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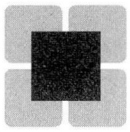

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Lipid-regulating and antiatherosclerotic therapy: current options and future approaches

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SUMMARY Increased understanding of the mechanisms of cholesterol-lowering therapy and other lipid risk factors has suggested new potential strategies for preventing and treating coronary heart disease (CHD). Although these new strategies hold promise, our first, best strategy for reducing the toll of CHD is to use current guidelines for treating dyslipidemia and other risk factors.

KEY POINTS Investigators have identified characteristics of rupture-prone lesions that may underlie 80% to 90% of all CHD events. Current evidence suggests that lipid-altering therapy stabilizes lesions, inhibiting plaque rupture. New drugs might inhibit cholestrol biosynthesis at a step other than that mediated by HMG-CoA reductase inhibitors. Another approach might be to alter the activity of enzymes or proteins that regulate lipoprotein metabolism. Angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers, and beta-adrenergic blockers have all shown indications of antiatherosclerotic activity unrelated to any lipid-regulating activity. Few conclusions can be drawn about what role antioxidant therapy will ultimately have. Although genetic strategies may prove ideal for treating individuals with severe genetic disorders, they are likely to be less useful in most of the population, in whom environmental factors are the predominant determinants of CHD rates.

INDEX TERMS: HYPERCHOLESTEROLEMIA; RISK FACTOR REDUCTION; LIPID-LOWERING AGENTS CLEVE CLIN J MED 1996; 63:31–41

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THE LAST FEW decades have brought great advances in our understanding of the complex relation between lipoproteins and atherogenesis. Cholesterol-lowering therapy reduces the incidence of coronary heart disease (CHD) and, in secondary prevention, has been shown to reduce total mortality.

The lipid abnormalities associated with atherosclerosis include elevated plasma concentrations of low-density lipoprotein (LDL) cholesterol, low concentrations of high-density lipoprotein (HDL) cholesterol, and possibly, elevated concentrations of triglyceride. Prospective clinical trials have shown risk-factor modification to be effective for reducing the incidence of CHD, and public health efforts that emphasize risk-factor reduction have contributed to a substantial decline in the rate of CHD in the United States.

Unfortunately, CHD remains the leading cause of disability and death in this country. Additional clinical strategies are needed to reduce this heavy burden. Possible future strategies include further re-

TABLE 1
DESIGN OF REGRESSION STUDIES WITH SIGNIFICANT REDUCTIONS IN CORONARY HEART DISEASE EVENT

Study*	Intervention	Enrollment at baseline (n)	Mean age (years)	% Men	Mean time on trial (years)
FATS[3]	Lovastatin 20–40 mg/day and colestipol 30 g/day, or niacin 4–6 g/day and colestipol 30 g/day	146	47	100	2.5
POSCH[4]	Partial ileal bypass surgery	838	51	91	9.7†
STARS[5]	Diet, or diet and cholestyramine 16 g/day	90	51	100	3.3
ACAPS[6]	Lovastatin 20–40 mg/day‡	919	62	52	2.8
SCRIP[7]	Diet, exercise, smoking cessation, and lipid-regulating drugs	300	57	86	4
PLAC I[8,9]	Pravastatin 40 mg/day	408	57	78	3
PLAC II[10,11]	Pravastatin 10–40 mg/day	151	63	85	3
REGRESS[12]	Pravastatin 40 mg/day	885	56	100	2

*FATS, Familial Atherosclerosis Treatment Study; POSCH, Program on the Surgical Control of the Hyperlipidemias; STARS, St. Thomas' Atherosclerosis Regression Study; ACAPS, Asymptomatic Carotid Artery Progression Study; SCRIP, Stanford Coronary Risk Intervention Project; PLAC I, Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; PLAC II, Pravastatin, Lipids, and Atherosclerosis in the Carotids; REGRESS, Regression Growth Evaluation Statin Study
†Because the intervention evaluated in POSCH was surgery, mean follow-up of all participants is given rather than trial duration
‡ACAPS participants were randomized to one of four treatment groups: lovastatin plus 1 mg/day warfarin, lovastatin plus warfarin placebo, lovastatin placebo plus warfarin, or lovastatin placebo plus warfarin placebo; data presented in this table and *Table 2* are not stratified according to randomization to warfarin or its placebo

finements in the guidelines for managing dyslipidemia, new drugs in existing classes of agents, new uses for existing drugs, entirely new classes of agents, and gene therapy. Although we may look optimistically toward the future of antiatherosclerotic therapy, our first, best strategy for reducing the toll of CHD is the use of current guidelines for treating dyslipidemia and reducing other risk factors. This review will discuss the current management of lipid risk factors in adults and the scientific and clinical basis of possible future approaches.

