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CLINICAL PERSPECTIVE

Hyperlipidemia: Diagnostic and Therapeutic Perspectives

CHRISTIE M. BALLANTYNE, SCOTT M. GRUNDY, ALBERT OBERMAN, ROBERT A. KREISBERG, RICHARD J. HAVEL, PHILIP H. FROST, AND STEVEN M. HAFFNER

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Primary Prevention of Coronary Heart Disease

Christie M. Ballantyne
Department of Medicine
Baylor College of Medicine
Houston, Texas 77030

CORONARY heart disease (CHD) is the leading cause of death in both men and women in the United States, causing almost 500,000 deaths annually (1). Each year, 1.1 million Americans have a myocardial infarction (MI) or fatal CHD; 650,000 are first events, and 50% of men and 63% of women who die suddenly of CHD have no prior symptoms (1). In addition to the enormous human cost, the total economic cost of CHD each year is estimated at $118 billion, including direct costs of $55 billion for hospitals and nursing homes, physicians and other health care professionals, drugs, and home health and other medical durables, as well as indirect costs for lost productivity caused by morbidity and mortality (1).

The pain, suffering, and cost of CHD is even more distressing because so many CHD events are preventable. Available clinical trial evidence confirms that CHD morbidity and mortality can be reduced by treating risk factors such as dyslipidemia; lipid-regulating therapy can reduce the relative risk for CHD events by 25–35% (2). However, although CHD mortality rates are decreasing overall, many high-risk patients without known CHD do not receive appropriate treatment. In an analysis of data from the Atherosclerosis Risk in Communities (ARIC) study, using a retrospective surveillance system, CHD death decreased by 4–5% and recurrent MI decreased by 2–3% annually from 1987 to 1994, whereas first MI did not change (+0.1% in men, −0.2% in women) (3).

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Address correspondence to: Robert A. Kreisberg, M.D., Dean and Vice President for Health Affairs, University of South Alabama, CSAB 170, Mobile, Alabama 36688-0002.

National Cholesterol Education Program (NCEP) treatment guidelines

The United States NCEP guidelines for the diagnosis and treatment of hypercholesterolemia stratify individuals on the basis of risk categories (4). At highest risk for a CHD event are individuals with known CHD or other atherosclerotic vascular disease; for individuals without known CHD, the guidelines further categorize risk according to the number of CHD risk factors present. Positive risk factors in the NCEP algorithm for primary prevention are age (≥45 yr in men; ≥55 yr, or premature menopause without estrogen-replacement therapy, in women), family history of premature CHD (MI or sudden death before age 55 in father or other male first-degree relative, or before age 65 in mother or other female first-degree relative), current cigarette smoking, hypertension (≥140/90 mm Hg, or on antihypertensive medication), low high-density lipoprotein cholesterol (HDL-C) (<35 mg/dL), and diabetes mellitus. High HDL-C (≥60 mg/dL) is a negative risk factor in the algorithm; if present, one risk factor is subtracted from the total number of risk factors.

In the most recent NCEP guidelines for primary prevention, initiation levels for therapy and goals of treatment are determined by whether the total number of risk factors for an individual is less than two or two or more. In patients with less than two risk factors and low-density lipoprotein cholesterol (LDL-C) 160 mg/dL or greater, dietary therapy should be initiated with a goal of reducing LDL-C to less than 160 mg/dL. In patients with two or more risk factors, dietary therapy should be initiated if LDL-C is 130 mg/dL or greater, with a goal of reducing LDL-C to less than 130 mg/dL. Drug therapy should be considered in patients with less than two risk factors whose LDL-C remains 190 mg/dL or greater on diet therapy and in patients with two or more risk factors whose LDL-C remains 160 mg/dL or greater on diet. As with diet therapy, the goal of drug therapy is to reduce LDL-C to less than 160 mg/dL and less than 130 mg/dL, respectively. The NCEP guidelines recommend delaying drug therapy in men younger than 35 yr of age and in premenopausal

women, unless LDL-C is 220 mg/dL or greater or unless additional risk is present.

In addition to individuals qualifying for drug therapy on the basis of the above cutpoints, the NCEP guidelines recommend the use of clinical judgment in determining whether to initiate drug therapy in individuals whose LDL-C is below the initiation level for drug therapy yet above goal despite diet therapy. Included for primary prevention are patients with less than two risk factors who are middle-aged or older and have a LDL-C of 160–189 mg/dL and patients with two or more risk factors who have a LDL-C of 130–159 mg/dL.

Clinical trial evidence

At the time the most recent NCEP guidelines were written, most of the available clinical trial evidence on lipid-lowering therapy was limited to patients with severe hypercholesterolemia and agents with low efficacy that was exacerbated by poor compliance because of adverse effects. Consequently, these agents did not show a beneficial effect on total mortality, and the relative benefits and risks of using lipid-lowering drug therapy, particularly in primary prevention, remained unclear. Since that time, however, widespread use of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has provided long-term data establishing the safety and efficacy of statin therapy. Five major clinical event trials enrolling almost 31,000 patients have provided data that have greatly influenced evidence-based clinical judgment, establishing the benefit of statin therapy on CHD morbidity and mortality in primary as well as secondary prevention, and in patients with mild to moderate as well as severe LDL-C elevations.

West of Scotland Coronary Prevention Study (WOSCOPS). WOSCOPS studied the effects of pravastatin as primary prevention in 6595 men with severely elevated LDL-C of 155 mg/dL or greater on two assessments and 174 mg/dL or greater on at least one assessment (5). Pravastatin (40 mg/day) reduced mean LDL-C from 192 mg/dL to 159 mg/dL. At a mean follow-up of 5 yr, the primary end point of nonfatal MI or CHD death as a first event was significantly reduced by 31% with pravastatin, and total mortality was reduced by 22%.

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). AFCAPS/TexCAPS extended the benefit of lipid-lowering therapy as primary prevention to patients whose LDL-C was only mildly to moderately elevated (6). Lipid criteria included LDL-C of 130–190 mg/dL, or 125–129 mg/dL with total cholesterol/HDL-C more than 6, and HDL-C 45 mg/dL or less in men and 47 mg/dL or less in women. Mean baseline LDL-C in the 6605 patients randomized was 150 mg/dL; eighty-three percent of the study population had baseline LDL-C below the initiation level for drug therapy in the NCEP guidelines. Lovastatin (20–40 mg/day) reduced LDL-C to 115 mg/dL, an average reduction of 25%. The primary end point, first acute major coronary event (fatal or nonfatal MI, unstable angina, or sudden cardiac death), was significantly reduced by 37% with lovastatin, and fatal or nonfatal MI was significantly reduced by 40%. For the primary end point, similar relative risk reductions occurred across all tertiles of baseline LDL-C: 142 mg/dL or less, 143–156 mg/dL, and 157 mg/dL or greater.

Implications affecting treatment decisions

The AFCAPS/TexCAPS investigators estimate that approximately 8 million Americans without CHD have lipid profiles similar to the patients in AFCAPS/TexCAPS, including an estimated 6 million Americans who would not currently be recommended for drug therapy using the NCEP cutpoints presented above (6). Although clinical trials of statin therapy have demonstrated benefits in patients whose LDL-C would generally be considered borderline high, extending treatment to everyone who might potentially benefit based on the AFCAPS/TexCAPS results would require enormous resources. A recent analysis of National Health and Nutrition Examination Survey data (NHANES III) for 1988–1994 estimates that including all patients for whom the NCEP guidelines recommend the use of clinical judgment in determining whether to initiate drug therapy would require treating 28.4 million Americans, including 17.5 million without CHD but who have two or more risk factors in the NCEP algorithm (7). Therefore, clinical judgment must be informed not only by scientific evidence but also by cost-effectiveness issues (2, 8).

The number of patients who need to be treated to prevent one clinical event increases dramatically as one moves from secondary to primary prevention and from severe to milder LDL-C elevations (Fig. 1). For example, among the severely hypercholesterolemic CHD patients enrolled in the Scandinavian Simvastatin Survival Study (9), 12 would need to be treated to prevent one event, compared with 30–34 in the Long-Term Intervention with Pravastatin in Ischaemic Disease study (10) and the Cholesterol and Recurrent Events trial (11), which were conducted in CHD patients with milder

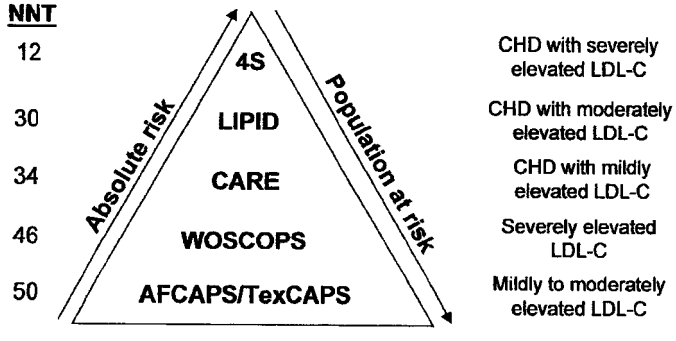

FIG. 1. Recent clinical event trials of lipid-lowering therapy. The number needing to be treated (NNT) to prevent one clinical event increases markedly when treating patients without known CHD and with lower cholesterol concentrations. However, the majority of individuals with CHD do not have markedly elevated cholesterol; similarly, the largest number of individuals who will have a CHD event come from the largest population at risk, individuals with only mildly to moderately elevated cholesterol. To ensure that the largest number of individuals who may benefit from therapy receive appropriate treatment, refined risk assessment strategies are necessary. AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study (6); CARE, Cholesterol and Recurrent Events study (11); LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease study (10); 4S, Scandinavian Simvastatin Survival Study (9); WOSCOPS, West of Scotland Coronary Prevention Study (5).

LDL-C elevations. In contrast, 46 WOSCOPS patients and 50 AFCAPS/TexCAPS patients needed to be treated to prevent each event. In both WOSCOPS and AFCAPS/TexCAPS, higher-risk patients could be identified if other risk factors besides LDL-C were examined. The benefit of therapy as measured by the absolute risk reduction or the number needing to be treated to prevent one event is more dependent on the absolute risk for CHD than the level of LDL-C in any population studied. It is, therefore, imperative to identify the highest-risk patients to ensure appropriate therapy and the optimum use of health care resources.

Although the NCEP guidelines stratify patients on the basis of CHD risk, these three broad categories, based on the presence or absence of CHD, a dichotomization of summed risk factors as less than two or two or more, and LDL-C level, may be inadequate to assess an individual's actual risk for a CHD event. One approach is to identify groups with extremely high risk, such as individuals with diabetes mellitus (12), and consider their risk to be the same as patients with CHD (*i.e.* a CHD equivalent) (13), or to redefine levels for risk stratification (*e.g.* HDL-C <40 mg/dL). If diabetes mellitus is considered a CHD equivalent, then impaired glucose metabolism could potentially be considered a major risk factor. An alternative method is to calculate an individual's absolute CHD risk taking into account not only each risk factor present but also the severity of each risk factor. One such algorithm has been developed by the investigators of the Framingham Heart Study (14). The Framingham risk prediction equation calculates 10-yr CHD risk based on an individual's sex, age, cholesterol or LDL-C level, HDL-C level, blood pressure, presence or absence of diabetes, and whether or not the individual smokes. Treatment decisions can then be made on the basis of more precise risk assessment. An analysis comparing the predictive value of previous Framingham equations with the NCEP guidelines found that Framingham was significantly more accurate (area under the receiver operating characteristic curve, 0.85, compared with 0.74 for the NCEP guidelines) and had greater sensitivity (70% compared with 45% for the NCEP guidelines); specificity was only slightly reduced (82% compared with 86%) (15). The most recent Framingham prediction equation has been validated in some (16) but not all (17) populations.

Absolute risk is used to determine intensity of treatment in guidelines developed by the International Task Force for Prevention of Coronary Heart Disease/International Atherosclerosis Society (18) and by the Joint Task Force of the European Society of Cardiology, European Atherosclerosis Society, European Society of Hypertension, International Society of Behavioural Medicine, European Society of General Practice/Family Medicine, and European Heart Network (19) (Table 1). Both guidelines provide tools for estimating an individual's risk for a CHD event; the former also stratifies LDL-C treatment goal on the basis of absolute risk, whereas the latter uses risk to determine the need for lipid-lowering drug therapy. Although lipid lowering for the prevention of CHD is the focus here, both these international guidelines emphasize the multifactorial nature of CHD and the need for reduction of all modifiable risk factors.

In addition to calculating absolute risk by using more sophisticated algorithms, another method to improve risk assessment is the use of additional diagnostic tests (2). Measurement of nontraditional risk factors, such as lipoprotein(a), high-sensitivity C-reactive protein (20), fibrinogen, homocysteine, plasminogen activator inhibitor 1, and inter-

TABLE 1. International guidelines for CHD prevention

Risk level	Definition	LDL-C goal (mg/dL)
International Task Force for Prevention of Coronary Heart Disease (18)		
Small increase in risk	1 RF[a] of moderate degree, TC/HDL-C 4 or 5, smoking 10 cigarettes/day, or 3rd quintile of PROCAM algorithm[b] (risk for CHD event ~0.3%/yr in middle-aged men)	<160 (diet therapy)
Moderate increase in risk	1 RF[a] of severe degree, 2 RFs of moderate degree, diabetes without macrovascular complications, or 4th quintile of PROCAM algorithm[b] (risk for CHD event ~0.7%/yr in middle-aged men)	<135 (diet therapy; + drug therapy if needed after ≥6 months of diet)
High risk	History of MI, presence of atherosclerosis, ≥3 RF[a], ≥2 RFs of severe degree, major genetic hyperlipidemia, diabetes with macrovascular complications, or 5th quintile of PROCAM algorithm[b] (risk for CHD event ~2.3%/yr in middle-aged men)	<100 (diet + drug therapy)
Joint Task Force of European and Other Societies on Coronary Prevention (19)		
Low (1° prevention)	<5% 10-yr absolute risk for CHD event[c]	<115 (diet therapy)
Mild (1° prevention)	5–10% 10-yr absolute risk for CHD event[c]	<115 (diet therapy)
Moderate (1° prevention)	10–20% 10-yr absolute risk for CHD event[c]	<115 (diet therapy)
High (1° prevention)	20–40% 10-yr absolute risk for CHD event[c]	<115 (diet + drug therapy)
Very high (1° prevention)	>40% 10-yr absolute risk for CHD event[c]	<115 (diet + drug therapy)
2° prevention	Established CHD or other atherosclerotic disease	<115 (diet + drug therapy)

RF, Risk factor; PROCAM, Prospective Cardiovascular Münster Study; TC, total cholesterol.

