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Treatment of Dislipidemia and the ATP III Guidelines

The Adult Treatment Panel (ATP) I was the first iteration of guidelines of the National Cholesterol Education Program (NCEP) that encouraged the appropriate detection, evaluation and management of high blood cholesterol. In 1988, it established a strategy for primary prevention of coronary heart disease (CHD) in patients with low-density lipoprotein cholesterol (LDL-C) of 160 mg/dL or greater or borderline high LDL-C of 130 to 159 mg/dL. Five years later, a revision of the guidelines was released (the ATP II report), which recommended reductions in LDL-C to less than 100 mg/dL in patients with established CHD for primary prevention of cardiovascular events. Published in 2001, the ATP III report recommends further reduction of LDL-C in certain patients with factors that increase the risk for CHD.¹ This review summarizes the ATP II recommendations and outlines the implications of the report on cardiovascular health.

Clinical Trials

Several studies have identified LDL-C as a major predictor of future cardiovascular events (such as acute myocardial infarction and stroke).²⁻⁶ Secondary prevention trials such as The Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) trial, and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study have shown that reduction of LDL-C is associated with a reduction in major coronary events, regardless of pre-treatment cholesterol levels. In addition, LDL-C above 100 mg/dL has been shown to be highly predictive of coronary event risk. In the LIPID study a reduction of 39 mg/dL in total cholesterol (TC) was associated with 22% fewer coronary events, and a 20.3 % reduction in LDL-C with cholestyramine in the Lipid Research Clinics Coronary Primary Prevention Trial was associated with 18% fewer events.

Based on an observational study, it was concluded that initiation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (the "statins") immediately after acute myocardial infarction (AMI) was not more beneficial than initiation just prior to hospital discharge. In addition, patients with LDL-C below 130 mg/dL may be at increased risk of recurrent AMI and mortality if the statin is initiated immediately after the AMI during the acute coronary syndrome.⁷

In primary prevention studies such as the Lipid Research Clinics Coronary Prevention Trial, the West of Scotland Coronary Prevention Study (WOSCOPS) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), mean LDL-C reduction obtained through drug therapy has been found to be predictive of reductions in the risk of cardiovascular events.⁸⁻¹⁰ Evidence from these trials is conclusive: cardiovascular event risk reduction decreases with reductions in LDL-C.

The New ATP III Guidelines

In concert with the American Diabetes Association and the European Atherosclerosis Society, the ATP III emphasizes the importance of the identification of patients at risk for CHD and aggressive lowering of LDL-C.¹¹ The ATP III recommendations build on the recommendations of ATP II, endorsing aggressive LDL-C lowering in CHD patients, emphasizing LDL-C reduction as the primary target of therapy, clarifying the stratification of LDL-C goals by risk category, identifying subpopulations appropriate for screening, targeting patients with high LDL-C for drug treatment, and further endorsing therapeutic lifestyle changes (TLC), such as weight reduction and physical activity, as an important dimension of risk reduction. In addition, ATP III includes an emphasis on primary prevention, secondary prevention measures for high-risk groups, a new classification for LDL-C, HDL-C and triglycerides, an emphasis on guideline implementation and adherence, expansion of TLC recommendations to include increased physical activity and additional diet changes.

ATP III includes modified risk categories used to guide LDL-C lowering goals (table 1). Risk is based on LDL-C levels, the presence of CHD, atherosclerosis as evidenced by peripheral arterial disease, abdominal aortic aneurysm, or symptomatic carotid artery disease, and the presence of other major risk factors. Independent major risk factors include age, gender, hypertension and a family history of CHD, as well as

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factors that may be modifiable such as obesity, inactivity and an atherogenic diet.

The highest risk categories include CHD and CHD risk equivalents. A CHD "risk equivalent" is defined as any factor that carries the same risk of a major coronary event as an established CHD. More than 20 patients out of 100 individuals with a CHD risk equivalent will have a new or recurrent CHD event within 10 years. ATP III classifies diabetes mellitus (DM) as a CHD risk equivalent because of its associated increased risk of CHD within 10 years of diagnosis and its risk of mortality due to AMI. Primary prevention is encouraged in patients with multiple risk factors (table 2).

Patient Assessment

It is estimated that approximately 40% of all adult Americans aged 20 to 74 years should undergo fasting lipoprotein analysis, and 29% are candidates for dietary therapy.¹² In the

Table 1. Risk Categories

RISK CATEGORY	LDL GOAL
CHD or CHD risk equivalent	<100 mg/dL
Multiple (>1) risk factors	<130 mg/dL
0-1 risk factors	<160 mg/dL

Note: CHD, coronary heart disease.