HOW DOES THERAPY REDUCE RISK?

Fewer events, and slowed progression, but regression uncommon

Recent clinical trials have strengthened the case for aggressive lipid management in patients at high risk for CHD events, particularly those with known atherosclerotic disease. The Scandinavian Simvastatin Survival Study (4S) demonstrated that drug therapy for hypercholesterolemia in high-risk patients (those with a history of angina or myocardial infarction) can significantly reduce the rates of total mortality and morbidity and mortality due to CHD.[1] Additionally, a number of studies have used angiography or ultrasonography to show that lipid-regulating therapy can slow the progression of atherosclerosis. However, regression of atherosclerosis is less common. A variety of processes can contribute to an increase in lumen area, including depletion of lipids from lesions, compensatory vascular remodeling, and thrombus resolution.[2]

Although not designed primarily to study clinical endpoints, several of these "regression studies" showed unexpectedly low rates of cardiac events in the intervention groups compared with the control groups, despite relatively short periods of treatment—usually 2 to 3 years (*Tables 1* and *2*).[3–12] Most of these trials used more intensive lipid-regulating therapy than did earlier clinical trials, in which clinical outcomes diverged more slowly, and in which the full effect of risk reduction was achieved by 5 years.[13] Although a graded correlation exists between the rate of progression and the risk of events,[14–16] the modest anatomic benefit and the infrequency of outright regression suggest that factors other than increased lumen area contributed to the benefits observed.

TABLE 2
RESULTS OF REGRESSION STUDIES WITH SIGNIFICANT REDUCTIONS IN CORONARY HEART DISEASE EVENTS

Study*	Outcomes measured	Results
FATS[3]	Change in percent stenosis	–0.7 percentage points in the lovastatin-colestipol group –0.9 percentage points in the niacin-colestipol group +2.1 percentage points in the control group ($P = .003$)
	Regression of ≥ 10 percentage points in at least one lesion without progression elsewhere	32% of patients in the lovastatin-colestipol group 29% of patients in the niacin-colestipol group 11% of patients in the control group ($P = .005$)
	Coronary heart disease (CHD) death, myocardial infarction (MI), or revascularization	3 events in the lovastatin-colestipol group 2 events in the niacin-colestipol group 11 events in the control group ($P = .01$)
POSCH[4]	Overall progression of atherosclerosis (determined by a review panel at 9.7 years)	55% of patients in the intervention group 77% of patients in the control group ($P < .001$)
	CHD death or MI	82 events in the intervention group 125 events in the control group ($P < .001$)
STARS[5]	Overall change in mean absolute width of coronary segments	+0.003 mm in the diet group +0.103 mm in the diet-cholestyramine group –0.201 mm in controls
	Decrease in mean absolute width of coronary segments (progression)	4 of 26 patients in the diet group 3 of 27 patients in the diet-cholestyramine group 11 of 24 patients in the control group
	CHD death, MI, coronary artery bypass grafting (CABG), or percutaneous transluminal coronary angioplasty (PTCA)	3 events in the diet group ($P < .05$) 1 events in the diet-cholestyramine group ($P < .01$) 10 events in the control group
ACAPS[6]	Rate of change in intimal-medial thickness (IMT) of carotid segments	–0.009 mm/year in the lovastatin groups +0.006 mm/year in the lovastatin placebo groups ($P = .001$)
	CHD death, MI, or stroke	5 events in the lovastatin groups 14 events in the lovastatin placebo groups ($P = .04$)
SCRIP[7]	Rate of change in minimal diameter of coronary segments	–0.024 mm/year in the intervention group –0.045 mm/year in controls ($P < .02$)
	CHD death, MI, CABG, PTCA	25 events in the intervention group 44 events in the control group ($P = .05$)
PLAC I[8,9]	MI occurring after 90 days	5 events in the intervention group 17 events in the control group ($P \leq .01$)
	Rate of change in mean lumen diameter	–0.02 mm/year in the pravastatin group –0.04 mm/year in the placebo group ($P = .16$)
	Rate of change in minimal lumen diameter	–0.03 mm/year in the pravastatin group –0.05 mm/year in the placebo group ($P = .04$)
PLAC II[10,11]	Overall progression in IMT of carotid segments	Not significantly lower with intervention
	Rate of progression of IMT of the common carotid	+0.0295 mm/year in intervention group +0.0456 mm/year in controls ($P = .03$)
	Any coronary event or any death	5 events in the intervention group 13 events in the control group ($P = .04$)
REGRESS[12]	Overall change in mean segment diameter	–0.06 mm in the pravastatin group –0.10 mm in the placebo group ($P = .019$)
	Overall change in median minimum obstructive diameter	–0.03 mm in the pravastatin group –0.09 mm in the placebo group ($P = .001$)
	Death, MI, CABG, PTCA, or cerebrovascular accident	11% of patients in the intervention group 19% of patients in the placebo group ($P = .002$)