[a] Age, sex, physical activity and diet, history of atherosclerotic disease, family history of CHD, cigarette smoking, body weight, central obesity, blood pressure, clinical evidence of cardiovascular disease, plasma lipids and lipoproteins [triglyceride, TC, LDL-C, HDL-C, TC/HDL-C ratio, lipoprotein(a)], diabetes mellitus, metabolic syndrome (insulin resistance), fibrinogen, factor VIIc, plasminogen activator inhibitor 1, and homocysteine.

[b] RF in PROCAM algorithm: age, systolic blood pressure, LDL-C, HDL-C, triglyceride, smoking, diabetes mellitus, family history of MI, and angina pectoris.

[c] RF: TC, systolic blood pressure, smoking, age, and sex.

cellular adhesion molecule 1 levels, may refine risk assessment, as may new technologies such as carotid ultrasound, ultrafast computed tomography, and magnetic resonance imaging. These tests may better stratify individuals who are at intermediate risk for future events based on a Framingham score. Results from the ongoing Subclinical Cardiovascular Disease Study of the United States National Heart, Lung, and Blood Institute should clarify which traditional and nontraditional risk factors and diagnostic tests are useful and cost-effective in identifying high-risk patients.

Conclusions

Although the NCEP guidelines, by providing for the use of clinical judgment in determining whether to initiate lipid-lowering drug therapy in patients with borderline LDL-C elevations, allow for evolving information on the benefits and safety of lipid-lowering drugs, the guidelines remain limited because of their simplified risk stratification algorithm. Emerging clinical trial data indicate that patients with LDL-C levels ranging from mildly to seriously elevated receive benefit from lipid-lowering therapy but that other risk factors besides LDL-C are important in assessing CHD risk and benefit from therapy. Risk prediction tools that reflect the substantial contribution of risk factors in addition to LDL-C can provide more refined risk assessment, which in turn can improve cost-effectiveness by identifying high-risk patients and targeting them for more aggressive intervention.

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Cholesterol-Lowering Therapy in Secondary Prevention: Remaining Issues

Scott M. Grundy
Departments of Clinical Nutrition and Internal Medicine and the Center for Human Nutrition
University of Texas Southwestern Medical Center at Dallas
Dallas, Texas 75235-9052

THE DISCOVERY of HMG CoA reductase inhibitors (statins) (1) opened the door to more effective reduction of recurrent coronary morbidity and mortality in patients with established coronary heart disease (CHD). The addition of statin therapy to already proven regimens of secondary prevention—low-dose aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors—enhances the overall efficacy of preventive efforts. Thus, aggressive medical therapy in secondary prevention is increasingly being recognized as an alternative to invasive intervention [*i.e.* coronary angioplasty and coronary artery bypass graph (CABG)] (2). This major change in emphasis reflects an increasing body of evidence supporting the efficacy of medical therapy. Nonetheless, use of medical therapy in secondary prevention undoubtedly carries unresolved issues. Here, I will review the current status of cholesterol management in secondary prevention and will examine some of the key remaining issues. First, however, the scientific evidence for the benefit of reducing serum cholesterol levels in patients with established CHD can be reviewed.

Secondary prevention trials of cholesterol-lowering therapy

A role for cholesterol-lowering therapy in secondary prevention has been solidified by a series of controlled clinical trials. These are of several types and have been carried out over a period of more than 3 decades. The trials have been of increasing sophistication and statistical power. They can be classified into three categories: earlier trials, angiographic trials, and statin trials. The evidence that each category brings to bear on the issue of secondary prevention can be reviewed briefly.

Early secondary prevention trials. Between 1965 and 1990, a series of secondary prevention trials of cholesterol-lowering therapy were carried out. Some used dietary therapy, others drug therapy. Their results provided suggestive evidence of benefit from lowering serum cholesterol levels; none, however, convincingly and definitively showed that cholesterol-lowering therapy is clinically efficacious. In 1990, Rossouw *et al.* (3) performed a meta-analysis of these earlier secondary prevention trials. The analysis, which was updated in 1993 (4), revealed that therapy reduced serum cholesterol levels, on average, by about 15% compared with placebo. Overall, the groups receiving therapy experienced a 26% reduction in nonfatal myocardial infarction, a 14% decline in fatal myocardial infarction, an 11% decrease in all cardiovascular deaths, and a 9% reduction in total mortality. Importantly, this analysis revealed no increase in noncardiovascular deaths; hence, it supported the overall safety of cholesterol-lowering therapy. This meta-analysis carried significant influence in the decision of the National Cholesterol Education Program (NCEP) to place increased emphasis on cholesterol management in patients with existing CHD (4).

Angiographic trials. During the past decade, another series of investigations of cholesterol-lowering therapy tested whether cholesterol reduction will slow the progression of coronary atherosclerosis or will reverse existing coronary lesions. Aggressive therapy was employed, often using drugs in combination. Changes in coronary plaque size were compared in treatment and control groups by coronary angiography. When the results of these trials are reviewed as a whole, they reveal that lowering serum cholesterol concentrations without question reduces the rate of progression and promotes some regression of coronary lesions (5). Still, changes in lesion size, although statistically significant, were relatively small and would not be expected to reduce clinical events. Contrary to expectations, however, major coronary events in patients receiving therapy fell by about one third (5). This remarkable discrepancy between gross changes in coronary lesions and occurrence of major coronary events contributed importantly to the concept that cholesterol-lowering therapy enhances coronary plaque stability and lowers the probability of plaque rupture, the primary cause of major coronary events.

A more recent angiographic trial was the Post-Coronary Artery Bypass Graft (Post-CABG) trial (6). Post-CABG tested whether aggressive lowering of low-density lipoproteins (LDLs) will retard the progression of atherosclerotic disease more effectively than will a moderate reduction of LDL levels. Thus, therapies were adjusted to produce two levels of LDL reduction; concentrations of LDL-cholesterol on the two arms of therapy averaged about 135 mg/dL and less than 100 mg/dL. The therapeutic arm having the lower LDL-cholesterol concentration experienced a lesser progression in coronary disease than the one with higher concentrations. The results of Post-CABG (6) supports aggressive cholesterol-lowering therapy in secondary prevention.

Statin trials. The greatest advance in secondary prevention comes from three major trials using statins: the Scandinavian Simvastatin Survival Study (4S) (7), Cholesterol and Recurrent Events (CARE) (8), and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) (9). The positive results of each of these three trials strongly confirms the benefit of cholesterol-lowering therapy in secondary prevention. The major features of each trial can be examined briefly.

The 4S trial (7) examined the efficacy and safety of simvastatin in hypercholesterolemic patients with established CHD. Several centers in Scandinavia participated. The primary end point was total mortality; secondary end points were various major coronary events. These 4444 patients received either simvastatin or placebo for 5.4 yr. The dose of simvastatin was adjusted to reduce total cholesterol to less than 200 mg/dL compared with placebo. LDL-cholesterol concentrations declined on simvastatin therapy by 35%. Treatment with statins reduced total mortality, the primary end point, by 30%; major coronary events fell by 35%, coronary revascularization by 37%, and coronary mortality by 42%. The incidence of strokes also was lower on statin therapy. These benefits accrued without significant side effects; of particular note, simvastatin therapy was not accompanied by an increase in mortality from noncardiovascular causes.

The CARE study (8) included 4259 patients (14% women) with existing CHD. It took place in North America and lasted 5 yr. Patients at entry had "average" cholesterol levels (mean, 209 mg/dL). Therapy consisted of 40 mg/day pravastatin *vs.* placebo. On pravastatin therapy, LDL-cholesterol concentrations fell from 137 mg/dL to an average of 98 mg/dL. Pravastatin therapy reduced major, recurrent coronary events by 25%, coronary deaths by 24%, revascularization procedures by 27%, and stroke by 31%. No significant side effects from pravastatin therapy were revealed. The CARE trial (8), thus, extended the evidence of benefits from cholesterol-lowering therapy to CHD patients having only average cholesterol levels at baseline.

The LIPID trial (9) was carried out in Australia and New Zealand. It compared 40 mg/day pravastatin with placebo in 9014 patients with established CHD. Entry criteria and LDL-cholesterol levels of LIPID (9) resembled those of the CARE study (8). Compared with placebo, pravastatin therapy reduced major coronary events by 29%, coronary deaths by 24%, revascularization procedures by 24%, stroke by 20%, and total mortality by 23%. All reductions proved to be statistically significant. No significant side effects of pravastatin therapy were reported.

Subgroup analysis of these three trials (7–9) revealed that statin therapy significantly lowered major coronary events in men and women, in older and younger patients, in smokers and nonsmokers, in hypertensive and normotensive patients, and in patients with and without diabetes. Thus, the benefit of statin therapy in secondary prevention seems to extend to most, if not all, subgroups.

Goals for LDL-cholesterol in secondary prevention

The recent clinical trials of statin therapy demonstrate that reducing LDL-cholesterol levels will significantly and meaningfully reduce both coronary morbidity and mortality in patients with established CHD. These results raise two questions: (1) what is the appropriate goal for LDL-cholesterol lowering in secondary prevention? and (2) what is the optimal LDL-cholesterol level with respect to development of

coronary atherosclerosis and CHD risk? These questions are especially germane for secondary prevention. NCEP guidelines (4) propose that the goal for LDL-cholesterol in secondary prevention should equate to the optimal LDL-cholesterol level. Four lines of evidence bear on the issue of the optimal LDL-cholesterol level. They deserve a brief review.

Evidence from basic science. A large body of basic research supports the concept that LDL is an atherogenic agent. Most of the cholesterol accumulating in coronary plaques is derived from circulating atherogenic lipoproteins, of which LDL is the most abundant. Recent research further suggests that LDL is a proinflammatory agent (10). Until recently, atherogenesis was considered to be a passive response to damaging external influences (11). This view grew partly out of pathological studies showing that smooth muscle cells are the major type of cells of atheroscleortic plaques. From this observation investigators inferred that plaque development represents a very low grade of inflammatory reaction. This view of atherogenesis no longer pertains. More recent research has revealed that the "active site" of atherogenesis consists mainly of macrophages—cells having greater inflammatory qualities. Thus, the "leading edge" of atherogenesis contains a higher grade of inflammation than previously recognized. Among the agents that may elicit this inflammatory reaction, LDL emerges as the strongest candidate (10). Most investigators agree that LDL must undergo modification with the arterial wall before it can attract and activate macrophages and, hence, initiate atherogenesis. Several modifications—oxidation (12), glycation (13), and enzymatic degradation (14)—indeed, occur *in vivo.* A multitude of recent investigations in various *in vitro* and *in vivo* models indicate that these modified forms of LDL have an atherogenic potential.

Another line of research from animal models confirms that LDL is a highly atherogenic lipoprotein. This evidence comes from studies in which hypercholesterolemia is induced by cholesterol feeding and from animals that have genetic modifications causing hypercholesterolemia (15–17). Atherosclerosis containing lipid-laden macrophages or smooth muscle cells generally does not develop in the absence of some elevation of LDL or related atherogenic lipoproteins. Studies in various models of atherogenesis, both *in vitro* and *in vivo*, thus support the concept that the optimal level is the lowest LDL level. In a word, basic research makes a strong case for prevention of atherogenesis "the lower, the better" for LDL cholesterol levels.

Epidemiological evidence. Numerous prospective studies (18) provide a wealth of information on the relation between total cholesterol (and LDL cholesterol) and the incidence of CHD. Early prospective studies suggested that a threshold relation exists between cholesterol levels and incidence of CHD (19–21). The threshold seemed to be a total cholesterol of about 200 mg/dL, which corresponds to a LDL cholesterol of about 130 mg/dL. Only above this threshold level did risk for CHD seem to rise. Subsequent larger studies (18, 22) refuted this threshold concept and showed that the relationship between total cholesterol and CHD incidence is continuous over a broad range of cholesterol levels. Indeed, risk for CHD declines down to a total cholesterol level of at least 150 mg/dL, corresponding to a LDL-cholesterol level of about 100 mg/dL. The shape of the line defining this relationship is curvilinear (or log-linear) (18). Multiple prospective studies (18) confirm this log-linear relationship and support a value for the optimal LDL-cholesterol being 100 mg/dL or less. The strengths of the epidemiological data are 2-fold: (1) the results are consistent across multiple studies; and (2) the studies include a very large number of subjects. Although epidemiological associations are always subject to confounding factors, multivariate analysis of the available data provides as strong evidence as possible through epidemiology for an optimal of LDL-cholesterol being 100 mg/dL or less.

Angiographic studies. The angiographic studies, reviewed above, revealed that LDL-lowering therapy will slow progression of coronary lesions, promote regression, and reduce major coronary events (5). Most of these studies used aggressive cholesterol-lowering therapy, and many reached a LDL-cholesterol level of 100 mg/dL or less. These results provide some support for these very low levels being optimal. In addition, the Post-CABG trial (6) specifically compared moderate *vs.* aggressive cholesterol-lowering therapy; in this trial, the treatment arm that reached an average LDL-cholesterol of below 100 mg/dL showed more favorable changes in coronary lesions than the arm having an average level of about 130 mg/dL. The Post-CABG trial, in particular, directly supports an optimal LDL cholesterol level being 100 mg/dL or less.