Table 2. LDL-C Cholesterol Thresholds by Risk Category

RISK CATEGORY	INITIATE TLC	INITIATE DRUG THERAPY	LDL-C GOAL
CHD or CHD risk equivalent (10-yr risk > 20%)	≥ 100 mg/dL	≥ 130 mg/dL 100-129 mg/dL optional	< 100 mg/dL
2 risk factors (10-yr risk ≥ 20%)	≥ 130 mg/dL	≥ 130 mg/dL; 10-yr risk 10-20% ≥ 160 mg/dL; 10 yr risk <10%	< 130 mg/dL
0-1 risk factor	≥ 160 mg/dL	≥ 190 mg/dL 160-189 mg/dL optional	< 160 mg/dL

Table 3. Lipid Classification

CLASSIFICATION	LDL-C	TC	HDL	TG
Optimal	< 100 mg/dL	< 200 mg/dL	≥ 60 mg/dL	< 150 mg/dL
Abnormal	100-129 mg/dL		< 40 mg/dL	
Borderline high	130-159 mg/dL	200-239 mg/dL		150-199 mg/dL
High	160-189 mg/dL	≥ 240 mg/dL		200-499 mg/dL
Very high	≥ 190 mg/dL			≥ 500 mg/dL

Note: LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL, high-density lipoprotein; TG, triglycerides

Lipid Treatment Assessment Project (L-TAP) only 18% of patients with CHD achieved LDL-C consistent with NCEP goals of less than 100 mg/dL.¹³ Similar results were reported in Europe, indicating that adequate cholesterol-lowering is not being accomplished.¹⁴ Assuming that dietary modifications reduce LDL-C by 10%, lipid-lowering drugs would be needed in 7% of adults (2.7 million Americans). Assessment of the patient should take into account the changes introduced by ATP III including the classification of low HDL cholesterol which was increased from less than 35 mg/dL to less than 40 mg/dL, lowered triglyceride thresholds and the more aggressive goal of LDL-C of less than 100mg/dL (table 3).

Metabolic Syndrome

Metabolic syndrome is considered a secondary target of risk reduction therapy after LDL-C. Metabolic syndrome patients may have a combination of life-habit and emerging risk factors. These include abdominal obesity, atherogenic dyslipidemia including increased triglycerides, small LDL particles, low HDL cholesterol, increased blood pressure, insulin resistance and prothrombotic and proinflammatory states.

Primary Prevention

Primary prevention reduces risk of CHD. Secondary dyslipidemia should be ruled out before initiation of TLC and then drug therapy. After excluding or treating secondary causes, the goal LDL-C should be identified depending on the absolute risk for CHD or the probability of having a CHD event. The higher the risk, the lower the LDL-C goal.

Secondary Prevention

The goal of therapy with ATP III in secondary prevention is to lower LDL-C to less than 100 mg/dL to prevent recurrent events or the onset of CHD in patients with CHD risk equivalents. Lipid profiles are required in order to provide guidance for LDL-lowering therapy.

Drug Therapy

Antihyperlipidemics are most effective in high-risk patients, since the absolute risk of CHD is greater than that of low risk patients. Therefore, the threshold for the initiation

Table 4. Effect of Lipid Lowering Drugs

DRUG CLASS	LDL-C	HDL	TG	MONITORING PARAMETERS
Statins	↓5-20%	↑10-35%	↓20-50%	ALT, AST, muscle soreness, tenderness and pain
Bile Acid Sequestrants	↓15-30%	↑3-5%	No change or ↓	Indigestion, bloating, constipation, abdominal pain, flatulence, nausea
Niacin	↓5-25%	↑15-35%	↓20-50%	ALT, AST, flushing, itching, tingling, headache, nausea, gas, heartburn, fatigue, rash and peptic ulcer, FBS and uric acid
Fibric acid derivatives	↓18-55%	↑5-15%	↓7-30%	Abdominal pain, dyspepsia, headache, drowsiness and cholelithiasis

Note: LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FBS, fasting blood sugar

of drug therapy depends on risk-benefit considerations. Patients who should receive antihyperlipidemic therapy include patients with CHD, a risk of CHD greater than 20% over 10 years, DM and LDL-C levels greater than 130 mg/dL. Patients achieving lower LDL-C levels have a greater risk reduction.