*FATS, Familial Atherosclerosis Treatment Study; POSCH, Program on the Surgical Control of the Hyperlipidemias; STARS, St. Thomas' Atherosclerosis Regression Study; ACAPS, Asymptomatic Carotid Artery Progression Study; SCRIP, Stanford Coronary Risk Intervention Project; PLAC I, Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; PLAC II, Pravastatin, Lipids, and Atherosclerosis in the Carotids; REGRESS, Regression Growth Evaluation Statin Study

Plaque composition, as well as size, may determine risk

Current evidence suggests that lipid-altering therapy stabilizes lesions, inhibiting plaque rupture.[2] Indeed, most clinical manifestations of coronary atherosclerosis appear to be caused by rapid thrombotic occlusion at the site of a ruptured plaque. Investigators have identified a group of rupture-prone lesions that may underlie 80% to 90% of all CHD events.[2,17] These "culprit lesions" have several characteristic histological features, including a large, eccentric lipid pool, a weak fibrous cap, and high macrophage density at the shoulders of the cap. Although severely stenotic arteries are more likely to become occluded than moderately stenotic vessels, lesions causing less than 50% stenosis are more prevalent and are responsible for the majority of cardiac events. Thus, the major determinant of clinical sequelae appears to be plaque composition and not the degree of lumen obstruction.

Lipid-altering therapy may help stabilize plaque in a number of ways. It may not only deplete the lipid pool in lipid-rich lesions (thereby lowering shear stress), but it may also normalize endothelial function, inhibit coagulation, and diminish the inflammatory response.

Normalizing endothelial function

Elevated LDL cholesterol levels and other common CHD risk factors such as hypertension, diabetes mellitus, and cigarette smoking can disturb the multiple regulatory functions of the endothelium.[18] Experiments in animals and humans indicate that these risk factors impair endothelial vasodilation by decreasing the activity of endothelium-derived relaxing factor (nitric oxide), resulting in paradoxical vasoconstriction in response to endothelium-dependent vasodilators. Further, when elevated plasma cholesterol levels are lowered, endothelium-dependent vasoregulation and blood flow improve.[19–21]

Thus, lowering the cholesterol level may reduce vasospasm in patients with significant atherosclerosis and therefore may reduce the likelihood of plaque rupture. Nitric oxide also appears to suppress other potentially atherogenic processes, including smooth-muscle cell proliferation and platelet and monocyte adhesion, and is the subject of ongoing investigation.[18]

Inflammatory processes in CHD

Inflammatory processes are an important component of atherosclerosis, which is similar to a chronic infection characterized by macrophage activation and cytokine production. Inflammation may also play a role in acute coronary events. For example, Liuzzo et al[22] reported that elevated levels of C-reactive protein and serum amyloid A protein in patients hospitalized for coronary syndromes were strongly predictive of subsequent unstable coronary events. However, elevated levels of these acute-phase reactants may indicate inflammatory processes that are a consequence, rather than an instigator, of unstable coronary syndromes.

