

The following abstracts, from medical journals containing literature on the management of cholesterol, were selected for their relevance to this Special Report.

Survey: Most Cholesterol Treatment Fails

In this survey of 4888 patients with dyslipidemia, only 38% of patients receiving lipid-lowering therapy (85% with drugs) achieved the low-density lipoprotein cholesterol treatment target set by the National Cholesterol Education Program (NCEP). All patients in the survey were being treated by primary care physicians who were heavy prescribers of cholesterol-lowering medications. The success rate was highest (68%) in the low-risk patients with fewer than 2 risk factors and no evidence of coronary heart disease (CHD) and lowest (18%) in those patients with established CHD. Drug therapy was significantly more effective ($P < 0.001$) in all patient risk groups. There was little difference in success rates between compliant patients and noncompliant patients. The authors conclude that the full range of lipid management options available at the time of this survey (1996) was not used effectively. As potential causes, they cite low dosages, limited drug effectiveness, inappropriate choice of drugs, intolerance, and noncompliance. They recommend more aggressive use of cholesterol-lowering drug therapy to achieve NCEP targets.

Pearson TA, Laurora I, Chue H, Kafonek S. The Lipid Treatment Assessment Project L-TAP. *Arch Intern Med* 2000;160:459-467.

Managed Care Cholesterol Program Measures Progress

A group model health maintenance organization with 350,000 members initiated a disease management program for dyslipidemia in patients with coronary artery disease (CAD). Based on the protocols and guidelines of an existing nurse-managed program of cardiac rehabilitation for CAD patients, the new program is a pharmacist-managed and physician-monitored service that encourages proper lipid testing and drug treatment in patients at high risk of CAD. Preliminary results of the new service in 1716 patients over a 10-month period were encouraging. The data show an improvement in the low-density lipoprotein cholesterol (LDL-C) screening rate (from 55% to 97%), in the percentage of patients with an LDL-C below 130 mg/dL (from 58% to 84%), and in the percentage of patients with an LDL-C below 100 mg/dL (from 22% to 48%). Other markers of CAD care, including aspirin and β -blocker use and patient satisfaction, have also improved. These short- and intermediate-term surrogate outcomes illustrate the incentives and unique opportunities managed care organizations have to improve management of hypercholesterolemia.

Merenich JA, Lousberg TR, Brennan SH, Calonge NB. Optimizing treatment of dyslipidemia in patients with coronary artery disease in the managed care environment (The Rocky Mountain Kaiser Permanente Experience). *Am J Cardiol* 2000;85:36A-42A.

Secondary Prevention Is Cost Effective

Using a range of assumptions and risk estimates developed in a previous

study (the Coronary Heart Disease Model) this analysis evaluated the cost effectiveness of various cholesterol-lowering therapies, according to specific risk factors, including age, sex, smoking status, blood pressure, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. In individuals who had already had a coronary event, statin therapy was calculated to cost less than \$50,000 per quality-adjusted life-year (QALY). Thus, secondary prevention with a statin was deemed cost effective for all risk subgroups and even cost saving in some high-risk groups. Primary prevention with a step 1 diet was cost effective for most risk subgroups (from \$1900 per QALY to \$500,000 per QALY). However, primary prevention with a statin was not cost effective for younger men and women with few risk factors. The authors acknowledge study limitations, such as their assumption of the average wholesale price for drugs and their neglect of diabetes and family history as risk factors.

Prosser LA, Stinnett AA, Goldman PA, et al. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann Intern Med* 2000;132:769-777.

