HYPERLIPIDEMIA:
Treatments for the New Millennium*

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Hyperlipidemia is recognized as one of the major risk factors for Coronary Heart Disease (CHD). Dietary therapy and use of hypolipidemic drugs are central to management. In the fall, the National Cholesterol Education Program (NCEP) will convene an expert panel to begin work on new guidelines for managing hyperlipidemia. The work should be complete during the year 2000. The new guidelines will not differ greatly from the current ones (Table I.),[1] but indications for more aggressive pharmacologic treatment in high risk patients will be added. This *Heartbeat* will present the rationale for current and new treatment options and urge better compliance.

Table I. Current NCEP Guidelines

Patients with…	**Initiate Therapy if LDL-C is (mg/dL)**		**NCEP Goal**
	Diet Alone	Diet+Drug	**(mg/dL)**
No CHD and <2 risk factors	>=160	>=190	<160
No CHD and >=2 risk factors	>=130	>=160	<130
CHD	>100	>=130	<=100

All of the data supports the guidelines and the ***aggressive*** treatment of elevated cholesterol, especially in higher risk patients. Treatment should be directly related to risk. There is no hard data about the science, but the data does show that reducing low density lipoprotein cholesterol (LDL-C) reduces risk. The benefit may come not from lipid lowering but from other mechanisms.

Some of the strongest and most compelling evidence to date about the impact of lipid-lowering has come from using the 3 -hydroxy -3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors **(statins)**. A meta-analysis[2] of recently completed primary and secondary intervention trials have shown that significant reductions in LDL-C (30%) and total cholesterol (TC-20%) achieved with statins resulted in significant reductions in morbidity and mortality associated with CHD. They also showed reductions in the incidence of stroke (29%) and total mortality (22%). There was no significant evidence of an increase in either non-cardiovascular deaths or cancer incidence out to ten years. A recent Canadian study [3] supports the benefits and cost-effectiveness of statins among persons younger than 75 years at high risk.

The morbidity benefits occur early in the course of statin treatment and have led to suggestions that these drugs possess anti-atherogenic effects over and above their lipid lowering effects.

These include:

- improving endothelial dysfunction
- stabilizing vulnerable atherosclerotic plaque
- reducing thrombosis and inflammation
- improving fibrinolytic activity
- reducing frequency of transient myocardial ischemia

These effects are the rationale for the early and aggressive use of statins in acute cardiovascular syndromes. The risk of death in patients with unstable angina pectoris or an acute myocardial infarction (MI) is substantially higher in the immediate phase (<1 month) than in the intermediate or long-term phase (>3 months) after the acute event.

*Are we tired of this yet?

Early use should be guided by a fasting lipid profile obtained within 48 hours after the acute cardiovascular event. After this narrow time frame, inflammatory mediators cause an increase in triglycerides and lipoprotein(a) [Lp(a)] and a decrease in high density lipoprotein cholesterol (HDL-C) and LDL-C. These changes peak 4 to 7 days after acute MI and resolve 2 months later. Lipid profile and liver function studies should be obtained 2 months after the acute event to evaluate response to therapy and possible side effects. Meanwhile, this post-acute event period provides an opportunity both to screen for and to initiate appropriate risk factor modification.

A large number of patients went on to have coronary events in spite of having LDL-C levels <100 mg/dL that did not need treatment or having drug treatment that successfully lowered their LDL-C to goal levels. This has led to further study. Recent clinical trials and interpretation of the data supports and will expand the current treatment guidelines:

Triglycerides (TG)