Active inflammation may promote clinical disease by promoting the degradation of connective tissue, leading to plaque rupture. Macrophage density is typically high at the point of plaque rupture, as mentioned above.[2] Further, in vitro, cytokines have been shown to stimulate smooth muscle cells to produce metalloproteinases, enzymes that selectively degrade the major components of the extracellular matrix.[23]

Life-style modifications and primary prevention

These developing concepts have important implications for the care of patients with documented coronary atherosclerosis. In patients with multiple risk factors for CHD, there is probably little realistic difference between those who have had a clinical event and those who have not. High-risk patients without symptomatic CHD can also expect to benefit from lipid-regulating therapy.

The clinical benefit of therapy in asymptomatic patients likely to have coronary atherosclerosis is suggested by the results of the Asymptomatic Coronary Atherosclerosis Progression Study (ACAPS),[6] in which 919 men and women with early carotid atherosclerosis but no history of major cardiovascular symptoms were randomized to receive lovastatin therapy or placebo; participants were also randomized to receive warfarin or placebo and advised to take aspirin daily. Fourteen cardiovascular events were recorded in patients not treated with lovastatin, compared with five in lovastatin-treated patients ($P = .04$), and overall mortality was reduced significantly. Hence, in a high-risk but asymptomatic population, lipid-regulating therapy was accompanied by a rapid clinical benefit.

However, the greatest benefit of risk reduction will ultimately be seen in population-based primary prevention, by virtue of the sheer numbers of people who eventually develop CHD, many of whom die of their first event or are severely disabled. Further, the

life-style modifications that are the foundation of CHD prevention have the additional benefit of decreasing the risk for other major diseases, such as cancer and type II diabetes mellitus. A number of clinical trials currently under way will further evaluate the benefits of various nonpharmacologic and pharmacologic treatments in primary prevention.

CURRENT TREATMENT GUIDELINES

The ongoing National Cholesterol Education Program of the National Institutes of Health has developed guidelines for managing dyslipidemia in adults and in children, as well as for standardizing blood lipid measurements. The second Adult Treatment Panel (ATP II) presented updated recommendations in 1993.[24]

Total risk-factor profile determines treatment

The ATP II report emphasizes the importance of assessing overall CHD risk status in determining the type and intensity of therapy needed. Accordingly, the ATP II provides clinical definitions of the major CHD risk factors, including the nonlipid ones (*Table 3*), and provides separate algorithms for primary and secondary prevention. However, the ATP II report also notes that its guidelines for risk factor assessment are population-based estimates and should be implemented with clinical judgment. The clinician should consider the severity of risk factors, as well as the interaction of multiple risk factors, which tends to increase risk in a greater-than-additive manner.

TABLE 3
RISK FACTORS OTHER THAN LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVEL*

Risk factor	Definition
Age	Men ≥ 45 years Women ≥ 55 years or premature menopause without estrogen-replacement therapy
Family history of premature coronary heart disease	Definite myocardial infarction or sudden death before age 55 in first-degree male relative, or before age 65 in first-degree female relative
Current cigarette smoking	
Hypertension	Blood pressure ≥ 140/90 mm Hg (confirmed on several occasions) or taking antihypertensive medication
Low high-density lipoprotein (HDL) cholesterol level	< 35 mg/dL, confirmed by measurements on several occasions
Diabetes mellitus	
Protective factor: high HDL cholesterol level†	≥ 60 mg/dL

*From the second Adult Treatment Panel report, reference 24
†If the HDL cholesterol level is ≥ 60 mg/dL, subtract one risk factor

TABLE 4
RECOMMENDATIONS FOR MANAGING ELEVATED LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS*

Risk level and intervention	Low-density lipoprotein cholesterol level (mg/dL)	
	Initiation level	Goal level
Coronary heart disease (CHD) absent and fewer than two other risk factors		
Dietary therapy	≥ 160	< 160
Drug therapy	≥ 190	< 160
CHD absent and two or more risk factors		
Dietary therapy	≥ 130	< 130
Drug therapy	≥ 160	< 130
CHD present		
Dietary therapy	> 100	≤ 100
Drug therapy	≥ 130	≤ 100