A treatment gap exists with approximately 20% of high-risk patients meeting the optimal LDL-C of less than 100mg/dL. Statins are the most effective lipid lowering agents, although combination of a statin with one of the other lipid lowering agents may be required.⁶⁻¹⁰ In addition, new highly effective medications should result in more effective control of LDL-C, reducing the morbidity and mortality of CHD in high-risk patients (table 4).

Economic Impact of ATP III

Agents such as aspirin and antihypertensives used in CHD preventive therapy are estimated to result in costs of \$50,000 per life-year saved (LYS) and are considered cost effective. Costs of cholesterol-lowering drugs for secondary prevention in CHD are estimated at \$12,000 per LYS as compared to \$25,000 per LYS for primary prevention. As an additional comparator in the 4S Study, the cost saved from reduced length of hospital stays for CHD events decreased the cost of simvastatin by 88% to \$0.28 per day.¹⁵⁻¹⁹

Decision-makers concerned with health care costs may question the impact of ATP III on increased drug utilization and costs. Lifestyle modification is the most cost-effective means to reduce the risk of CHD, but lipid goals may not be reached, and drug therapy may be required.

Costs are expected to decline with patent expirations on drugs such as lovastatin although new, more expensive agents are on the horizon.¹⁵⁻¹⁹ The increased costs associated with implementing ATP III recommendations may be lessened somewhat with the use of generic antihyperlipidemic agents.

While not as potent as simvastatin or atorvastatin, generic lovastatin is well tolerated and should be considered in patients who do not achieve satisfactory LDL-C reduction with TLC. Lovastatin may be used as monotherapy or in combination with other antihyperlipidemics such as niacin.

Evolving Drug Therapy

Aggressive LDL-C lowering as recommended by ATP III may not always be achieved with statin monotherapy, and mixed hyperlipidemias may re-

quire the use of more than one agent. The addition of niacin to a statin results in an additional 10 to 12% reduction of LDL-C. In patients titrated from niacin 500 mg with lovastatin 10 mg to niacin 2 gm with lovastatin 40 mg, LDL-C was reduced by 47%, HDL increased by 30% and triglycerides reduced by 42%.²⁰ As no major randomized controlled trial has assessed the efficacy and safety of this combination in large numbers of patients, it should not be used as first-line therapy.

Bile acid sequestering (BAS) agents are not systemically absorbed, but provide an additional 10 to 12% reduction in LDL-C. In combination with a statin, BAS agents or niacin are both effective in polygenic and familial hypercholesterolemia (FH) where monotherapy with a statin is not adequate.²¹⁻²²

More potent statins, including pitavastatin and rosuvastatin, are in clinical development. In patients with heterozygous FH, pitavastatin at doses of 2 mg or 4 mg per day was shown to reduce LDL-C by 40 and 48%, respectively. Similar results were seen in other forms of hyperlipidemia.²³ A reduction of up to 65% in LDL-C was observed with rosuvastatin in FH.²⁴ Atorvastatin was compared to rosuvastatin following a 6-week dietary adjustment period and an 18-week dose escalation period. LDL-C was decreased by 57.9% with rosuvastatin 80 mg and at each dose studied a significantly greater LDL-C reduction was seen with rosuvastatin than with atorvastatin ($p < 0.001$).²⁵ Rosuvastatin significantly increased HDL-C and apolipoprotein A-1, and in patients with FH, significantly reduced TC levels.²⁶

New drug classes are under development. Bile acid transport inhibitors (BATIs) block the ileal sodium-dependent bile acid (taurocholic) transport mechanism, preventing the enterohepatic recycling of bile acids and LDL-C, similar to BAS agents.²⁷ Two BATIs have entered phase 2 clinical trials with an associated reduction in LDL-C of 10% reported in one trial.²⁸

Cholesterol absorption inhibitors (CAIs) such as ezetimibe have been assessed in phase 2 and phase 3 clinical trials. As monotherapy, ezetimibe was not as effective as statins in lipid lowering, although it has shown excellent results when combined with simvastatin.²⁹⁻³⁰

Conclusion

Therapeutic modalities have been proven through years of research and patient follow-up to be effective in the prevention and treatment of CHD. The more aggressive guidelines for the management of lipid abnormalities recommended by the ATP III will succeed in decreasing the morbidity and mortality of CHD, only if implemented in a cost-efficient and successful manner. ■