Randomized clinical trials. The recent statin trials (7–9) were not designed to specifically address the issue of the optimal LDL-cholesterol level. These trials nonetheless documented a definite benefit of LDL lowering. They all justify aggressive LDL reduction in most patients with established CHD. Subgroup analysis of the data of two trials, 4S (23) and CARE (24), further attempted to examine the relation between LDL-cholesterol levels and recurrent coronary morbidity in patients with CHD. The CARE analysis (24) suggested a threshold relationship; it found no clear benefit from reducing LDL-cholesterol levels to below 125 mg/dL. Subgroup analysis of the 4S trial (23), in contrast, suggested a log-linear relationship, with a continuous relationship to a LDL levels and CHD events down to a concentration of 100 mg/dL. Subgroup analysis has not been reported for the LIPID trial (9); however, in the primary analysis (9), benefit of statin therapy seemed to be attenuated at LDL-cholesterol concentrations below 130 mg/dL. It must be noted that subgroup analyses of statin trials lack the statistical power to provide a definitive answer to the question of the optimal LDL-cholesterol in CHD patients. These trials are much smaller than previous large prospective studies (18, 22), and they may not have the power to differentiate between a threshold and curvilinear relationship between LDL-cholesterol levels and new coronary events.

Goals for LDL-lowering therapy. The NCEP has taken the position that in patients with clinical CHD the goal of LDL-lowering therapy should be the optimal LDL-cholesterol level (5). The strongest evidence for defining an optimal level

comes from the large body of epidemiological data. These data indicate that a level of LDL cholesterol of 100 mg/dL or less is optimal. This level is supported by basic science research, which favors the concept of "the lower, the better"; a goal of 100 mg/dL or less also is consistent with the results of angiographic trials and, to some extent, with subgroup analysis of secondary prevention trials.

Management of LDL-cholesterol. Most patients with established CHD will require LDL-lowering drugs. The American Heart Association recommends that essentially all patients with CHD whose LDL-cholesterol levels exceed 130 mg/dL at baseline be started on a LDL-lowering drug (25). For most patients, the drug of first choice will be a statin, but bile acid sequestrants are an alternative for some patients. When LDL-cholesterol levels range from 100–129 mg/dL at baseline, clinical judgment is needed whether to start drug therapy immediately, or whether to maximize nondrug therapy in the attempt to achieve the goal of therapy.

If the patient achieves a LDL-cholesterol level in the range of 100–129 mg/dL on either drug therapy or maximal nondrug therapy, consideration must be given whether to intensify LDL-lowering therapy to achieve the goal for LDL-cholesterol of 100 mg/dL or less. Several options are available. For patients on maximal nondrug therapy, a LDL-lowering drug can be started; usually only small doses of a statin will be required to achieve the goal of therapy. For those already on a statin, the dose can be raised; alternatively, a bile acid sequestrant can be combined with the statin. Another option is to leave the LDL-cholesterol level in the range of 100–129 mg/dL and to maximize control of other risk factors. The following discussion will expand on this latter option; this discussion also will consider adjunctive therapies even when the goal of 100 mg/dL or less for LDL-cholesterol is achieved.

Atherogenic dyslipidemia

Another common disorder of lipoprotein metabolism in patients with CHD is atherogenic dyslipidemia (26). This form of dyslipidemia is characterized by a triad of defects: elevated triglyceride-rich lipoproteins (TGRLPs), increased small LDL particles, and low high-density lipoprotein (HDL)-cholesterol levels. Most patients with atherogenic dyslipidemia have all three abnormalities. These aberrations of lipoprotein metabolism are the result of excessive production of three factors by the liver: TGRLP (27), apolipoprotein CIII (28), and hepatic lipase (29). The occurrence of this latter triad of lipoprotein regulators seems to be common. Overproduction of TGRLP tends to elevate plasma levels of these lipoproteins; the elevation of TGRLP is accentuated by increased availability of apolipoprotein CIII, which inhibits the action of lipoprotein lipase (30). The concomitant increase in hepatic lipase promotes the catabolism of HDL and lowers HDL-cholesterol levels (29). An elevation of both TGRLP and hepatic lipase seems to be responsible for the formation of small LDL particles, as well.

In CHD patients who exhibit atherogenic dyslipidemia, consideration can be given to modifying the disorder with drug therapy. Although some investigators believe that atherogenic dyslipidemia rivals elevated LDL-cholesterol as a cause of atherosclerosis, evidence from clinical trials gives priority to the lowering of LDL-cholesterol levels in secondary prevention. Therefore, if drugs are used to treat atherogenic dyslipidemia, they usually will be combined with a regimen that already contains a LDL-lowering drug. Several different pharmacological approaches are available for management of atherogenic dyslipidemia; considerations of therapy for lipoprotein abnormality in triad can be considered separately.

Elevated serum triglyceride and TGRLP. Multiple lines of data support an independent atherogenic role for some forms of TGRLP, notably remnant lipoproteins (26). Remnants typically are raised in patients having moderate hypertriglyceridemia (31). Some investigators (32, 33) postulate that remnant lipoproteins are even more atherogenic than LDL; although this may be true, concentrations of remnants in normolipidemic persons usually are lower than those of LDL. Once hypertriglyceridemia develops, however, remnant levels increase substantially. Fortunately, on a percentage basis, the statins reduce remnant lipoproteins similarly to LDL (34). This is a major advantage of statins: they reduce all categories of atherogenic lipoproteins. Statins, therefore, are the first line of drug therapy in CHD patients who have elevated serum triglycerides and atherogenic dyslipidemia. Results of statin trials suggest that the benefits of statins are not attenuated in patients with higher levels of plasma triglycerides (23, 24).

An important question is whether additional benefit derives from combining a triglyceride-lowering drug with a statin in patients with atherogenic dyslipidemia. Two kinds of triglyceride-lowering drugs are available: nicotinic acid and a fibric acid. Nicotinic acid is more effective for lowering triglycerides and for favorably modifying other lipoproteins, but, unfortunately, it also causes more side effects. A fibric acid, therefore, may be more practical for most patients. Clinical trials (35–37) suggest that triglyceride-lowering drugs reduce the risk for CHD in patients with elevated triglycerides. But, whether incremental benefit accrues from combining a fibric acid with a statin in patients with atherogenic dyslipidemia is not known. Although combination drug therapy has a strong rationale, it must be kept in mind that about 1 in 50 patients who receives a statin plus fibrate will develop clinical myopathy. If this combination is used, therefore, the patient must be appropriately cautioned and monitored for the development of myopathy. Despite the danger of myopathy, a patient with CHD whose triglyceride levels remain above 200 mg/dL on statin therapy deserves consideration of an added fibrate or nicotinic acid.

Increased small LDL particles. Most patients with elevations in serum triglyceride have concomitant increases in small LDL particles. Several publications (38, 39) suggest that these particles are independently atherogenic. Nonetheless, the basic therapy for increased small LDL particles is the same as that outlined for patients with elevated triglycerides. Statin therapy reduces the number of small LDL particles in circulation as well as reducing concentrations of LDL-cholesterol. The addition of nicotinic acid or a fibric acid to statin therapy will transform many of the small LDL particles into normal-sized

LDL (40); this, too, theoretically could reduce risk. No other therapies specifically targets small LDL.

Low HDL-cholesterol. In CHD patients on statin therapy a low level of HDL-cholesterol continues to denote increased risk for recurrent coronary morbidity (7, 8). Raising HDL concentrations simultaneously with lowering of LDL levels, therefore, may further reduce risk. The triglyceride-lowering drugs, nicotinic acid and fibric acids, will raise HDL concentrations to some extent (41). Nicotinic acid is the more effective HDL-raising agent, and it is the preferred drug to use in combination with a statin in CHD patients with "isolated low HDL" (41). Again, however, nicotinic acid causes more side effects than do fibric acids, and fibric acids have been shown to produce some increase in HDL-cholesterol levels when combined with a statin (34, 42).

Metabolic syndrome

Two types of patients commonly develop premature CHD. One is the cigarette smoker who has a moderately elevated LDL-cholesterol and often is not obese. The other is the patient with abdominal obesity who has insulin resistance. The latter patient often has the metabolic syndrome, a condition characterized by atherogenic dyslipidemia, elevated blood pressure, a prothrombotic state, and an elevated plasma glucose (43). The glucose can occur either as impaired fasting glucose (plasma glucose 110–126 mg/dL) or categorical type 2 diabetes (plasma glucose >126 mg/dL) (44). Insulin resistance is at the heart of the metabolic syndrome (45, 46) and, hence, is the primary target of therapy. The major causes of insulin resistance and the metabolic syndrome include obesity, physical inactivity, and heredity. First line therapies for the metabolic syndrome are weight reduction in overweight persons and increased physical activity. For overweight patients with established CHD, referral to a dietitian for nutritional counseling is recommended. Likewise, referral to a program of cardiac rehabilitation that includes an appropriate program of physical activity can be advised.

Active pharmaceutical research currently is seeking for drugs to treat insulin resistance. Two categories of agents already exist that can be classified first-generation agents for reducing insulin resistance. One of them, metformin, reduces insulin resistance by decreasing hepatic glucose output (47). The other class, thiazolidinediones, improves insulin sensitivity in peripheral tissues, seemingly in adipose tissue and muscle (48). Neither class of agents is currently used routinely to treat insulin resistance in nondiabetic patients. Their long-term safety and efficacy for this purpose remains to be demonstrated. The development of more effective agents to lessen insulin resistance would be welcome and may well be forthcoming before long.

Atherogenic dyslipidemia. The treatment of this component of the metabolic syndrome through modification of lipoprotein metabolism with triglyceride-lowering drugs was discussed before. The potential for treatment of dyslipidemia through reduction of insulin resistance is considerable, as illustrated by the well known improvement in atherogenic dyslipidemia during weight reduction and increased physical activity. If effective drugs to treat insulin resistance are successfully developed, they could provide an alternate (or added) approach to management of atherogenic dyslipidemia.

Hypertension. Many patients with hypertension manifest insulin resistance. Because multiple factors contribute to the development of hypertension, the precise contribution of insulin resistance to the development of hypertension is uncertain. It has been postulated that insulin resistance induces multiple adverse responses (*e.g.* increased sympathetic tone, sodium retention, and vasoconstriction). Moreover, the fact that obesity and physical inactivity, the major causes of insulin resistance, both tend to raise the blood pressure add support for a causal connection between insulin resistance and hypertension. Although insulin resistance may predispose to hypertension, a given person's responsiveness to insulin resistance can vary. A differential responsiveness is suggested by the difference in susceptibility of different ethnic groups to develop hypertension under the influence of insulin resistance. Again, when insulin resistance seems to be one component in the development of hypertension, weight reduction and increased physical activity should be part of the treatment regimen.

Prothrombotic state. One of the components of the metabolic syndrome is a prothrombotic state. This is characterized by several abnormalities in coagulation, among which is an increased level of PAI-1 (26). Low-dose aspirin is standard therapy in CHD patients. Inhibition of platelet aggregation by aspirin may help to offset the prothrombotic state. Combination of aspirin therapy with low doses of warfarin, although theoretically efficacious, has not become routine therapy.

Hyperglycemia. Many patients with the metabolic syndrome have impaired fasting glucose, which usually indicates the presence of insulin resistance. No specific drug therapy is indicated for impaired fasting glucose, although at least one clinical trial is underway to test the benefit of drugs that reduce insulin resistance. Certainly weight reduction and increased physical activity are well advised in most patients with impaired fasting glucose. When categorical type 2 diabetes develops, control of hyperglycemia becomes imperative; in patients with overt diabetes the hemoglobin A1c levels should be kept to near normal levels.

Estrogen replacement therapy in postmenopausal women

Several observational studies (49–52) suggest that estrogen-replacement therapy in postmenopausal women will reduce the risk for myocardial infarction. The results suggested benefit from estrogen replacement appeared in women both with and without pre-existing CHD. For this reason, the NCEP (4) in 1993 recommended that priority be given to estrogen-replacement therapy over cholesterol-lowering drugs in postmenopausal women. Subsequently, however, a recent clinical trial, the Heart and Estrogen/Progestin Replacement Study (HERS) (53) has cast doubt on the benefit of estrogen therapy in postmenopausal women who have established CHD. The results of HERS were disappointing; estrogen-replacement therapy failed to reduce risk for recurrent coronary morbidity and mortality. Indeed,

any small benefit in coronary risk reduction that occurred in the treatment group was seemingly offset by side effects of estrogen therapy. At the same time, the secondary prevention studies of cholesterol-lowering therapy (7–9) have shown a definite risk reduction in women as well as men. These clinical trials strongly suggest that priority should be given to use of cholesterol-lowering drugs over estrogen-replacement therapy in secondary prevention. Larger studies of estrogen-replacement therapy in primary prevention are currently being carried out, but their results will not be available for several years.

Cholesterol-lowering therapy in elderly patients

In the past, there was a widely held view that cholesterol-lowering therapy is unlikely to be efficacious in elderly patients. This view derived from observational studies that showed that relative risk for CHD associated with high serum cholesterol levels declines with aging. Several reports, although not all, suggested that at some point after age 70 a high cholesterol concentration no longer contributes to coronary risk (54). Two facts, however, refute the loss of clinical significance of elevated cholesterol. First, with advancing age, as relative risk declines, the attributable risk rises. The attributable risk is the difference between absolute risk at higher cholesterol levels and the absolute risk at lower levels. Because absolute risk increases with age, the attributable risk also increases even when relative risk declines. Indeed, because of a high population attributable risk, treatment of elevated cholesterol levels in elderly patients could yield more net benefit than treatment of middle-aged patients. Still, more convincing evidence comes from the recent clinical trials of cholesterol-lowering therapy (7–9). All of the recent trials of statin therapy indicate that lowering of serum cholesterol levels continues to reduce risk for myocardial infarction into advance age. Therefore, a general consensus now holds that most patients with established CHD should receive aggressive cholesterol-lowering therapy, at least up to age 75 (54). Even above this age, reduction of serum cholesterol concentrations should reduce risk, although institution of polytherapy regimens in very old persons requires an appropriate weighing of risks and benefits.