*From the second Adult Treatment Panel report, reference 24

Although the ATP II report gives increased prominence to HDL cholesterol and triglyceride levels, the primary goal of lipid-regulating therapy is still to lower the LDL cholesterol level. In primary prevention, the ATP II advocates that all adults 20 years of age or older have their total and HDL cholesterol levels measured at least every 5 years. Depending on the results of these measurements, a full fasting lipoprotein analysis may be indicated to determine the LDL cholesterol level. If the LDL cholesterol level is high (≥160 mg/dL), or if it is borderline high (130 to

TABLE 5
CLASSIFICATION OF PLASMA TRIGLYCERIDE LEVELS*

Plasma triglyceride concentration (mg/dL)	Classification	Comments†
< 200	Desirable	
200–400	Borderline high	Lipid-lowering drug therapy in patients with primary triglyceride elevations in this range may be considered if one of the following is present: Coronary heart disease (CHD) A positive family history of premature CHD Concomitant hypercholesterolemia and low concentration of high-density lipoprotein (HDL) cholesterol A genetic dyslipidemia associated with premature CHD Multiple other risk factors
400–1000	High	The clinical significance of high triglyceride levels is unclear; they are usually due to a mixture of primary and secondary factors Emphasis should be given to controlling secondary causes such as diabetes mellitus, alcohol, medications, and obesity Triglyceride-lowering drugs may be necessary to reduce risk for pancreatitis, particularly if the patient has a history of acute pancreatitis
> 1000	Very high	Vigorous attempts to lower triglyceride levels should immediately be made to reduce risk for pancreatitis As in all patients with elevated triglyceride levels, secondary conditions should be identified and treated

*From the second Adult Treatment Panel report, reference 24
†Life-style measures, including diet modification, weight control, regular exercise, smoking cessation, and restriction of alcohol consumption (in some patients), are the primary therapy for all patients with elevated triglyceride levels

159 mg/dL) and two or more other risk factors are present, dietary therapy is recommended (*Table 4*). Intake of fat, saturated fat, and cholesterol should be limited, overweight patients should lose weight, and sedentary patients should increase their physical activity. The management of high plasma triglyceride levels is summarized in *Table 5*.

Primary prevention: Diet therapy usually suffices

In primary prevention, dietary therapy is sufficient in most cases. Lipid-regulating drugs should be reserved for patients who remain at high risk after a full trial (usually 6 months) of intensive life-style modifications alone. Generally, the clinician should consider drug therapy in addition to diet if the LDL cholesterol level remains 190 mg/dL or higher, or 160 mg/dL or higher if two or more other risk factors are present (*Table 4*). A more conservative approach is advised in men younger than 35 years and in premenopausal women, because these groups have a low risk for CHD. Conversely, an overly conservative approach is not warranted in otherwise-healthy elderly patients, because the attributable risk associated with hypercholesterolemia is high in this group.

Secondary prevention: More intensive treatment warranted

A more aggressive LDL cholesterol goal of 100 mg/dL or less is recommended in secondary prevention. Patients with established atherosclerotic disease should have a full fasting lipoprotein analysis performed annually. If the LDL level is greater than 100 mg/dL, therapy should be initiated (*Table 4*). The ATP II recommends somewhat more intensive dietary therapy for secondary prevention than for primary prevention. Drug therapy should be considered in addition to diet if the LDL cholesterol level remains 130 mg/dL or greater despite maximal diet therapy.

Drug therapy may be required in addition to diet

Five major classes of drugs are approved by the US Food and Drug Administration for treating dyslipidemia (*Table 6*).[24,25] The bile-acid sequestrants, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, and nicotinic acid are the most effective agents for lowering LDL cholesterol levels. The fibric-acid derivatives and nicotinic acid are the most effective triglyceride-lowering agents. For mixed dyslipidemia, the fibric-acid

derivatives, nicotinic acid, and the HMG-CoA reductase inhibitors are first-line agents, although nicotinic acid is relatively contraindicated in diabetic dyslipidemia because it worsens glucose control. Probucol effectively lowers LDL cholesterol levels but also has strong HDL–cholesterol-lowering activity and was recently withdrawn from the market by the manufacturer.