Extended-Release Niacin Beats Gemfibrozil in Lowering HDL-C

This multicenter double-blind trial compared extended-release niacin (Niaspan, 1000 to 2000 mg at bedtime) with gemfibrozil (600 mg twice daily) in 173 patients with low high-density lipoprotein cholesterol (HDL-C [\leq 40 mg/dL]). The extended-release version of niacin is intended to reduce the flushing associated with this class of agent. At 2000 mg daily, niacin raised HDL-C levels by 26%, twice as much as gemfibrozil. At 1000 mg, the increase of 15% was approximately equal to the gemfibrozil effect. At 1500 and 2000 mg, the niacin product also proved better than gemfibrozil at raising the apolipoprotein A1 level (9%

and 11% versus 4%) and reducing the lipoprotein (a) level (-7% and -20% versus no change). Whereas gemfibrozil reduced triglyceride levels by about 40%, about twice as much as niacin, the fibrate also increased the low-density lipoprotein cholesterol level (by 9%) versus minimal changes with niacin. Discontinuation rates in the 2 groups were similar. Flu syndrome was reported more often in patients taking niacin, and dyspepsia was more common with gemfibrozil. The authors recommend further study of niacin in patients with low HDL-C.

Guyton JR, Blazing MA, Hagar J, et al. Extended-release niacin vs gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. *Arch Intern Med* 2000;160:1177-1184.

New Bile Acid Sequestrant Has Low Incidence of Gastrointestinal Side Effects

This was a 6-week placebo-controlled trial to determine the best low-density lipoprotein cholesterol (LDL-C)-lowering dose of a potent new bile acid-sequestering agent, colesevelam hydrochloride (Cholestagel). In 137 adult men and women with hypercholesterolemia (LDL-C > 160 mg/dL), the nonsystemic polymer was found to reduce LDL-C in a dose-dependent manner, from a 1.5% reduction in the 1.5 g/day group, to a 19.1% reduction in the 3.75 g/day group. Colesevelam also increased high-density lipoprotein cholesterol levels at these 2 dosages (by 11.2% and 8.1% respectively). Median triglyceride levels did not change from baseline, nor were there significant changes from the placebo treatment group. With the exception of 3 patients (10%) in the 2.25-g/day colesevelam group who reported diarrhea, there were no statistically significant differences among treatment groups in the incidence of adverse gastrointestinal (GI) events. Only 4 (2.7%) of 149 patients, all taking colesevelam, left the

study because of digestive system complaints. Overall compliance with colesevelam was 93%. Based on the beneficial lipid reduction and the minimal unpleasant GI side effects, the authors conclude that colesevelam may offer an alternative to other bile acid sequestrants and systemic lipid-lowering drugs for individuals requiring moderate ($\leq 20\%$) LDL-C reduction. They also note its potential for combination use.

Davidson MH, Dillon MA, Gordon B, et al. Colesevelam hydrochloride (Cholestagel). *Arch Intern Med* 1999;159:1893-1900.

Cholesterol Is Major Risk Factor in Young Men

This study reviewed long-term cardiovascular mortality and cholesterol data from young men (18 through 39 years) originally studied in the 1960s or 1970s in 1 of 3 previous clinical studies: the Chicago Heart Association Detection Program in Industry, the Chicago Peoples Gas Company, and the Multiple Risk Factor Intervention Trial. The researchers evaluated the relationship between total serum cholesterol measured when these men were young and the follow-up mortality data found in current records (eg, Social Security Administration, National Death Index, company records). Based on the baseline lipid test and the follow-up data from more than 80,000 young men, unfavorable serum cholesterol levels in youth were found to strongly correlate with a risk of later mortality. For young men with a serum cholesterol of 240 mg/dL or greater, the coronary heart disease (CHD) mortality risk was 2.15 to 3.63 times greater than in men with favorable levels (< 200 mg/dL). Men with a favorable baseline serum cholesterol had an estimated greater life expectancy of 3.8 to 8.7 years. The researchers conclude that young men with elevated serum cholesterol have a substantially increased risk of CHD, cardiovascular

death, and all-cause mortality. The authors say their results underscore the importance of population-wide early primary prevention of unfavorable cholesterol levels with an improved lifestyle and diet.

Stamler J, Daviglius ML, Garside DB, et al. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA* 2000;284:311-318.