Summary

A strong and growing body of evidence underlies the concept that medical therapy is efficacious for secondary prevention of CHD. The combination of cholesterol-lowering therapy, antiplatelet therapy, antihypertensive mediation, and beta-blockers will lead to a substantial reduction in risk for recurrence of major coronary events (*e.g.* unstable angina and acute myocardial infarction) (2). Among these protective agents, cholesterol-lowering therapy seems to be the most efficacious. The major target of cholesterol-lowering therapy is LDL-cholesterol. For this purpose, the statins are the first line of therapy. Whether modification of other lipoprotein abnormalities with other drugs will provide incremental benefit remains to be determined with certainty. Nonetheless, results of several clinical trials (35–37) strongly suggest that reduction of serum triglycerides and correction of the other abnormalities of atherogenic dyslipidemia, with either fibric acids or nicotinic acid, also will reduce risk. Thus, the combination of a statin with a fibric acid (or nicotinic acid) in CHD patients with atherogenic dyslipidemia may be worthwhile. Until clinical trials have been carried out to compare combination therapy with monotherapy with statins alone, the rationale for combination therapy must be based on theoretical probability rather than proved benefit. Certainly a reasonable theoretical case can be made for combination lipid-lowering therapy in some patients with established CHD. At the same time, most patients needing combined drug therapy will have insulin resistance and the metabolic syndrome. In these patients, attention must be given to control of nonlipid risk factors as well as lipid risk factors. In particular, an effort should be made to reduce overall insulin resistance by weight control and increased physical activity. The enthusiasm for cholesterol-lowering drugs in secondary prevention should not be allowed to overshadow the benefits to be achieved from a broad-based approach to risk reduction.

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Hypertriglyceridemia and Coronary Heart Disease

Albert Oberman
Department of Medicine
Division of Preventive Medicine
The University of Alabama at Birmingham
Birmingham, Alabama 35205-4785

Robert A. Kreisberg
Department of Medicine
University of South Alabama
Mobile, Alabama 36688-0002

THE INTRICATE association between hypertriglyceridemia (HTG) and coronary atherosclerosis has been difficult to unravel. The key issue is whether HTG directly causes atherosclerotic cardiovascular disease (CVD) or whether it is merely a marker for a cluster of CVD risk factors. HTG is intimately related to a constellation of metabolic abnormalities linked to atherosclerosis, often termed the metabolic syndrome (1). This syndrome consists of a lipid triad of high triglyceride (TG): 1) small dense low-density lipoprotein (LDL) particles and low high-density lipoprotein cholesterol (HDL-C) plus insulin resistance; 2) hypertension; and 3) a prothrombotic state. Furthermore, statistical analyses to determine whether TG is an independent risk factor for coronary heart disease (CHD) are complex and difficult to interpret. This is due, in part, to the greater biologic variability in TG levels (coefficient of variation, ~20%) than in cholesterol (2, 3). Most importantly, if the effect of TG is mediated through decreased HDL-C, small dense LDL, or enhanced thrombogenicity, then adjustments for these variables highly related to TG should be made with caution in multivariate models studying TG effects. It is quite possible that the true risk of HTG is underestimated when adjustments are made for closely correlated metabolic abnormalities, such as reduced HDL-C that is in the pathway leading to atherosclerosis.

There is a growing awareness of the potential atherogenicity of TG-rich lipoproteins (TGRLPs), including very low-density lipoproteins (VLDL), chylomicrons, and their remnants, which is reflected, in part, by HTG (4–7). A fasting TG

level alone may be a relatively insensitive test for detection of abnormalities in TGRLPs. This risk association for CVD varies with the size and composition of the different TGRLPs (5, 6, 8). TGRLPs, on a particle basis, contain far more cholesterol than does LDL. Although the percentage of the particle represented by cholesterol is less in TGRLPs than in LDL, the absolute amount of cholesterol per particle is greater because of the larger size of the particle (8, 9). The cholesterol in TGRLPs contained in small VLDL, remnant VLDL, and intermediate density lipoprotein (IDL) are included in the calculated LDL cholesterol (LDL-C) derived from the Friedewald equation (2). This equation, although useful, is inaccurate when the TG level is 400 mg or higher due to the variable cholesterol enrichment of VLDL or to an increased IDL with higher cholesterol to TG ratios (2, 3).

Despite these issues, epidemiologic, interventional, and pathophysiologic studies support a relationship between HTG and atherosclerosis. Because intervention by cholesterol lowering in major trials reduces the risk of first-time or recurrent CHD events only by about 35% (10–13) compared with placebo, identification of other potential targets for therapy to further reduce the risk becomes important (14, 15). Although uncertainties about the role of TG exist, much is known about the relation of HTG to CVD. Consequently, treatment of HTG and, more specifically, increased levels of TGRLPs is more rational than intervention for the growing list of emerging, but more speculative, CHD risk factors such as procoagulants, Lp(a), small dense LDL-C, homocysteine, insulin resistance, and inflammatory markers (14, 15). We will briefly review the epidemiologic and interventional data, discuss the potential mechanisms by which HTG is related to CHD, and present recommendations for therapy.

Epidemiologic studies

Elevated TG and reduced HDL-C is a common pattern seen among patients who have had a myocardial infarction (MI) and among coronary-prone families (16). The idea that IDL and VLDL are associated with the development and progression of CHD is not new. Gofman *et al.* (17) recognized the importance of TGRLPs more than 40 yr ago and derived an atherogenic index based on lipids weighted toward the lipoprotein Sf fraction 12–400. In 1959, Albrink and Man (18) reported an association between TG levels and CHD. Subsequently, Albrink (19) postulated that two lipid disorders were atherogenic, one was related to cholesterol and involved LDL, and the other was related to TG and involved VLDL.

An early prospective study from the Cardiovascular Health Center (Albany, NY) corroborated this association of TG with CHD (20). Later, prospective studies concluded that TG was a risk factor for MI and CHD deaths, even after adjustment for other risk factors. After a 14-yr follow-up in the Stockholm Prospective Study, plasma TG was more important as a risk factor for new MI than cholesterol in a logistic multivariate analysis (21). When the men were divided into four groups according to cholesterol and TG levels, the rate of new MI was highest in those men who had high levels of both plasma lipids. In the Paris Prospective Study, TG contributed to CHD risk after adjustment for other risk factors when the cholesterol was less than 220 mg/dL (22). With extended mean follow-up of 11 yr, only TG exhibited a significant effect on CHD deaths among those with impaired glucose tolerance or diabetes (23).

In other prospective studies, the strong association between TG level and CHD in univariate analyses disappeared when other risk factors, particularly HDL-C, were added in multivariate analyses. In the Honolulu Heart Study, the TG value at ages below 60 was an independent predictor of CHD, but not at older ages (24). The Framingham Heart Study reported that elevated TG levels increased the risk of CHD among women but not men after adjustment for HDL-C (25). There was no independent association of TG levels with the 12-yr incidence of death from CHD in the Lipid Research Clinic follow-up study, except for subgroups of younger subjects with lower HDL-C and LDL-C levels (26). The association was small and not statistically significant after adjustment for plasma glucose level. Yet the Caerphilly and Speedwell studies reported TG independently related to CHD risk (27). The 1992 NIH Consensus Development Panel on Triglyceride, High Density Lipoprotein and Coronary Artery Disease concluded that there was insufficient evidence for causality between high levels of plasma TG and CHD, but that TGRLPs can be atherogenic (4).

Evidence from new, larger prospective studies and meta-analyses inextricably link TG to CHD. Austin *et al.* (28) have performed meta-analyses on population-based prospective studies, ensuring that elevations in fasting TG preceded the onset of fatal and nonfatal CHD events. Sixteen studies representing 2,445 events among 46,413 men followed for an average of 8.4 yr and five studies representing 439 events among 10,864 women followed for an average of 11.4 yr were included. A 1-mmol/L (~90 mg/dL) increase in TG was associated with a 32% increase in CHD in men and a 76% increase in CHD in women. After adjusting for HDL-C and other pertinent variables in studies with data available, there still was a significant increase of 14% for men and 37% for women (Fig. 1). In this study (28) and others (25, 29, 30), TG tends to be a more potent risk factor among women.

In the Prospective Cardiovascular Munster Study (PROCAM), an observational follow-up of 4559 middle-aged men, patients with a LDL to HDL-C ratio greater than 5.0 and TG more than 2.3 mmol/L (200 mg/dL) had the highest cardiovascular risk (31). This 4% of the population accounted for 25% of the CHD risk. Additional follow-up revealed a significant and independent association of TG to the incidence of major coronary events (32). In the Copenhagen Male Study, men in the middle and highest TG tertiles had relative CHD risks of 1.5 and 2.2, respectively, after adjusting for other factors, including LDL-C and HDL-C (33). There also was a clear gradient of risk with increasing TG levels within each level of HDL-C (Table 1). In the Baltimore Observational Long Term Study of 740 consecutive patients who underwent diagnostic coronary arteriography (70% of whom had established CHD), those with a baseline fasting TG more than 100 mg/dL had a significantly reduced survival from coronary events (34). This 18-yr follow-up study showed TG to be a significant and independent predictor of coronary events even when HDL-C and diabetes were considered. In the Bezafibrate Infarction Prevention registry, elevated TG

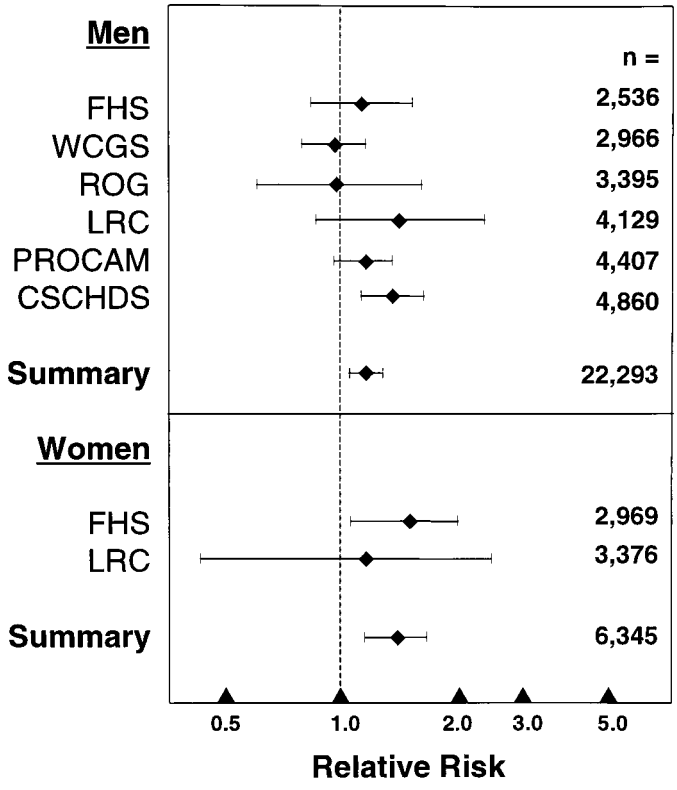

FIG. 1. Meta-analysis of TG and CVD. Multivariate-adjusted relative risk (RR) estimates and 95% confidence intervals for the association between incident CVD and a 1-mmol/L increase in TG, by gender, for those studies that adjusted for HDL-C. RR values are given on the x-axis on a natural logarithm scale. The y-axis lists each study included in the meta-analysis, ordered by sample size, and the summary RR. FHS, Framingham Heart Study; WCGS, Western Collaborative Health Study; ROG, Rome Occupational Groups; LRC, Lipid Research Clinics Follow-up Study; PROCAM, Prospective Cardiovascular Munster Study; CSCHDS, Caerphilly and Speedwell Collaborative Heart Disease Studies. Note: In a recent report from the PROCAM study, in which the follow-up period was extended to 8 yr, the multivariate RR reached statistical significance. (Modified from Ref. 28.)

levels were associated with a small but independent increased 5-yr mortality risk among CHD patients. A subgroup of these patients with elevated total cholesterol and LDL-C seemed to have an added risk (29). Evidence from observational studies and clinical trials indicates patients with a high LDL to HDL-C ratio and TG values above 200 mg/dL may benefit most from intervention (31, 35, 36).

Randomized controlled trials

Angiographic progression of CHD in the Montreal Heart Study was directly related to the concentration of IDL and inversely related to HDL-C levels (37). In the Monitored Atherosclerosis Regression Study, VLDL and IDL were directly related to progression of coronary artery lesions (38). In this study, progression of mild to moderate lesions was related to the levels of TGRLPs, particularly when LDL-C levels had been reduced. TGRLPs also predicted progression of coronary lesions in the NHLBI-type II study (39). In the Cholesterol Lowering Atherosclerosis Study, the content of apolipoprotein (apo) C-III, an inhibitor of lipoprotein lipase carried by VLDL, was directly related to progression of coronary atherosclerosis (40). The program on the surgical control of the hyperlipidemia (POSCH) also demonstrated coronary artery progression related to VLDL (41). The benefit of treating hypercholesterolemia with simvastatin was unaffected by baseline plasma TG levels in the 4-S Study (42); however, in the Cholesterol and Recurrent Events study pravastatin was more effective in reducing clinical events in patients with CHD and average LDL-C levels whose TG concentrations were less than 146 mg/dL (43).