FUTURE DIRECTIONS IN RISK ASSESSMENT

Future guidelines will likely extend screening recommendations to include additional CHD risk factors, and may place additional emphasis on HDL cholesterol and triglyceride levels. Epidemiologic data indicate that raising the HDL cholesterol level might be as effective as lowering the LDL cholesterol level in reducing CHD risk, a proposition yet to be directly confirmed by clinical trials.

Other lipid risk factors

High-density lipoproteins. HDL has been hypothesized to inhibit atherosclerosis directly by reverse cholesterol transport, and may have other beneficial effects as well. Of particular interest is the distribution of the A apolipoproteins in HDL. Observational data and experiments in vitro and in transgenic mice suggest that HDL containing apolipoprotein (apo) A-I but not apo A-II protects against atherosclerosis, whereas HDL with both apolipoproteins is neutral. Schultz et al[26] reported that the extent of diet-induced atherosclerosis in transgenic mice expressing human apo A-I and apo A-II was 15-fold greater than in mice expressing apo A-I only.

Triglyceride-rich lipoproteins. Although an independent epidemiologic correlation between triglyceride levels and CHD risk has not been consistently observed, evidence is growing that triglyceride-rich lipoproteins contribute to the development of CHD. A number of factors could mask such an association. Austin[27,28] notes that the wide variability of triglyceride levels and the close metabolic relation between HDL and triglyceride-rich lipoproteins may result in underestimation of such an association in multivariate analyses.

Moreover, disorders that produce similar triglyceride elevations may differ greatly in the extent to which they are associated with premature atherosclerosis. An association has been found between triglyceride-rich lipoproteins and progression of mild and moderate atherosclerotic lesions,[29,30] and these lipoproteins are reported to have procoagulant effects.[31] The role of postprandial lipemia in atherogenesis has not been extensively studied.

Lipoprotein [a]. Elevated lipoprotein[a] (Lp[a]) levels appear to be a significant risk factor for CHD, particularly in the presence of high LDL cholesterol levels, although this risk has not been well characterized and the distribution of Lp[a] levels in populations is highly skewed. An Lp[a] concentration of 30 mg/dL is commonly accepted as the threshold for increased CHD risk. Lp[a] may exert direct atherogenic effects by promoting thrombosis and smooth-muscle cell proliferation.[32]

TABLE 6
APPROVED DRUGS FOR DYSLIPIDEMIA*

Bile-acid sequestrants		
Lipid effects:†	HDL-C:	↓ 15%–30%
	LDL-C:	↑ 3%–5%
	TG:	↑ or no effect
Drugs and daily dose:	Cholestyramine	4–24 g
	Colestipol	5–30 g
HMG-CoA reductase inhibitors		
Lipid effects:	HCL-C:	↓ 20%–40%
	LDL-C:	↑ 5%–15%
	TG:	↓ 10%–20%
Drugs and daily dose:	Fluvastatin	20–40 mg
	Lovastatin	10–80 mg
	Pravastatin	10–40 mg
	Simvastatin	5–40 mg
Nicotinic acid (NA)		
Lipid effects:	HDL-C:	↓ 10%–25%
	LDL-C:	↑ 15%–35%
	TG:	↓ 20%–50%
Drugs and daily dose:	Crystalline NA	1.5–6 g
Fibric-acid derivatives‡		
Lipid effects:	HDL-C:	↓ 10%–15%
	LDL-C:	↑ 10%–15%
	TG:	↓ 20%–50% (may↑)
Drugs and daily dose:	Gemfibrozil	1200 mg
	Clofibrate	2000 mg
	Fenofibrate	300 mg

*Adapted from information in the second Adult Treatment Panel report, reference 24, and Yeshurun and Gotto, reference 25
†LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride
‡Clofibrate is not considered a first-line agent because of associated toxicity; fenofibrate is approved but not currently available in the United States

Combinations of lipid risk factors

The combination of elevated triglyceride and low HDL cholesterol levels has been found to occur in conjunction with the insulin resistance syndrome, which is also characterized by hyperinsulinemia, hyperglycemia, hypertension, and possibly hyperuricemia, microalbuminuria, microvascular angina, and increased plasminogen activator inhibitor 1 (PAI-1) levels. This risk factor profile constitutes a syndrome predisposing to atherosclerosis.[33] The syndrome may also include the presence of small, dense LDL, which has been associated with increased risk for myocardial infarction.[34]