References

- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993;269:3015-3023.
- Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256:2823-2828.
- Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol concentrations and coronary heart disease in a population with low cholesterol concentrations. *Br Med J* 1991;303:276-282.
- The Lipid Research Clinics Coronary Primary Prevention Trial Results I: Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351-364.
- Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-1307.
- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; 279:1615-1622.
- Newby KL, Arni K, Manjushri VB, et al. Early statin initiation and outcomes in patients with acute coronary syndrome. *JAMA* 2002;287:3087-3095.
- Sacks FM, Pfeffer MA, Moye LA, et al, for the cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; 335:1001-1009.
- Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1382-1389.
- The Long-term Intervention with Pravastatin in Ischemic Heart Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol events. *N Engl J Med* 1998;339:1349-1357.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-2497.
- Schulman KA, Kinoshita B, Jacobson TA, et al. Reducing high blood cholesterol level with drugs: cost-effectiveness of pharmacologic management. *JAMA* 1990;264:3025-3033.
- Pearson TA, Laurora I, Chu H, Kafonek S. The Lipid Treatment Assessment Project (L-TAP). A multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein goals. *Arch Intern Med* 2000;160:459-467.
- EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries. Principal results from EUROASPIRE II Euro Heart Survey Program. *Eur Heart J* 2001;22:554-572.
- Goldman L, Weinstein MC, Goldman PA, et al. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. *JAMA* 1991;265:1145-1151.
- Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease, mortality and cost: the coronary heart disease policy model. *Am J Pub Health* 1987;77:1417-1426.
- Weissfeld JL, Weissfeld LA, Holloway JJ, Bernard AM. A mathematical representation of the expert panel's guidelines for high blood cholesterol case finding and treatment. *Med Decis Making* 1990;10:135-146.
- Pederson TR, Kjekshus J, Berg K., et al. Cholesterol lowering and the use of healthcare resources. Results of the Scandinavian simvastatin survival study. *Circulation* 1996; 93:1796-1802.
- Koren MJ, Smith DG, Hunninghake DB, Davidson MH, McKenney JM, Weiss SR. The cost of reaching National Cholesterol Education Program (NCEP) goals in hypercholesterolemic patients. A comparison of atorvastatin, simvastatin, lovastatin, and fluvastatin. *Pharmacoeconomics* 1998;1:59-70.
- Kashyap ML, Evans R, Simmons PD, Kohler RM, McGovern ME. New combination niacin/statin formulation shows pronounced effects on major lipoproteins and is well tolerated [Abstract]. *J Am Coll Cardiol* 2000;35:326A.
- Eriksson M, Hadell K, Holme I, Walldius G, Kjellstrom T. Compliance with and efficacy of treatment with pravastatin and cholestyramine: A randomized study on lipid-lowering in primary care. *J Intern Med* 1998;243:273-380.
- Hunninghake D, Insull W, Toth P, Davidson D, Donovan JM, Burke SK. Co-administration of colessevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis* 2001;158:407-416.
- Teramoto T, Saito Y, Nakaya N. Clinical evaluation of NK-104 (itavastatin) in the long-term treatment of patients with hyperlipidemia [Abstract]. Presented at the XIIth International Symposium on Atherosclerosis, Stockholm, Sweden, 2000, June 25-20:53.
- Olsson AG, Pears J, McKeller J, Mizan J, Raza A. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. *Am J Cardiol* 2001;88:504-508.
- Stein E, Strutt KL, Miller E, Southworth H. ZD4522 is superior to atorvastatin in the treatment of patients with heterozygous familial hypercholesterolemia [Abstract]. *J Am Coll Cardiol* 2001;37:292A.
- Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583-1952.
- Root C, Smith CD, Winegar DA, Brieady LE, Lewis MC. Inhibition of ileal sodium-dependent bile acid transport by 2164U90. *J Lipid Res* 1995;36:1106-1115.
- Stein EA, Rhyne JM, McKenney J, Bays H, Roth E, Breed S, Roller R. Intestinal bile acid transport (IBAT) inhibition: results of a 4 week pilot study of 264w94, a novel IBAT inhibitor in hypercholesterolemia [Abstract]. XIV International Symposium on Drugs Affecting Lipid Metabolism. 2002.
- Bays H, Drehobi M, Rosenblatt S, et al. Low-density-lipoprotein cholesterol reduction by SCH 58235 (ezetimibe), a novel inhibitor of intestinal cholesterol absorption in 243 hypercholesteremic subjects: results of a dose-response study [Abstract]. *Atherosclerosis* 2000;51:133.
- Kosoglou T, Meyer I, Musiol B, et al. Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin [Abstract]. *Atherosclerosis* 2000; 151: 135.