TABLE 1. RR with 95% confidence limits for ischemic heart disease[a] (8-yr follow-up) by tertile of fasting serum TG and HDL-C

HDL-C level, mg/dL (thirds)	TG level, thirds		
	78.0 mg/dL (39.0–96.6) (n = 982)	117.8 mg/dL (97.5–140.9) (n = 973)	217.1 mg/dL (141.8–1984.6) (n = 951)
38.7 (11.2–45.7)	1	1.6 (0.6–4.0)	2.1 (0.9–5.2)[b]
51.1 (46.1–56.9)	1	1.8 (0.9–3.6)[b]	2.1 (1.0–4.4)[c]
68.1 (57.3–133.9)	1	1.1 (0.6–2.2)	2.7 (1.2–6.0)[d]
Overall	1	1.5 (1.0–2.3)[c]	2.2 (1.4–6.0)[e]

Values are mean mg/dL (range). *P* values for Cox proportional hazards regression analyses are adjusted for age and other potentially confounding factors. In all analyses, the lowest third of TG is regarded as reference category and set to 1. The table is modified from Ref. 33.

[a] RR adjusted for age and potential confounders: LDL-C, HDL-C, alcohol use, tobacco, physical activity, body mass index, systolic and diastolic blood pressure, hypertension, noninsulin-dependent diabetes mellitus, glucosuria, and low social class.

[b] $P < 0.02$.

[c] $P < 0.05$.

[d] $P < 0.01$.

[e] $P < 0.001$.

In the St. Thomas Atherosclerosis Regression Study, an angiographic study, on trial small dense LDL as well as IDL particles were associated with CHD progression (48). In the Stanford Coronary Risk Intervention Project, a predominance of small dense LDL at baseline predicted the therapeutic response of lipid-lowering therapy on CHD progression (49). Because TG levels are the most important determinant of LDL size, these observations suggest that TGRLPs may, in part, moderate an atherogenic effect through change in content and structure of LDL. Because the primary purpose of these studies was to evaluate the effects of LDL-C lowering, it is theoretically possible that TG and TGRLPs finally emerge as a risk factor when the role of LDL-C in atherosclerosis is corrected or minimized. If so, pharmacotherapy to address persisting or concomitant abnormalities in TGRLPs in patients with CHD may result in yet further risk reduction.

Interpreting trials of TG-lowering and CHD can be diffi-

cult because TG-lowering drugs (fibrates, nicotinic acid) also change the concentrations of LDL-C and HDL-C, the size of the LDL particle, and the concentration of fibrinogen and PAI-1 (50). From a pragmatic standpoint, it may not be important to know whether TG is an independent CHD risk factor or is a marker associated with atherogenic factors because atherosclerosis is multifactorial and its treatment should address HTG and all associated atherogenic factors. It is unusual for a patient to have an isolated high TG level without other coronary risk factors. This makes it difficult to attribute benefit of therapy to a change in one parameter when all changes may be anti-atherogenic. The precise mechanism may not be important if therapeutic intervention decreases morbidity and mortality.

In the Bezafibrate Coronary Atherosclerosis Intervention Trial, 81 young men with CHD were randomized to treatment with bezafibrate or placebo after baseline coronary angiography (51). Coronary angiography was repeated after an interval of ~30 months. Bezafibrate reduced angiographic progression of coronary atherosclerosis by ~65% (assessed by changes in minimum luminal diameter). In addition, clinical events occurred in 11 placebo patients but in only 3 bezafibrate-treated patients. In this study, there was no change in the concentration of LDL-C, whereas HDL-C increased by 9% and TG decreased by 35%. Overall, changes in angiographic parameters and clinical events were similar to those observed with statin regression trials.

In the Lopid Coronary Atherosclerosis Trial, 375 men with CHD and low HDL-C were randomized to treatment with placebo or gemfibrozil (52). Angiograms obtained at entry into the study were compared with those completed at 32 months. LDL-C decreased by 12% (from 148 mg/dL to 130 mg/dL), TG decreased by 40% (from 152 mg/dL to 92 mg/dL), and HDL-C increased by 12% (from 34 mg/dL to 38 mg/dL). These changes were associated with slowed progression of atherosclerotic lesions.

In the Helsinki Heart Study, a 5-yr randomized trial conducted exclusively in men without prior CHD, gemfibrozil reduced the risk of fatal CHD and nonfatal MI by 35% (from 4.1% to 2.7%; an absolute risk reduction of 1.4%) (53). By way of comparison, the absolute risk reduction in other primary prevention studies was 2.4% in the West of Scotland Coronary Prevention Study and 2.3% in the Air Force/Texas Coronary Atherosclerosis Prevention Study. The changes in LDL-C did not completely explain the response. Over 80% of the risk reduction from gemfibrozil occurred in men whose LDL to HDL-C ratio was more than 5 and whose TG was more than 200 mg/dL (35). Interestingly, this was the same group of men in PROCAM who were at highest risk of CHD. In the Veterans Administration HDL-cholesterol Intervention Trial, 2531 veterans with CHD and HDL-C less than 40 mg/dL and LDL-C less than 140 mg/dL were randomized to receive placebo or gemfibrozil for 5 yr (54). The combined clinical end point of fatal CHD and nonfatal MI was reduced by 22% (absolute reduction, 4.4%), even though LDL-C levels were unchanged by gemfibrozil. TG was reduced by 31% (from 166 mg/dL to 115 mg/dL), and HDL-C was increased by 6.8% (from 32 mg/dL to 34.2 mg/dL). The reduction in events was greater than predicted by the epidemiologic relationship between HDL-C and CHD (55). This strongly suggests that changes in other lipoproteins, coagulation factors, or other etiologic factors may have been important.

Overall, these studies further support the concept that measures that reduce levels of TGRLPs retard progression of CHD and decrease clinical events.

Pathophysiology

HTG indicates that there are increased numbers and/or increased size and TG content of TGRLPs. HTG is genetically, biochemically, and clinically heterogeneous. Some patients with HTG are at increased risk of developing CHD, and some are not; currently, it is impossible to separate those who are from those who are not based solely on their TG level. This suggests that certain TGRLPs may be atherogenic or are associated with metabolic abnormalities that are atherogenic. When HTG is due to large TG-enriched VLDL, there may be relatively less VLDL-C than when it is due to increased numbers of small/remnant VLDL, which carry proportionately more cholesterol (56). The contribution of these different-sized VLDL particles to non-HDL-C would be very different.

It is also likely that TGRLPs change the composition or amounts of other lipoproteins to create a more atherogenic milieu. Furthermore, there is an inverse relationship between TG level and the presence of small dense LDL particles (5). Except when the pattern of small dense LDL particles is inherited, changes in TG over the relatively narrow range of 80–250 mg/dL is associated with a change in LDL size and a shift from large buoyant particles to small dense particles. Approximately 90% of persons with TG of 250 mg/dL will have converted to an atherogenic LDL profile characterized by a predominance of small dense particles (57). This raises several questions: 1) are small dense LDL particles responsible for the atherogenicity of TGRLPs? 2) are small LDL particles a marker for atherogenic TGRLPs? and 3) should we pay more attention to changes in TG levels below 200 mg/dL, a range considered by the National Cholesterol Education Program (NCEP) to be normal but shown in several studies to confer excess risk (33, 34)?

A prevailing concept is that HTG due to the accumulation of IDL, small VLDL, and remnants of VLDL and chylomicrons will be atherogenic because their relatively small particle size enables them to infiltrate the artery wall in a manner similar to LDL (58) and initiate the cascade of events that lead to atherosclerosis (59). These events include lipoprotein oxidation, adherence, and migration of monocytes into the artery wall; differentiation of monocytes into macrophages; formation of foam cells; recruitment of T-lymphocytes; and the development of inflammation; all are related to the release of adhesion molecules and other cytokines (59). Another explanation for the atherogenicity of IDL and small VLDL is their ability to be converted to LDL. In addition, the association of a hypercoagulable state with HTG may promote thrombosis in patients with underlying atherosclerosis (1). Larger TGRLPs (large VLDL, chylomicrons), such as occur with estrogen replacement, the use of alcohol, and in patients with familial HTG and familial hyperchylomicronemia, are less likely to enter the wall of the artery and, therefore, may be less atherogenic. It is nevertheless possible that

lipolysis of such particles at the arterial surface may have pathologic consequences. For some individuals a more atherogenic form of HTG may be suspected by the finding of a strong family history of premature CHD or by the presence of disorders associated with an increased risk of CHD, such as diabetes mellitus, chronic renal disease, and familial combined hyperlipidemia. TGRLPs may be more important for the progression of mildly stenotic coronary artery lesions (<50% diameter stenosis) than for severe stenosis (6). This may have important clinical relevance because it has been well documented that the lesions predictive of coronary events tend to be through plaque rupture in atheromata, constricting less than 50% of the coronary artery lumen (60).

We need better clinical laboratory techniques to differentiate patients with atherogenic HTG from those with nonatherogenic HTG, much as we now do by fractionating cholesterol in patients with hypercholesterolemia and separating those with increased LDL-C from those with increased levels of HDL-C. Some studies have pointed out the importance of apo B in distinguishing patients who are at greater *vs.* lesser risk for CHD (45, 61, 62). Apo B is the major apo in chylomicrons, VLDL, IDL, and LDL. In contrast to cholesterol, there is a constant 1:1 molar ratio of apo B per LDL and VLDL particle, providing an estimate of atherogenic lipoprotein particle number (62). Currently, because of a lack of standardization of the procedure, the use of apo B as a risk factor cannot be generally recommended for clinical purposes. However, the correlation between non-HDL-C (total cholesterol minus HDL-C) and apo B 100 concentrations seems to be especially strong in patients with TG less than 300 mg/dL (correlation coefficient, 0.95), as well as in those with higher TG (correlation coefficient, 0.80) (63). The non-HDL-C index provides another means for assessing the atherogenicity of plasma lipids and potential for lipid-lowering therapy. Once the lipoprotein abnormality has been established, non-HDL-C in hypertriglyceridemic patients may be a better guide than LDL-C to CVD risk and efficacy of lipid-lowering agents (63). The LDL-C may underestimate the risk contributed by elevated TGRLPs because the cholesterol in remnant lipoproteins is not taken into account (64). Non-HDL-C contains all of the cholesterol present in lipoprotein particles now considered to be potentially atherogenic [VLDL, IDL, LDL, and Lp(a)]. Unlike the Friedewald formula, this index does not require any assumptions about the relation of VLDL-C to plasma TG concentrations. Perhaps the non-HDL-C value is the best currently available way of making a distinction among atherogenic lipoprotein profiles (65).

Another consideration is postprandial increases in TG, which may be a more important indicator of atherogenicity than the fasting TG level (66). Postprandial levels of TG and small chylomicron remnants have been related to CHD and progression of coronary atherosclerosis (5, 67, 68). Plasma TG at 2 h, LDL-C, and basal proinsulin also independently related to the common carotid intima-media thickness in healthy middle-aged men when other risk factors were taken into account (69). The postprandial increase in TG (the area under the curve following a fat challenge) is directly related to the fasting TG level even when it is within the normal range. Consequently, exposure of the endothelium and vessel wall to atherogenic TGRLPs will be better reflected by the mean daytime TG level than by the fasting TG level.

In addition to the atherogenicity of TGRLPs, it is likely that the numerous nonlipid metabolic abnormalities associated with insulin resistance play an important role in the development of CHD (1). Consequently, simply reducing the concentration of TGRLPs and TG levels with drugs may only partially reduce risk if insulin resistance and its attendant abnormalities are not also corrected with aggressive lifestyle changes: weight loss, exercise, and so forth. Even though the mechanisms are poorly understood, TGRLP levels are important in the development of CVD (7). Current evidence indicates that TG should be evaluated and reduced to the most desirable levels as dictated by the lipoprotein profile and accompanying nonlipid risk factors. The NCEP Adult Treatment Panel II modified the criteria proposed by the 1992 Consensus Development Conference and defined HTG as borderline high (200–400 mg/dL), high (400–1000 mg/dL), and very high (>1000 mg/dL) (70). Whether these cutoffs are optimal for treating HTG and whether lowering TG can reduce CHD events awaits appropriate large-scale trials.

Provisional therapeutic recommendations

The evidence from research on basic mechanisms, epidemiologic relationships, and the few randomized controlled trials relating TG to CVD is compelling, as is the plausibility that TGRLPs are atherogenic (71). This inevitably leads to the conclusion that patients with increased TGRLPs (as reflected by the TG concentration) merit therapy. However, the TG threshold for initiation of therapy and the goals of therapy cannot be clearly articulated. Consequently, recommendations concerning therapy must be provisional and amenable to prompt revision, as our understanding of this controversial area evolves. We propose that a desirable TG level is less than 150–200 mg/dL and that the non-HDL-C level should be less than 160 mg/dL [sum of LDL-C ≤130 mg/dL + VLDL-C ≤30 mg/dL (TG ≤150 mg/dL)] in high-risk patients and less than 130 mg/dL in those who have CVD. Therapy should be considered when the TG or non-HDL-C exceeds these limits. As a general rule, the desirable non-HDL-C level can be estimated by adding 30 mg/dL to the current NCEP guidelines for LDL-C.

The non-LDL-C level should be optimized in patients with combined hyperlipidemia (≤160 mg/dL for primary prevention and ≤130 mg/dL for secondary prevention). The target TG for achieving this goal would be 150 mg/dL if NCEP LDL-C goals are also achieved. The non-HDL-C will be important for assessing the efficacy of therapy in patients at high risk of CHD, such as those with combined hyperlipidemia, type 2 diabetes mellitus, and end-stage renal disease, in whom dyslipidemia is common. In type 2 diabetic patients, as well as those with CVD, the LDL-C and non-HDL-C goals should be less than 100 mg/dL and less than 130 mg/dL, respectively, because the risk of fatal CHD and nonfatal MI in asymptomatic diabetic patients is similar to that of nondiabetics with established CHD (72).