Low-Density Lipoprotein Cholesterol Reduction After Coronary Artery Bypass Graft: Lower Is Better

Three years ago, researchers reported that patients receiving aggressive low-density lipoprotein cholesterol (LDL-C) reduction after their coronary artery bypass graft (CABG) had significantly less progression of vein bypass narrowing at 4.3 years postprocedure. This study extends those angiographic findings by following the patient cohort for another 3 years and measuring clinical outcomes. Follow-up data for all but 3 of the 1351 original patients were gathered. In patients with aggressive therapy (mean LDL-C, 93 mg/dL), the rate of cardiovascular death or nonfatal infarction was 15.1% compared with 20.3% in those with moderate LDL-C reduction (mean LDL-C, 136 mg/dL ($P = 0.03$)). Coronary revascularization rates were reduced from 27.3% to 19.2% in patients assigned to the aggressive strategy ($P = 0.0006$). (Separately, the study also showed some clinical benefit of low-dose anticoagulation therapy.) As pointed out in an accompanying editorial, these absolute reductions of 5% for cardiovascular death and nonfatal infarction and 8% for revascularization translate to only 20 and 12.5 patients, respectively, who must be treated more aggressively to prevent one of these major endpoints. The authors conclude that patients with

coronary artery disease should have their LDL-C reduced to less than 100 mg/dL, according to National Cholesterol Education Program guidelines.

Knatterud GL, Rosenberg Y, Campeau L, et al. Long-term effects of clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass graft trial. *Circulation* 2000;102:157-165.

The Cost of Reaching National Cholesterol Education Program Goals

This review article provides background on the epidemiology, costs, and main treatment strategies for coronary artery disease and then reviews the pharmacoeconomics that drive decision making for dyslipidemia treatment in primary and secondary prevention settings. The published data suggest that secondary prevention is more cost effective than primary prevention but that the costs of primary prevention are actually in line with those of accepted medical intervention (such as percutaneous transluminal coronary angioplasty and coronary artery bypass grafting). Most of the economic data presented are based on statin clinical studies. The results of one recent study reviewed here show that atorvastatin was significantly more likely to help patients achieve National Cholesterol Education Program (NCEP) goals more quickly (eg, 53% of patients at initial dosages compared with 33% of those on simvastatin) and that as a result the "cost to reach NCEP goals" was lower for atorvastatin. Studies have also shown that atorvastatin was the most cost-effective statin in terms of annual cost per percentage reduction in low-density lipoprotein cholesterol. The author points out that acquisition costs are a

paramount consideration in these and all economic analyses. One conclusion is that focusing only on secondary prevention may be short-sighted, but, because of costs, specific risk groups should be targeted in primary prevention.

McKenney JM. The cost of treating dyslipidemia using National Cholesterol Education Program (NCEP) Guidelines. *Pharmacoeconomics* 1998;14(suppl 3):19-28.

Spending on Cholesterol Medications in the 1990s

This paper reports on US retail prescriptions for cholesterol-lowering medications from 1991 to 1997. The database captured about 70% of all retail pharmacy prescriptions (in 35,000 pharmacies) but did not account for prescribing in health maintenance organizations that do not use retail pharmacies. Overall, the number of prescriptions for cholesterol-lowering medications increased from 22.5 million in 1991 to 39.9 million in 1997. As a proportion of all medications dispensed, the use of statins increased from 47% to 78% over this same period. Use of the other main classes of agents either fell slightly (niacin, bile acid sequestrants) or remained about the same (fibrates). The trend over this period shows increasing use of simvastatin and decreasing use of lovastatin. The authors point out that these data antedate the publication of the many recent statin trials showing clear clinical benefits in terms of morbidity and mortality with aggressive low-density lipoprotein cholesterol lowering. The authors also conclude that despite the doubling of prescriptions for cholesterol-lowering medications in the mid-1990s, these agents are probably still underprescribed given the current recommendations for treatment.

Siegel D, Lopez J, Meier J. Use of chole-