TG's are now considered a critical aspect of treating patients with hyperlipidemia. TG's have been shown to be atherogenic and significantly interrelated to HDL-C and LDL-C metabolism. When TG levels are >150 mgm/dL, LDL-C is almost always a small dense particle that is highly oxidizable and very atherogenic, especially in a patient with glucose intolerance or diabetes mellitus. Therefore, for patients with a systemic vascular disease (CHD, peripheral arterial disease [PAD] or cerebral vascular disease) diabetes mellitus (DM), or multiple risk factors, the treatment goal should be to normalize all the lipoproteins. The goal LDL-C should be <100mg/dL (NCEP guidelines) and TG and HDL-C goals should be <150 mgm/dL and >45 mgm/dL respectively. There are many treatment options to reach these important goals. Treatment should always include weight loss, low fat diet, exercise, alcohol cessation, and discontinuation of medications with potential adverse lipid effects. Medical treatment includes statins and/or niacin (if not diabetic). and/or fibrates.

Low HDL-C

Several studies have shown that the following medications which increase HCL-C are related to decreased CHD events:

- Gemfibrozil: The Helsinki Heart Study[4] and VA-HIT [5]
- Statins: The 4S,[6] LIPID,[7] WOSCOPS,[8] and AFCAPS/TexCAPS.[9]

These studies showed that low HDL-C levels were associated with the highest event rates, but there was a significant reduction of coronary events with either statins or fibrates.

Dyslipidemia in Diabetes Mellitus (DM)

Diabetes mellitus is associated with a 2-to-4 fold excess risk of CHD. Primary emphasis and therapy should be to lower LDL-C levels. The American Diabetic Association goal is to reduce LDL-C's to levels recommended for patients with pre-existing CHD (<=100 mgm/dL). The initial therapy should be statins with the addition of a resin if necessary to reach the LDL-C goal.

The most common lipid abnormality in DM is elevated TG levels and decreased HDL-C levels. Intervention with fibrates to lower TG levels and increase HDL-C levels appears to lower risk of recurrent events.

The initial therapy for increased TG's is improved glycemic control. Additional TG lowering can be achieved with high dose statins (for patients with both high LDL-C and high TG levels) or fibric acid derivatives. Statins do not necessarily raise HDL-C levels, however. In some cases combined therapy may be needed. Be

aware that there is an increased, but low, risk of myositis associated with the combination of statins with niacin or fibrates and especially with gemfibrozil (Lopid) or fenofibrate (Tricor). [The risk is 0.2 % with statins and up to 0.26% when statins are combined with gemfibrozil.]

High doses of statin could eliminate the need for combination therapy. The combination of statins with niacin is extremely effective in modifying diabetic dyslipidemia, with the largest increase in HDL-C levels, but the combination may significantly worsen hyperglycemia. This combination should be used cautiously, using low doses (<=2g of niacin/day) with frequent glucose monitoring.

CHD Prevention in Women

A recent consensus report[10] of the American Heart Association (AHA) and the American College of Cardiology (ACC) recommends:

- Statins or other lipid lowering agents, not hormone replacement, should be considered first-line therapy for postmenopausal women with elevated lipid levels.
- Current lipid targets for women should be more aggressive (150mg/dL for TG and 45mg/dL for HDL-C.
- Tight control of risk factors and glucose because DM increases CHD risk in women 3 to 7-fold compared to 2 to 3-fold in men.

Diet and Exercise

Weight loss and increased physical activity will help decrease TG and increase HDL-C and also modestly lower TC and LDL-C levels. With perfect compliance (rare) you may get a 10% reduction of LDL-C. Recommendations from the AHA have suggested that maximal dietary therapy typically reduces LDL-C 15-25mg/dL. If total LDL-C exceeds the goal by >25mg/dL, physicians may decide to institute pharmacologic therapy at the same time in high risk patients (i.e. those with known CHD, PAD, cerebral vascular disease, two or more CHD risk factors or patients with very high LDL-C levels >=200mg).

Elevated Cholesterol and Age

Aggressive lipid management is beneficial, regardless of age, particularly in patients at high risk. However individuals over age 65 are currently less likely to be prescribed appropriate lipid–lowering treatment. Aggressive screening and treatment of patients at high risk would save countless lives and decrease morbidity and costs associated with cardiovascular disease. Benefits have been shown to extend to age 75. Each patient has to be evaluated individually and treatment should be based on indications and physiologic age.