The following guidelines for lipid management for hypertriglyceridemic patients are suggested:

- Repeat fasting lipid (total cholesterol, LDL-C, HDL-C, TG) measurements must be obtained to confirm the presence of HTG and associated lipid abnormalities before initiating therapy. Secondary causes of HTG also should be excluded at this time.
- Lifestyle changes are fundamental and should be implemented as the first line of therapy. Such changes should include weight reduction (73, 74), use of diets that limit saturated fat (75–77) regular physical activity (74, 78, 79), cessation of cigarette smoking (80), reduction or elimination of alcohol consumption (81), and, if diabetic, fastidious control of hyperglycemia (82, 83). HTG in diabetic patients is multifactorial, and intensive glycemic control will often improve HTG but not normalize the TG. Associated metabolic abnormalities should also be addressed to reduce the global risk of CVD.
- The only role for fish oil (ω-3 fatty acids) supplements is in treating resistant HTG inadequately controlled by diet and drugs. The TG response to fish oil is dose dependent; TG concentrations decrease up to 30% at a daily dose of 3 g and up to 50% at a daily dose of 9 g (44). Intake of fish oil has a minimal, although variable, effect on cholesterol and tends to slightly increase LDL-C. It also enhances fibrinolysis and reduces platelet aggregation (84). Contrary to earlier views, fish oil supplementation does not seem to alter glucose tolerance (85).
- *Elevated LDL-C and TG 200–400 mg/dL* (Fig. 2). The first priority of therapy in patients with HTG is treatment of an elevated LDL-C (70). The more potent statins frequently will control HTG as well as increased LDL-C, particularly when the increase in LDL-C is proportionally greater than the increase in TG when the TG is less than 400 mg/dL. The magnitude of the TG reduction with statins is directly related to the baseline TG value (44). Resins are not recommended for LDL-C reduction if TGs are borderline or higher because they tend to increase VLDL synthesis and TG levels (44). Generally, statins do not reduce TG by more than 35–40%, and some patients require a greater reduction (86). If statins do not reduce the TG to less than 150–200 mg/dL, then additional therapy may be required. Nicotinic acid can be substituted for a statin, contingent on patient acceptance, with the hope of reaching a dose that optimally reduces LDL-C and TG and increases HDL-C. The use of nicotinic acid is relatively contraindicated in patients who have the metabolic syndrome, in whom it may precipitate frank diabetes, or patients who have diabetes, in whom it worsens hyperglycemia (87, 88). However, there is relatively little data to support these recommendations (87, 88). Larger, better designed trials of nicotinic acid for treating dyslipidemias in patients with diabetes are needed.

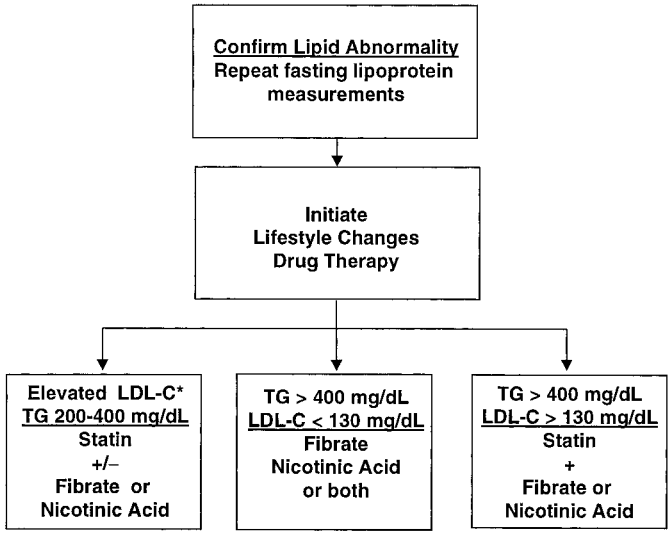

FIG. 2. Management of HTG. After careful assessment of the dyslipidemia, the initial effort should be directed toward lifestyle changes. Drug therapy depends on the level of TG elevation and whether or not it is accompanied by an elevated LDL-C.

Alternatively, fibrates or nicotinic acid can be added to a statin to take advantage of their complementary actions on lipoproteins. Despite the warnings against use of statins and fibrates or nicotinic acid in combination, they are usually safe and effective (50, 89–91). The major concern, severe myopathy and rhabdomyolysis, occurs in approximately 1% of patients on combination therapy (89). Such adverse events should be preventable by judicious use of this combination and careful monitoring. Factors that predispose to adverse interactions (*e.g.* hypothyroidism, renal failure, use of interacting medications, and so forth) should be identified before combining these drugs. To warrant the additional risk of using these drugs in combination, the risk of future CVD events should be high, at least 10% over the ensuing 5-yr period. The same is true for the combined use of statins with nicotinic acid. Statins are less effective in reducing the LDL-C in patients with combined hyperlipidemia than in patients with isolated increases in LDL-C. The LDL-C response to fibrates cannot be predicted accurately. This is due to increased efficiency of "downstream" conversion of VLDL to LDL. If these added LDL particles cannot be cleared from the blood, levels of LDL-C will increase during administration of fibrates.

- *TG more than 400 mg/dL and LDL-C less than 130 mg/dL.* Fibrates are the drugs of first choice for patients with TG more than 400 mg/dL and LDL-C less than 130 mg/dL. Nicotinic acid also may be a reasonable option if the TG is not excessively high. Because the mechanisms of action of fibrates and nicotinic acid are different, they can be successfully used in combination in some patients and should be considered in patients with massive HTG or those at risk for pancreatitis. Because of the limitations of the Friedewald equation, the LDL-C concentration cannot be calculated in such patients. Using a reliable method to directly measure LDL-C may be helpful. Therapy should be initiated with the goal of reducing TG to less than 400 mg/dL, allowing additional therapeutic decisions to be made when the LDL-C can be accurately assessed.

Patients with HTG of this magnitude frequently have a low or normal LDL-C, which tends to increase as the TG decreases. This may be a problem in patients with low or

normal LDL-C at baseline treated with fibrates. Fibrates, however, increase the buoyancy of LDL particles and perhaps makes them less atherogenic (57).

- *TG more than 400 mg/dL and LDL-C more than 130 mg/dL.* The drugs of choice for TG more than 400 mg/dL are fibrates and nicotinic acid. If tolerated, nicotinic acid in this situation may be preferable because of its LDL-C lowering effect. However, the addition of a statin may be necessary if the LDL-C is elevated. As noted above, the combination of fibrates and nicotinic acid can be used and should be considered in patients with marked HTG or those at risk for pancreatitis.

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The Role of Non-High-Density Lipoprotein-Cholesterol in Evaluation and Treatment of Lipid Disorders

Richard J. Havel and Philip H. Frost
Cardiovascular Research Institute and Department of Medicine
University of California–San Francisco
San Francisco, California 94143

PLASMA lipoproteins containing apolipoprotein B (apo B) are generally considered to be atherogenic, whereas high-density lipoproteins (HDLs) that lack apo B are considered to be antiatherogenic and, thus, to confer protection against atherosclerotic cardiovascular disease. The Adult Treatment Panel of the National Cholesterol Education Program (NCEP) recommends measurement of total cholesterol and HDL-cholesterol as a screening tool to estimate risk of coronary heart disease in healthy adults every 5 yr (1). The NCEP also recommends estimation of "low-density lipoprotein (LDL)"-cholesterol in all persons with low HDL-cholesterol (<35 mg/dL) and in those with total cholesterol more than 240 mg/dL to determine the need for dietary or drug treatment. For clinical purposes, LDL-cholesterol is estimated by the Friedewald Formula in subjects who have fasted overnight as: total cholesterol minus (HDL-cholesterol plus plasma triglycerides/5). In addition to "true" LDL-cholesterol, this value includes cholesterol in intermediate density lipoproteins (IDLs) and Lp(a), two relatively minor apo B-containing lipoproteins that are considered to be particularly atherogenic (2). Cholesterol in very LDLs (VLDLs), however, is not taken into consideration. It would be easy for the NCEP to include VLDL-cholesterol in risk estimation by simply subtracting HDL-cholesterol from total cholesterol to obtain "non-HDL-cholesterol." Several immediate practical and theoretical advantages would accrue. First, because total

and HDL-cholesterol change little after an ordinary meal, the patient would not need to fast overnight to determine whether treatment is indicated. Second, measurement of triglycerides, which does require fasting, would not be needed. Third, and most important, cholesterol in all potentially atherogenic lipoprotein species would be included. Here, we review the historical basis for choosing "LDL"-cholesterol over non-HDL-cholesterol for initial risk assessment and indicate why we believe the time has come to move to non-HDL-cholesterol as an alternative, not only for risk assessment, but also for evaluating the effectiveness of cholesterol-lowering therapies.

Evidence from early population studies, animal experiments, and clinical-pathological observations implicated plasma cholesterol as an important and even essential component of atherogenic risk (1). With the knowledge that all plasma cholesterol is carried in plasma lipoproteins came the realization that some species of lipoproteins may be particularly atherogenic and that others may even confer protection against plaque formation. One common monogenic form of hypercholesterolemia that confers greatly increased risk of premature coronary heart disease (heterozygous familial hypercholesterolemia) was found to be associated with striking elevation of LDL, with little or no change in the concentration of VLDL or HDL (3). Separation of cholesterol in VLDL, LDL (or IDL + LDL), and HDL by ultracentrifugation made it practical to classify primary (and presumably genetic) hyperlipoproteinemias by variable elevations of LDL and VLDL and, rarely, of chylomicrons (4). With the addition of lipoprotein electrophoresis, this led to a phenotypic classification of such abnormalities (5). Type IIa was phenotypically (but not genetically) equivalent to familial hypercholesterolemia. With the advent of a simple precipitation method to separate HDL from apo B-containing lipoproteins, the Friedewald formula could be applied to permit phenotypic classification without the need for ultracentrifugation (6). Thus, estimated LDL-cholesterol became a readily accessible analyte for investigators and clinicians. Early evidence had also accrued that at least some species of VLDL are particularly atherogenic, and it was evident that measurement of plasma triglycerides could provide a generally reliable measure of the concentration of triglyceride-rich lipoproteins, mainly VLDL (7). Questions were subsequently raised about the usefulness of plasma triglyceride concentrations as a risk indicator (8) and, thus, inferentially about the contribution of triglyceride-rich lipoproteins. Triglycerides continued to be measured, primarily to permit estimation of LDL-cholesterol in patients who fasted overnight.

It is now increasingly recognized that the dismissal of triglycerides as an independent atherogenic risk factor was incorrect (9). Single measurements of triglycerides may particularly underestimate their association with risk because of the inherently greater variability of triglycerides as compared with LDL-cholesterol and HDL-cholesterol and also because of the strong inverse relationship between the concentration of plasma triglycerides and HDL-cholesterol, which invalidates multivariate analysis involving these two analytes. Prospective studies of lesion progression and clinical outcomes have implicated remnant-like characteristics of triglyceride-rich lipoproteins (such as cholesterol-enrichment) in addition to or, in some cases, instead of LDL as culprit lipoproteins (10, 11). Other evidence suggests that, as with plasma cholesterol, concentrations of triglycerides conferring increased risk may fall well within the range commonly considered as "normal" because they are so prevalent (12). Furthermore, it has been consistently found that multiple lipoprotein abnormalities, particularly those involving all three major lipoprotein classes—moderately elevated LDL-cholesterol and low HDL-cholesterol, accompanied by hypertriglyceridemia (elevated VLDL)—confer a much higher relative risk of atherosclerotic disease than elevated LDL-cholesterol alone (2, 11). These multiple abnormalities are commonly associated with elements of the metabolic syndrome encompassing central obesity, insulin resistance, and hypertension, with or without overt type II diabetes mellitus.

Screening for dyslipoproteinemias as atherogenic risk factors should be simple, precise, and inexpensive. Inclusion of VLDL-cholesterol in screening by measurement of non-HDL-cholesterol fulfills these criteria better than the current NCEP algorithm and gets more directly at the issue of the cholesterol content of triglyceride-rich lipoproteins than measurement of triglycerides *per se* (13). In the Systolic Hypertension in the Elderly Program, plasma triglyceride concentration was an independent risk factor for coronary heart disease mortality in analyses that included LDL- and HDL-cholesterol, but not in analyses with non-HDL- and HDL-cholesterol (14).

Another approach to routine estimation of apo B-containing lipoproteins is immunochemical estimation of plasma apo B concentration. In several studies, apo B concentration has been a better marker of coronary heart disease than LDL-cholesterol (15). As might be expected, apo B concentrations are highly correlated with those of non-HDL-cholesterol. With a chemical approach to apo B estimation, correlation coefficients exceeded 0.9 in men with normal to modestly increased total cholesterol and triglyceride concentrations (16). Although the size and, presumably, the cholesterol content of LDL falls with increasing plasma triglycerides, the ratio of apo B to total cholesterol in that study was 0.6, irrespective of plasma triglyceride concentrations. The ratio of apo B to cholesterol is ≈0.6 in LDL and VLDL from normotriglyceridemic persons, but is usually lower than 0.6 in VLDL of persons with hypertriglyceridemia (17), reflecting cholesteryl ester-enrichment of hypertriglyceridemic VLDL. Measurement of non-HDL-cholesterol will include this cholesterol enrichment, but that of apo B will not. Although apo B can now be measured with adequate accuracy and precision (15), measurement of total cholesterol and HDL-cholesterol is already widely available and well standardized.

