems through reformulations, a few are pursuing development of nicotinic acid derivatives such as acifran and pirozadil. These compounds are believed to have similar mechanisms of action of nicotinic acid and presumably are equieffective, but have better side effect profiles. As a result of the CDP and CLAS studies and NCEP recomendations[3,8,12] it is anticipated that nicotinic acid and perhaps its derivatives will continue to grow in use for hyperlipidemia.

The HMG Co A (3-hydroxy-3-methylglutaryl Co enzyme A) reductase inhibitors are the newest class of hypolipidemic drugs to come down the development pipeline, and represent a significant breakthrough in the treatment of severe hyperlipidemia[13-18]. These compounds exert their lipid-lowering effects through inhibiting the synthesis of cholesterol. Only one such product has been

registered thusfar, **lovastatin** (mevinolin), which is indicated for treating Type II hyperlipidemia. Two other HMGCoAreductase inhibitors are in late phases of development. simyastatin (synvinolin) and pravastatin (eptastatin) Others are still at the preclinical stage. The biggest advantage of these drugs is efficacy: up to 40% reduction in LDL cholesterols[20]. They are also convenient (tablets, ODBID dosing) and well tolerated. However, because they are so new, no long term safety data are available. Based on clinical trials, lovastatin has been associated with hepatic abnormalities and myositis; ocular changes were also noted, but the relationship to lovastatin has not been established. Widespread experience in clinical practice will be needed to fully understand and characterize this class of compounds. This is one of the reasons that the NCEP has recommended these drugs as second line therapy, when diet, resins and nicotinic acid have failed to achieve acceptable LDL levels[12]. Even so, it is expected that these drugs will have a significant impact on the treatment of hyperli-pidemia and will be used in place of a number of other absorbable drugs (e. g. Vibrates), and in combination with non-absorbables.The **fibrates** act primarily on lipoprotein metabolisms[13-18]. Unlike other hypolipidemics however, they are most effective in reducing triglycerides and have only a moderate effect on cholesterol, and therefore would be most effective in Type IV hyperlipidemia. Fibrates are also used, however, to treat Types III and V hyperlipidemia. They have gained much more acceptance in Europe than they have in the United States. **Clofibrate's** use in the U. S. has declined significantly over the past five years due primarily to its unfavorable safety profile. In the WHO trial[19] the clofibrate group had an increase in all-cause mortality over the placebo group; clofibrate has also been associated with increases in transaminases, malignancies and gall bladder problems[13-19]. **Gemfibrozil,** on the other hand, has not suffered from the negative reputation of clofibrate, perhaps because it is generally better tolerated[13,19]. But also is associated with certain similar safety problems such as increased transaminases and tumor formation. Its long term effects on morbidity and mortality have been systematically evaluated in the Helsinki Heart Study[19].

Other fibrates such as **fenofibrate** and **bezafibrate**, which are not available in the U. S., are also doing very well in Europe. It will be very interesting to follow the impact of the NCEP recommendations and the Helsinki Heart Study on the medical community s perception of fibrates as a class, and on the market for gemBibrozil in particular. It is anticipated that use of the Vibrates in the U. S. will continue to decline over the long term in the face of better agents and as increasing emphasis is placed on reduction of LDL cholesterol, on increasing HDL cholesterol and on long term safety. The use of thyroid hormones such as **dextrothyroxine**, is steadily declining in the face of safer but perhaps not as effective agents. Thyroid hormones exert their hypolipidemic effect through altering cholesterol metabolism and are effective in Type II hyperlipidemia. These compounds are known to have adverse metabolic and cardiac effects (CDP study)[3] and the risk/benefit ratio is unacceptable for the vast majority of patients. Drug discovery research in the area of thyromimetics has thusfar been sparse in producing viable compounds.

Probucol, (a drug which has not yet been neatly classified) although currently popular, is also expected to decline in use in the future. It acts by affecting lipoprotein metabolism, achieves a reasonable degree of lipid lowering efficacy, and is used in Type II hyperli pidemia. However, it is associated with cardiac, renal and hepatic problems[13-18]. In addition, probucol has been shown to lower HDL which is believed to be a disadvantage[1]. HDL is thought to have a protective effect and increasing HDL should be beneficial; decresing HDL may increase the risk of CHD[1]. The risk/benefit ratio of this drug may become unacceptable as more is known about the role of HDL and better agents are made available.

There is a rational basis for combination use of a number of these drugs, given their various mechanisms of action and the multiple etiologies of hyperlipidemia. Most common of the combinations is that of a non-absorbable agent plus an absorbable agent, e. g., cholestyramine or colestipol plus nicotinic acid, gemfibrozil or lovastatin[13-18]. Such combinations can accomplish two goals: 1) an increase in efficacy due to the synergy of the multiple mechanisms of action at work; and 2) a decrease in undesirable side effects due to the lower doses of both agents needed to achieve the same effects. With the increasing concern for safety, better understanding of the available drugs and disease etiology, and future availability of more sophisticated compounds, combination use of these agents is expected to increase.

FUTURE PERSPECTIVES

There is still room for better hypolipidemics and many avenues of drug discovery research are yet to be explored in this area, such as compounds which interrupt the cholesterol synthesis pathway at steps other than HMG Co A reductase, compounds which affect bile acid conjugation, secretion and excretion, and compounds which affect LDL receptors. Use of hypolipidemics in appropriate individuals will decrease the risk of CHD. However, it has not yet been definitively proven that lowering lipids to acceptable levels will cause regression of atherosclerotic disease in symptomatic patients. This has led to the opening of another area of drug discovery research: the search for anti-atherosclerotic compounds—drugs which cause regression or stop the progression of atheromatous lesions. Virtually all

compounds in this field are still at preclinical stages of development. ACAT (acyl CoA: cholesterol acyl transferase) inhibitors, although they appear to have hypolipidemic activity, may be the first drug class to be shown to have anti-atherosclerotic activity. Drugs which affect arterial wall lipid metabolism, arterial cells and connective tissue, and endothelium are all candidates for intensive preclinical profiling and clinical research. Clinical development could be hampered by the current lack of sufficiently sensitive diagnostic tools and methodology which would allow for extensive and controlled clinical trials. Any drug which can be proven to beneficiary affect atheromatous lesions and have an acceptable benefit/risk ratio will represent the next significant advance in the treatment of atherosclerosis. In summary, atherosclerosis is a serious health problem which affects millions of people each year. One of the most controllable risk factors for atherosclerosis is hyperlipidemia. Therefore, there is an urgent need for detection and treatment of this disease if our society is to decrease cardiovascular morbidity and mortality. Numerous large scale trials have demonstrated the beneficial effects of various drug therapies in lowering lipids and reducing CHD morbidity and mortality. However, none of these agents is ideal and this fact has hampered the acceptance of widespread treatment by physicians and the public alike. Perhaps, though, the more critical questions physicians must face in light of these data is, “What is the goal of hypolipidemic therapy?” Is it to reduce LDL, increase HDL, improve the LDL/HDL ratio, reduce triglycerides, or a combination of these (i.e., modify the risk factor) or, is it Much is yet to be learned about atherosclerosis, m-Musch is yet to be learned about atherosclerosis, including the role of various lipids, lipoproteins and their interactions. Achieving this understanding, coupled with greater physician and public awareness of the need to treat hyperlipidemia and the advent of newer and better hypolipidemic as well as anti-atherosclerotic drugs, will hopefully bring the disease of atherosclerosis to the point where it is no longer the leading cause of death in western societies.

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