The combination of elevated LDL cholesterol and triglyceride levels and low HDL cholesterol levels appears to indicate a particularly high risk. Reanalysis of 5-year data from the Helsinki Heart Study,[35] a primary-prevention cholesterol-lowering trial conducted in middle-aged men, found that subjects in the placebo group with an LDL/HDL cholesterol ratio greater than 5 and a triglyceride level greater than 200 mg/dL (about 10% of the study population) had a relative risk for cardiac events of 3.8 compared with subjects in the placebo group with an LDL/HDL cholesterol ratio of 5 or less and a triglyceride level of 200 mg/dL or greater. Fibrate therapy essentially eliminated this excess risk, reducing CHD events by 71% in drug-treated subjects compared with placebo.

Improved lipid-regulating drugs in existing classes

As the mechanisms of action of currently approved lipid-regulating drugs become better understood, agents with enhanced activities should be developed. The bile-acid sequestrants are desirable agents because of their nonsystemic mode of action, but their unpalatability hinders patient compliance. Caplet and "light" preparations are more palatable. The drugs might also be made more effective at lower dosages.

Another goal is to develop a nicotinic-acid derivative or related compound as effective as crystalline nicotinic acid, but with fewer side effects. Sustained-release nicotinic acid is available and produces a lower incidence of some adverse effects such as flushing and gastrointestinal disturbances; however, the drug is strongly associated with increased hepatotoxicity.[36] The investigational HMG-CoA reductase inhibitor atorvastatin reportedly lowers LDL cholesterol and triglyceride concentrations more effectively than currently available HMG-CoA reductase inhibitors.[37] Fibric-acid derivatives with enhanced lipid-regulating effects might be developed as well.

New uses for existing drugs

Experiments need to be extended with angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers, and beta-adrenergic blockers, all of which have shown indications of antiatherosclerotic activity unrelated to any lipid-regulating activity.

Estrogen replacement therapy. Substantial observational epidemiologic data indicate that oral estrogen replacement therapy decreases the risk of CHD in postmenopausal women. The beneficial effects of oral estrogens on the lipoprotein profile may partly account for this cardioprotection. The ATP II recommends considering estrogen replacement therapy for moderately decreasing LDL cholesterol and moderately increasing HDL cholesterol levels in postmenopausal women at high risk of CHD after life-style measures are fully implemented. However, estrogens have not yet received an indication either for the regulation of lipids or the reduction of CHD risk by the Food and Drug Administration.

Several major clinical trials are under way to evaluate estrogen replacement therapy in preventing CHD. For example, the clinical trial component of the Women's Health Initiative will enroll 63 000 postmenopausal women 50 to 79 years of age and have a 9-year follow-up.[38] The hormone-replacement therapy arm of this study will examine estrogen alone or with progestin. Another goal of these trials is to characterize better the increased risk of endometrial cancer and (possibly) breast cancer associated with exogenous estrogen. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial,[39] unopposed estrogen caused a greater increase in HDL cholesterol than did estrogen–progestin regimens, but was associated with a high rate of endometrial hyperplasia; its use should therefore be limited to women without a uterus. In women with a uterus, cyclic micronized progesterone (not currently available) in combination with estrogen was the most favorable regimen.

New targets of intervention

Inhibiting cholesterol synthesis. A number of potential pharmacologic strategies are being investigated. One approach is to inhibit cholesterol biosynthesis with

drugs other than HMG-CoA reductase inhibitors. The utility of disrupting cholesterol biosynthesis at various steps depends on the toxicity of the substances that consequently accumulate, and on how effectively LDL-receptor expression is increased. A very early step in cholesterol biosynthesis, such as that mediated by HMG-CoA synthase, may be a suitable target. Inhibitors of squalene synthase[40] and of squalene epoxidase[41] have been reported to up-regulate LDL-receptor activity. Oxidosqualene cyclase is another potential target. A polar sterol derivative might be used to induce feedback inhibition of HMG-CoA reductase expression.