Non-HDL-cholesterol may better reflect changes in plasma lipoproteins occurring with lipid-lowering therapy than do changes in LDL-cholesterol alone (13). For example, lipid-lowering drugs (including the statins, fibrates, and nicotinic acid) all lower VLDL, IDL, and LDL concentrations. Furthermore, statins and nicotinic acid may reduce VLDL-cholesterol disproportionately to LDL-cholesterol (*i.e.* they reduce the cholesterol content of VLDL particles). In the Scandinavian Simvastatin Survival Study, baseline non-HDL-cholesterol predicted cardiovascular events in the placebo group better than baseline LDL-cholesterol, presumably because the former reflected the contribution of

TABLE 1. Mean serum lipids and lipoprotein cholesterol concentrations (mg/dL) for various ranges of serum triglycerides in 1043 consecutive patients seen in a lipid clinic practice (data from Ref. 13)[a]

Range of serum triglycerides (mg/dL)	N	Serum		Lipoprotein cholesterol				% Non-HDL cholesterol in VLDL
		Cholesterol	Triglycerides	VLDL	IDL + LDL	HDL	Non-HDL	
<201	548	263	123	18	191	54	209	8.6
201–400	270	276	277	49	184	43	233	21.0
401–600	73	285	502	99	149	37	247	40.1
601–1,000	70	293	797	143	118	32	261	54.8
1,001–2,000	43	363	1358	233	102	28	335	69.5
>2,000	39	622	3445	506	93	23	599	84.5

[a] Apolipoprotein E2/E2 homozygotes (n = 22) have been excluded.

Lipoproteins were separated by a combination of ultracentrifugation and precipitation techniques. LDL-cholesterol was calculated as the difference between serum cholesterol and cholesterol in HDLs and VLDLs [thus containing IDL and Lp(a) cholesterol].

triglyceride-rich lipoproteins to events (18). In those treated with simvastatin, percentage changes in non-HDL-cholesterol were equivalent to those in LDL-cholesterol in predicting event reduction, and both were greater than percentage changes in plasma apo B concentration. Available evidence, although sparse, is consistent with the expectation that changes in non-HDL-cholesterol are as good as LDL-cholesterol in predicting clinical benefit of therapeutic interventions directed at plasma lipoproteins.

How should this evidence be used? LDL-cholesterol has become the standard analyte, with HDL in a supporting role for risk assessment, and a nod to plasma triglycerides for those with levels exceeding 200 mg/dL (1). In our experience, the current algorithms are often confusing to practitioners. At least in theory, non-HDL-cholesterol alone (based on total cholesterol and HDL-cholesterol) should suffice, not only for screening, but also for initial risk assessment in primary prevention, obviating the need for a fasting blood specimen.

Measurement of non-HDL-cholesterol clearly becomes more important the higher the plasma triglyceride concentration. In a group of 548 lipid clinic patients with plasma triglyceride concentrations below 201 mg/dL (mean, 123 mg/dL), mean VLDL-cholesterol concentration was 18 mg/dL and that of LDL-cholesterol was 191 mg/dL (Table 1). Thus, VLDL-cholesterol constituted 8.6% of non-HDL-cholesterol. However, in those patients with higher plasma triglyceride concentrations, the percentage of non-HDL-cholesterol contributed by VLDL-cholesterol increased rapidly and exceeded 50% at triglyceride concentrations above 800 mg/dL. For individuals with plasma triglycerides below 200 mg/dL, non-HDL-cholesterol and LDL-cholesterol may be close to equivalent for risk assessment, and the latter could be retained. This approach, however, begs the question of why triglycerides should still be measured and the patient, thus, required to fast.

Elsewhere, we have suggested that the cut-points for risk assessment in primary and secondary prevention be raised by 30 mg/dL if non-HDL-cholesterol is used in place of LDL-cholesterol (2, 13). In consideration of the data shown in Table 1, that increment might be reduced to 20 mg/dL. This is the average VLDL-cholesterol concentration equivalent to plasma triglycerides of about 130 mg/dL, the level at which the "atherogenic lipoprotein phenotype" (characterized by reduced size of LDL particles and other changes in lipoproteins that are associated with increased coronary heart disease risk) becomes increasingly prevalent (Krauss, R. M., personal communication).

In summary, the use of non-HDL-cholesterol in primary prevention recognizes the contribution of triglyceride-rich lipoproteins to atherosclerotic disease and simplifies the physician's initial assessment of disease risk and the continuing response to therapy. When drugs are indicated, triglycerides should also be measured, however, to help establish a diagnosis and to guide specific therapy. The lipoprotein pattern will, therefore, still need to be assessed in some patients in the primary prevention setting and almost always for secondary prevention. Establishment of the lipoprotein pattern is also needed to evaluate kindred relationships.

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Is All Coronary Heart Disease Prevention in Type 2 Diabetes Mellitus Secondary Prevention?

Steven M. Haffner
Department of Medicine
University of Texas Health Science Center at San Antonio
San Antonio, Texas 78284-7873

DIABETES IS associated with a 2- to 4-fold increase in coronary heart disease (CHD) (1–3). In the overall population, clinically established CHD is associated with a 3- to 7-fold increase in CHD mortality (4). Plasma cholesterol levels are a strong predictor of risk in patients with clinical CHD (4) and diabetes (3). The much higher risk of CHD in patients with clinical CHD and diabetes has led both the National Cholesterol Education Program (NCEP) (5) and the American Diabetes Association (ADA) (6) to recommend lower goals for low-density lipoprotein cholesterol (LDL-C) in these risk groups.

Clinical trials of lowering of LDL-C in diabetic subjects with clinical CHD: subgroup analyses

The possible role of lipid lowering to reduce CHD in diabetic patients has been enhanced since the publication of data on the efficacy of lipid lowering with simvastatin (7, 8) and pravastatin (9) in diabetic subgroups with preexisting CHD. In the Scandinavian Simvastatin Survival Study (n = 202) (4S) (8), diabetic patients received more benefit from lipid lowering than did nondiabetic patients (55% *vs.* 32% reduction, respectively) in lowering major CHD (fatal + nonfatal CHD); in the Cholesterol and Recurrent Events (CARE) study (n = 586) (9), similar benefits were seen in diabetic and nondiabetic subgroups [27% *vs.* 25% reduction in CHD events (major CHD + revascularizations)]. Unfortunately, no current data exist on possible effectiveness of statins in diabetic patients without CHD. The Helsinki Heart Study (10) gemfibrozil reduced CHD in diabetic patients by 60%, although the result was not significant because of the small number of subjects (n = 135) and the lower event rate in this primary prevention cohort.

Diagnosis of CHD in diabetic subjects compared with nondiabetic subjects

Diabetic patients with CHD have a worse prognosis than nondiabetic patients with CHD (11–13). Because of high case fatality rates in diabetic patients with preexisting CHD (11–13) and previous data on the effectiveness of LDL-C lowering in diabetic subjects (8, 9), it has been suggested that new statin *vs.* placebo-controlled trials in the prevention of CHD should not be "initiated" in diabetic patients with preexisting CHD (14).

The 1-yr case fatality rate for first myocardiol infarction (MI) (from the onset of symptoms, thus including prehospitalization mortality) in the FINMONICA (13) was 45% in diabetic men and 39% in diabetic women. These 1-yr case fatality rates were significantly higher than the rates in nondiabetic patients (38% and 25%, respectively). Of the diabetic patients who died, 50% of men and 25% of women died before hospitalization. These patients, by definition, could not benefit from secondary prevention strategies, indicating that aggressive management of cardiovascular risk factors in diabetic subjects (especially diabetic men) should precede the onset of clinical CHD.

Current recommendations for treatment of dyslipidemia

The NCEP (5) suggests an initiation level for pharmacological therapy in subjects with clinical CHD more than 130 mg/dL and a treatment goal of less than 100 mg/dL. The recent ADA recommendation (6) modifies the above recommendation by suggesting the initiation level be 100 mg/dL or greater, whereas the goal remains less than 100 mg/dL. The lower initiation level was, in part, based on the greater risk of recurrent CHD in diabetic than in nondiabetic patients with clinical CHD. It may be questioned why the goal for diabetic subjects with prior CHD should not be much lower than 100 mg/dL (*i.e.* LDL <70 mg/dL); however, in the absence of clinical trial data in either diabetic or nondiabetic patients of better outcomes for much lower LDL cutpoints than with an LDL-C of 100 mg/dL, this was not indicated.

The current NCEP guidelines (5) for diabetic subjects without clinical CHD varies depending on the presence of at least two other cardiovascular risk factors. Thus, the LDL-C level for initiation of therapy varies from 160–190 mg/dL, and the LDL-C goal varies from 130–160 mg/dL. The new ADA guidelines (6) are considerably more aggressive. Considering that diabetic women are relatively (although perhaps not absolutely) at greater risk of CHD than diabetic men, the ADA considered all diabetic patients as having "2 risk factors." In addition, the ADA recommends that the LDL-C level for initiation of therapy and the goal of therapy be set at 130 mg/dL. A footnote to one of the tables in the ADA report suggested that the goal for LDL-C might be less than 100 mg/dL if there were additional CHD risk factors (smoking, family history of CHD, low high-density lipoprotein cholesterol, hypertension, or microalbuminuria). It is expected that many, if most, diabetic patients have additional risk factors for CHD.

Vascular disease in diabetic and nondiabetic patients with and without CHD

One possibility in assessing whether diabetic patients, irrespective of the presence of CHD, should have as aggressive lipid lowering as patients with clinically established CHD is to examine the risk of CHD and cardiovascular disease events in diabetic subjects with and without prior CHD (rel-

ative to nondiabetic subjects with and without prior CHD). In previous reports, the excess of CHD risk in patients with prior MI (3- to 7-fold) (4) is higher than the excess risk of CHD in diabetic patients (2- to 4-fold) (1–3), but comparisons are difficult across different populations. Furthermore, patients with diabetes are overrepresented in patients with prior MI (1–3), and diabetic patients with MI have a worse prognosis than nondiabetic patients with CHD (11–13). Thus, the risk of recurrent CHD in the overall population might be overestimated by the inclusion of diabetic patients in previous studies.

We have recently examined this issue in a 7-yr follow-up in 1373 nondiabetic subjects and 859 diabetic subjects from the East West study, a population-based study of diabetes in Finland (15). The 7-yr incidence of MI in nondiabetic patients with and without MI at baseline was 18.8% and 3.5%, respectively ($P < 0.001$), whereas the 7-yr incidence of MI in diabetic patients with and without MI at baseline was 45.0% and 20.2%, respectively ($P < 0.001$). The hazard ratio for CHD mortality for diabetic patients without prior MI compared with nondiabetic patients with prior MI was not significant (hazard ratio, 1.4; 95% confidence interval, 0.7, 2.6) after adjustment for age and gender, suggesting similar prognosis in the two groups.

To further assess this issue (16), we compared the intima-media wall thickness (IMT) in the common carotid artery (CCA) and internal carotid artery (ICA) in 43 diabetic patients with clinical CHD, 446 diabetic patients without clinical CHD, 47 nondiabetic subjects with clinical CHD, and 975 nondiabetic subjects without clinical CHD in the Insulin Resistance Atherosclerosis Study (IRAS). Both diabetes and CHD were associated with increased atherosclerosis in the CCA. Likewise, diabetes was significantly associated with increased atherosclerosis in the ICA; however, CHD was not associated with ICA IMT. As expected, diabetic patients with coronary artery disease had the greatest IMT CCA (0.948 mm), whereas nondiabetic patients without coronary artery disease had the least atherosclerosis (CCA, 0.792 mm). Subjects with diabetes but without CHD had slightly greater IMT (CCA, 0.868 mm) than nondiabetic subjects with CHD (CCA, 0.861 mm), although these differences were not statistically significant. These two preliminary reports suggest that diabetic patients without preexisting vascular disease have similar risk of CHD as nondiabetic subjects with vascular disease.

Would treating all diabetic patients as if they had clinical CHD be too costly?

If diabetic patients were treated to the same goal as nondiabetic patients with prior CHD, as defined by NCEP (5), the initiation level for pharmacological treatment of LDL-C would be more than 130 mg/dL and the LDL cholesterol goal would be less than 100 mg/dL; in this case, most diabetic patients would be eligible for pharmacologic lipid lowering therapy. This could imply a large increase in pharmacological therapy and, thus, could produce an objectionable increase in health care expenditures. No cost benefit data are available for lipid lowering in diabetic patients. Recent data based on 4S study (*i.e.* secondary prevention) suggest a 34% reduction in hospitalization (17), which would markedly reduce the cost of HMG-CoA reductase inhibitor therapy. In a further analyses of the 4S data (18), the investigators suggested that for some patients, pharmacologic therapy might be cost-saving, once indirect costs associated with morbidity of CHD were taken into account. Because the risk of CHD in diabetic patients without prior CHD is similar to that of nondiabetic subjects with prior CHD, it is possible that lipid lowering might be cost effective in diabetic patients even without prior CHD. However, cost-benefit studies should be done specifically for diabetic patients.

Conclusions

Diabetic subjects without prior CHD have a similar degree of atherosclerosis and rate of CHD as nondiabetic patients with prior CHD. Because LDL-C lowering with HMG-CoA reductase inhibitors seems to be at least as effective in diabetic patients as in nondiabetic patients, a strong case can be made that diabetic patients without vascular disease should be treated similarly to nondiabetic patients with vascular disease, with respect to aggressive treatment of lipid therapy. Definitive data, however, need to be collected from clinical trials in diabetic patients without vascular disease.