Lp(a) and Homocysteine

Increased levels are associated with increased risk. Screening for high levels should be considered in those with premature atherosclerosis, a strong family history of atherosclerosis and those with hypercholesterolemia resistant to conventional treatment. Niacin is the treatment of choice for lowering Lp(a) excess. Folic acid is the treatment for hyperhomocysteinemia. Optimal doses and benefits of treatment have not been established.

THREE PATIENT PROFILES AND TREATMENT GOALS:

Patients with isolated low HDL-C (<35 mg/dL), TC <200mg/dL, TG<200mg/dL)

- Primary prevention should be initiated in patients with diabetes mellitus (DM) or at least 2 other CHD risk factors. The focus should be on lowering LDL-C to target <=100 for DM or <=130 with other risk factors.
- Secondary prevention should also focus on LDL-C lowering to target <100mg/dL with a

statin. Fibrate therapy may also be considered to elevate HDL-C if LDL-C is already <100mg/dL.

Patients with low HDL-C, TG 200mg/dL to 500mg/dL, and TC >200mg/dL.

- Primary prevention should be directed at patients with DM or with >=2 CHD risk factors, focusing on therapies that reduce LDC-C and TG's
- Use statin as the first-line therapy, followed by niacin and then fibrates, or when needed, combination therapy. Combinations of statin and niacin are preferred, as they are better-tolerated with fewer side effects than when fibrates are included.

Patients with low HDL with TG 200mg/dL to 500mg/dL and TC <200mg/dL.

- Primary prevention should be directed at patients with DM, and possibly at insulin-resistant or high-risk subjects, with the focus on TG treatment. First-line therapy should be niacin or fibrates, with the latter preferred for those with DM or insulin resistance. However, niacin can be used in diabetics if glucose is well-controlled by either oral agents or insulin.
- Secondary prevention should also focus on TG treatment with niacin or fibrates. Gemfibrozil is the therapy of choice, with proven event reduction and better tolerability profile.

CLINICAL IMPLICATIONS:

- ❖ Follow NCEP recommendations.
- ❖ Always risk stratify and treat high risk patients more aggressively.
- ❖ Decreased LDL-C is synonymous with decreased risk.
- ❖ Statins are the most potent lipid–lowering drugs currently available.
- ❖ Use statins early in acute cardiovascular syndromes. Take advantage of the urgency of the moment.
- ❖ Event reduction has been proven by treating low HDL-C and high TG in patients with good TC and LDL-C levels and high risk disease.
- ❖ DM is high risk disease and should be treated as CHD (goal LDL-C<=100mg/dL).
- ❖ Low HDL-C and increased TC is the most common dyslipidemic pattern in DM and should be treated (goal TG <150mg/dL and HDL-C >45mg/dL).
- ❖ Pay more attention to women (AHA/ACC report)
- ❖ Consider instituting medical treatment at the same time as diet in high risk patients.
- ❖ Age alone should never be used as a criterion for treating or not treating.

Mario L. Maiese, D.O., F.A.C.C.

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[1] *JAMA* 1993; 269: 3015-23 (NCEP)
[2] *JAMA* 1997; 278: 313-21
[3] *Arch Intern Med 1999;* 159: 593-600
[4] *JAMA* 1988; 260: 641-51 (Helsinki)
[5] Presented at AHA 71st Annual Scientific Session, 11/98
[6] *Lancet* 1994; 344:1383-89 (4S)
[7] *Circulation* 1998; 97:1784-90 (LIPID)
[8] *N Engl J Med* 1995; 333:1301-07 (WOSCOPS)
[9] *JAMA* 1998; 279: 1615-22 (AFCAPS/ TexCAPS)
[10] *Circulation* 1999; 99: 2480-2484