Altering cholesterol metabolism. Another approach might be to alter the activity of enzymes or proteins involved in regulating lipoprotein metabolism. One example would be to enhance lipoprotein lipase activity (an action attributed to fibric-acid derivatives); other examples are to inhibit hepatic lipase, acyl-coenzyme A:cholesterol acyltransferase (ACAT), or possibly cholesteryl ester transfer protein (CETP). It is not yet clear, however, whether inhibitors of hepatic lipase, ACAT, or CETP would prevent atherosclerosis.

Preventing lipoprotein oxidation. Evidence indicates that lipoprotein oxidation contributes to the development of atherosclerosis. In vitro data indicate that oxidized LDL injures the endothelium, is efficiently taken up by macrophage receptors, and promotes leukocyte recruitment and adhesion. However, little is known about LDL oxidation in vivo, and the proposed atherogenic effects of oxidized LDL remain largely hypothetical.

Antioxidant administration has been observed to inhibit diet-induced atherosclerosis in several animal models, albeit inconsistently. Further, some epidemiologic data suggest that taking antioxidant vitamins lowers the risk for CHD. However, these data may be confounded by other factors associated with high intake of antioxidant vitamins, such as a lower intake of saturated fat. Additionally, two large clinical trials of antioxidants, the Alpha-Tocopherol, Beta Carotene Study[42] (not designed primarily to evaluate cardiovascular endpoints) and the Probucol Quantitative Regression Swedish Trial (PQRST)[43] have failed to show a clinical benefit. Because of substantial differences in the biological properties of antioxidants and the limited data available, few conclusions can be drawn about what role antioxidant therapy will ultimately have.

Gene therapy

Gene therapy shows much promise, but likely is several years from clinical use. Foreign DNA can be taken up directly by a target cell, or transfer can be mediated by cationic liposomes or viral vectors such as retroviruses and adenoviruses. Local delivery requires direct mechanical application (eg, with a catheter or implant) or a vector capable of specific binding. Not only must the delivery mechanism be safe and efficient, but for long-term applications, gene expression must also be stable and acceptably nontoxic.

Homozygous familial hypercholesterolemia, in which competent LDL receptors are absent, serves as a model for investigating gene therapy in CHD prevention. Grossman et al[44] reported sustained LDL cholesterol lowering in a subject with homozygous familial hypercholesterolemia after infusion of autologous hepatocytes modified ex vivo with a recombinant retrovirus containing the LDL-receptor gene.

Adenoviruses may prove more useful than retroviruses as vectors, because of their higher efficiency of transfection and because they are effective in nonreplicating cells. An adenovirus has been used in vivo to deliver human LDL-receptor DNA to Watanabe heritable hyperlipidemic rabbits (which are LDL-receptor deficient),[45] resulting in substantial lowering of serum cholesterol. However, transgene expression was stable for only 7 to 10 days, and cholesterol levels returned to baseline within 3 weeks. Subsequent doses were largely ineffective because neutralizing antibodies developed. Because of inherent safety advantages, synthetic DNA complexes may ultimately be preferable to viral vectors if sufficient efficiency can be achieved.

Researchers at Tufts University School of Medicine have obtained approval to conduct a clinical trial of gene therapy.[46] Vascular endothelial growth factor (VEGF) will be used to stimulate collateral vessel growth in patients who are not eligible for angioplasty but who have occluded superficial femoral arteries. Gene delivery will be via a coated balloon catheter. Similar angiogenic techniques could be applied to treat coronary atherosclerosis.

Another strategy might be to inhibit the expression of certain genes. Antisense oligonucleotides could be used to control gene expression and protein synthesis at several points; possible applications include the inhibition of smooth muscle cell proliferation in the arterial wall. Synthetic antisense oligonucleotides can be manufactured rapidly, and

theoretically offer considerable specificity. Although a number of investigators have reported inhibition of smooth muscle cell proliferation in vitro and in animal models using antisense oligonucleotides directed at the *c-myb* and *c-myc* genes,[47,48] a recent report indicates that this activity is not in fact related to an antisense mechanism.

Although genetic strategies may prove ideal for treating individuals with severe genetic disorders such as familial hypercholesterolemia, in populations the predominant determinants of CHD rates are environmental, as illustrated by epidemiologic studies.

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