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Hyperlipidemia: Diagnostic and Therapeutic Perspectives—Random Thoughts and Opinions

Robert A. Kreisberg
University of South Alabama
Mobile, Alabama 36688

IT IS CLEAR that secondary prevention of coronary heart disease (CHD) events is cost-effective. The emphasis now should be on making sure that all eligible patients are identified and treated; something that we have not done very well, so far. Although recurrent myocardial infarction (MI) has been reduced by 2–3% and CHD death by 4–5% annually, the incidence of first MI has not changed, representing a failure in primary prevention. Half of first MIs occur in patients without previous symptoms, and the sad fact is that 25–50% are fatal. Secondary prevention only works for those who survive their first event. Waiting until patients have symptoms of CHD is waiting too long for some. Primary prevention of CHD has obvious implications, particularly if patients at intermediate and high risk for cardiac events can be identified and treated. However, the prevention of clinical events is not the same as prevention of atherosclerosis. Prevention of atherosclerosis requires early and extensive lifestyle changes to prevent or retard the development of the earliest lesions, fatty streaks, and their progression to unstable lesions. As good as lipid-lowering therapy is, it is still imperfect because all intervention studies show a substantial residual risk of 65–70%. Consequently, prevention of disease is much better than prevention of events. Some of the residual risks in these patients reflect the presence of coexistent, but suboptimally treated, traditional CHD risk factors such as hypertension, smoking, and diabetes mellitus that were present, to varying degree, in patients participating in these studies. Some of the residual risks may also be due other recently identified but less well characterized and understood risk factors that also predispose to clinical events. These "emerging" or "conditional" risk factors include, but are not limited to, triglyceride-rich lipoproteins (TRLs), Lp(a), small dense low-density lipoprotein (LDL) particles, homocysteine, oxidative milieu, a procoagulant state, insulin resistance, and C-reactive protein (CRP). Although there is considerable basic information and epidemiologic data that support an important role for some of these factors in atherosclerosis, there is, as of yet, no clear evidence that specific therapy influences CHD risk. The use of antioxidant vitamins or folate, for example, makes perfect sense but may subsequently be incorrect. It is also clear that markers of inflammation, such as CRP, identify patients who have advanced unstable atherosclerotic lesions that are vulnerable to rupture. CRP may be an excellent test for targeting high-risk patients for primary or secondary prevention who would benefit from aggressive therapy.

In patients with established CHD cholesterol-lowering therapy prevents CHD events by presumably modifying the atherosclerotic plaque and making it less susceptible to rupture. This is due in large part to a reduction in LDL-cholesterol (LDL-C), reduced entry of LDL particles into the artery wall, a subsequent reduction in oxidized LDL, reduction or reversal of the ongoing inflammatory and immunologic responses in the vessel, and improvement in endothelial function and in myocardial perfusion. The relationship of the nonlipid properties of statins (on endothelial function, hemostasis, and the cellular, immune, and inflammatory responses of the vessel) to the atherosclerotic process are of great interest, but it is too soon to know whether these or other properties are important. It is becoming increasingly clear that drugs of the same class may not be completely identical. This may be true of the statins where LDL-C lowering may be the major, but not exclusive, mechanism by which CHD risk is reduced. Statins may have antiatherogenic properties independent of their lipid effects. Rigorous head-to-head studies are necessary to learn more about potential mechanisms of action and whether differences in statins are clinically important.

The issue of whether "lower is better" for LDL-C has been contentious. No intervention study has been designed to answer this question, and most of the statements about this issue come from post-*hoc* analyses of patients at progressively lower LDL-C levels. The number of patients in these subgroups is a small fraction of the number needed to have meaningful statistics. Indirect evidence from other studies support that "lower is better," and studies are underway to answer this question. In the postcoronary artery bypass graft trial an LDL-C of less than 100mg/dL was better than one of 135 mg/dL. In the Atorvastatin *versus* Revascularization Trial (AVERT), an LDL-C of ~75 mg/dL was better than one of ~119 mg/dL plus angioplasty. AVERT is an important study because 70% of patients randomized to angioplasty also received statins and had a mean LDL-C of 119 mg/dL, which is quite respectable and in the range associated with maximum benefit in the Cholesterol and Recurrent Events (CARE) study. Yet, those with much lower LDL-C did better. These data suggest that the major effect of statins is mediated by changes in LDL-C. Post-*hoc* analyses from the CARE study suggested that there was no additional value of LDL-C levels less than 125 mg/dL, whereas in the 4S post-*hoc* analyses lower was better. It is clear that the relationship of LDL-C to CHD events is curvilinear and that lower is better, but the reduction in CHD risk from further reduction of LDL-C becomes progressively smaller. The decision to aggressively reduce the LDL-C to less than 100 mg/dL depends on numerous factors, which include patient adherence, additional cost, the complexity of the regimen, and the likelihood that the target can be achieved.

True primary prevention means prevention of atherosclerosis. Because the lesions that ultimately cause CHD events later in life begin in childhood and can be well expressed in

young adults, early institution of healthy lifestyle practices is required. With the exception of persons with lipid/lipoprotein abnormalities that predispose to early atherogenesis, such as familial hypercholesterolemia or familial defective apolipoprotein B, most primary prevention will be prevention of clinical events in adults who have preclinical disease. In other words, therapy is now directed at prevention of events more than the prevention of disease. In this regard, much of primary prevention is actually secondary prevention because these patients often have extensive disease that has not yet become symptomatic. There is a continuum of risk among asymptomatic patients, some being at very low risk, others at intermediate risk, and some at very high risk. The presence of two or more CHD risk factors identifies the intermediate and high-risk patients. For example, a young menstruating woman with increased LDL-C but no other risk factors is at such low risk of developing CHD in the near future that pharmacotherapy is not cost-effective. In contrast, a middle-aged smoking man with hypertension, central obesity, impaired fasting glucose, and low high-density lipoprotein cholesterol (HDL-C) is a walking "time-bomb." Most patients fall between these two extremes. It is crucial to be able to identify patients without known heart disease who are at high risk for cardiovascular events in the near future. In the United States, the National Cholesterol Education Program guidelines or the Framingham equation can be used to predict risk. More recently, the American Heart Association has recommended the additional use of conditional (emerging) risk factors, the ankle-brachial systolic pressure ratio, exercise testing, and perhaps carotid ultrasound for further stratification of risk. The paradigm has changed from diagnosis to prognosis. The American Heart Association has also emphasized the adverse cumulative impact of multiple minor abnormalities in prediction of risk. There is general agreement that a 2–3% annual risk of clinical CHD events represents high risk.

The intervention studies with statins are impressive and reveal that therapy reduces CHD risk by 25–35%. Baseline risk varied from ~5% [Air Force Coronary Artery Prevention Study/Texas Coronary Artery Prevention Study (AFCAPS/TexCAPS), a primary prevention study] to 27% [Scandinavian Simvastatin Survival Study (4S), a secondary prevention study], so that absolute risk reduction varied from 1.5–9%. These numbers reflect the responses of "average" patients within each study and are only applicable to our own patients who have similar characteristics. CHD risk factors are variably present in these studies, putting the patients at higher or lower risk of a CHD event than for the study as a whole. All subgroups of patients within each of the studies benefited from cholesterol lowering (hypertensives, smokers, diabetics, men and women, and the elderly). However, those at the highest risk had greater absolute benefit (*e.g.* diabetics in the CARE study had an absolute risk reduction of ~8% *vs.* ~5% for the group as a whole for combined end points). These data indicate that the higher the baseline risk, the greater the benefit during therapy even if relative risk reduction is similar. The number of patients needed to treat (the reciprocal of the absolute risk reduction) for 5 yr to prevent a single event in the statin studies varies from ~12 to ~50 depending on the absolute risk reduction. The treatment of 12 patients for 5 yr to prevent an event is considered cost-effective, whereas the treatment of 50 patients for 5 yr is probably not. Physicians as well as patients must understand that if 12 patients must be treated for 5 yr to prevent one event, then the outcome of 11 of the 12 patients will not be changed by therapy; in other words, they have a 1 in 12 chance of benefiting. In contrast, for AFCAPS/TexCAPS the chance of benefit is 1 in 50 and may not be very attractive. Thus, clinical judgement and patient preferences must be taken into consideration. A family history of CHD is crucial in making these decisions; not all of the family predisposition to CHD can be attributed to hypertension, diabetes, dyslipidemia, and so forth. It has been stated that Winston Churchill abused his body and died in his 90s, whereas Jim Fixx was a health nut and died in his 50s. Genetics may well influence the vascular response to known or emerging CHD risk factors. After all, we all have seen patients with lifelong multiple CHD risk factors and no clinical disease and other patients with devastating disease and no obvious risk factors.

Whereas LDL-C is the most important atherogenic lipoprotein, other lipoprotein abnormalities are important and must be considered as management is "fine-tuned." It has been difficult to determine the relationship of triglyceride to CHD because of greater biologic variability in the triglyceride level and larger coefficients of variation when triglyceride is measured. Triglyceride is not directly atherogenic but indicates the presense of TRLs, some of which are atherogenic. The heterogeneity of TRLs plus the other potentially atherogenic lipoprotein abnormalities that accompany hypertriglyceridemia (small dense LDL and reduced levels of HDL-C) make it difficult to "tease out" the precise relationship and mechanisms. In addition, this form of dyslipidemia is characteristic of insulin resistance and the atherogenic metabolic syndrome. The calculated LDL-C level can be misleading because it includes Lp(a) as well as the cholesterol transported in small VLDL, intermediate density lipoprotein, and VLDL remnants. Consequently, the reduction in LDL-C produced by statins is due, in part, to a reduction in the cholesterol transported by these lipoproteins. When triglyceride levels are normal the calculated LDL-C is accurate; but when elevated, it is not. This is important because combined abnormalities of cholesterol and triglyceride predominate in patients with CHD, particularly if triglyceride levels of more than 200 mg/dL are considered abnormal. As described, the non-HDL-C, provides a convenient way to assess apoprotein B-containing lipoproteins (LDL and VLDL) and have a single parameter to express CHD risk in patients with combined hyperlipidemia. Large VLDLs carry little cholesterol relative to triglyceride and will have a smaller influence on this value than small VLDLs or LDLs where a greater percentage of the molecule is composed of cholesterol. Also, the blood sample need not be fasting, making the measurement of triglyceride at that time unnecessary. The non-HDL-C includes all potentially atherogenic lipoproteins, and most hypolipidemic drugs affect multiple lipoproteins. This concept is appealing and simplifies decision making for patients with combined hyperlipidemia.

One of the most important risk factors for CHD is diabetes mellitus. Diabetes mellitus and impaired glucose tolerance are disproportionately represented among patients with

CHD. Hyperglycemia is a late event in the natural history of the insulin resistance syndrome. Because insulin resistance exists from birth the vascular endothelium is exposed to a constellation of proatherogenic metabolic abnormalities for decades. This often leads to development of advanced macrovascular disease before the appearance of hyperglycemia and explains why there is a poor correlation between the duration of type 2 diabetes mellitus and the development of macrovascular disease. This has led to the concept that "the clock starts ticking" for atherosclerosis in type 2 diabetes long before the appearance of hyperglycemia. However, it is also clear that hyperglycemia worsens the biology of atherosclerosis. Acute, intermediate, and long-term morbidity and mortality following MI is worse in diabetic than in nondiabetic patients even when adjusted for the severity of CHD, the size of the infarct, the use of thrombolytic agents, or the interval between the time of the infarct and receiving medical care. Adaptation of the myocardium to the infarct is less efficient in patients with diabetes. If myocardial perfusion and adaptation following an infarct are influenced by the microvasculature, then glycemic control may be an important factor independent of its effect on the atherosclerotic lesion. Diabetics without clinical CHD are at the same risk of a CHD event as nondiabetics with CHD, implying that CHD prevention in asymptomatic patients with type 2 diabetes is secondary prevention. In the 4S, diabetics with CHD and elevated LDL-C were at approximately twice the risk of an event as nondiabetics. In the CARE study, diabetics with CHD and average American LDL-C levels had a 50% higher risk of CHD events than nondiabetics. Under virtually all conditions diabetics are at much higher risk than nondiabetics for CHD events and adverse outcomes. In the 4S and CARE study, diabetics had a greater reduction in absolute CHD risk than nondiabetics and, therefore, experienced greater cardioprotection. In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID), the differences between diabetics and nondiabetics with LDL-C lowering was not significant. In the recent Veterans Administration High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) (which included 625 diabetics with HDL less than 40 mg/dL, LDL-C less than 140 mg/dL, and TG less than 300 mg/dL), gemfibrozil reduced the relative risk of CHD events by 22% in diabetics (from 36% to 28% compared with nondiabetics, from 23% to 18%). The absolute risk reductions were 8% and 5%, respectively. The number of diabetics that need to be treated for 5 yr to prevent an event is ~12, comparable to what was observed in the 4S and CARE study. In contrast, glycemic control in the United Kingdom Prospective Diabetes Study (UKPDS) study was associated with only a 16% reduction in relative CHD risk over a period of 12 years, which was of marginal statistical significance. Perhaps better glycemic control than that achieved in the UKPDS would have been more effective in reducing CHD events; the mean Hgb $A1_C$ in the intensively treated group was only 0.9% lower than in the conventional group, and glycemic control in the intensively treated group actually worsened during the study. It is possible that better glycemic control than was achieved is required to prevent CHD. These results suggest that aggressive management of hypercholesterolemia and dyslipidemia, as well as other standard CHD risk factors in patients with type 2 diabetes, is more likely to influence CHD events than treatment of hyperglycemia. However, achieving good glycemic control has other obvious benefits.

Medicine and CHD, in particular, have never been more exciting. Impressive progress has been made in understanding atherosclerosis and preventing (CHD) events in the past decade. More impressive discoveries can be expected in the next 5–10 yr that may dramatically change our approach to the prevention and treatment of CHD. Lipids are only one part of this complex disorder, and endocrinologists must understand more than just the diagnosis and treatment of hyperlipidemia/dyslipidemia if we are to play an important future role in the prevention of CHD.

Somehow, most of the truly exciting work in this field is being done by lipid specialists and cardiologists and not by endocrinologists. After all, molecular biology is one of the things we do best and is a field in which we have been a leader. Is this yet another area that we have abdicated?