

PRACTICE INSIGHTS

Key Articles, Guidelines, and Consensus Papers Relative to the Treatment of Dyslipidemias—2005

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Hypercholesterolemia is a major risk factor for development of coronary heart disease. Proper diagnosis and adequate treatment are vital to reducing morbidity and mortality associated with elevated serum lipid levels. The amount of literature in this area is overwhelming. To aid practitioners and educators in organizing this large body of information, we compiled key articles, guidelines, and consensus papers relative to the treatment of dyslipidemias. Research articles were chosen based on the significance of findings, relevance to practice, quality of research, and timeliness; recent articles were given priority over earlier ones unless they demonstrated groundbreaking findings.

Key Words: dyslipidemia, cholesterol, guidelines, hypercholesterolemia, hypertriglyceridemia, coronary heart disease.

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Coronary heart disease (CHD) is the leading cause of death in the United States and other industrialized nations and is the chief cause of premature, permanent disability in the workforce. Hypercholesterolemia is a major risk factor for development of CHD. Thus, it is not surprising that cholesterol is the most "decorated" molecule in history, having contributed to as many as 13 Nobel prizes.¹ In the past 20 years, major strides have been made in the understanding and treatment of hypercholesterolemia and other dyslipidemias. Since its inception in 1985, the National Cholesterol Education Program (NCEP) has battled to reduce the prevalence of high blood cholesterol through educational campaigns and science-based practice guidelines.² However, cholesterol levels are still undertreated.³

The body of literature presented here provides a source of important references and practice guidelines for clinicians seeking to broaden their knowledge regarding treatment of dyslipidemias. Research articles were chosen based on significance of findings, relevance to practice, quality of research, and timeliness; recent articles were given priority over earlier ones unless they demonstrated groundbreaking findings. Selected review articles were included for their comprehensive overview and state-of-the-art perspective.

Epidemiologic Studies

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;256:2827–8.

The Multiple Risk Factor Intervention Trial, a CHD prevention trial, screened 356,222 men as

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possible participants. Overall mortality related to CHD was examined in relation to blood pressure, serum cholesterol levels, and cigarette smoking in men aged 35–50 years. The relationship between cholesterol levels and 6-year risk of death from CHD was steady, continuous, and graded. Of all CHD-related deaths, 46% were estimated to be excess deaths attributable to cholesterol levels of 180 mg/dl or greater, and almost half the excess deaths involved cholesterol levels in higher quintiles. In other words, there was no threshold of cholesterol level at which high risk occurred; risk of death was progressive with increasing total cholesterol levels.

Kronmal RA, Cain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age: a report based on the Framingham data. *Arch Intern Med* 1993;153:1065–73.

The Framingham Heart Study, initiated in 1948 in Framingham, Massachusetts, has been one of the leading longitudinal cohort studies of risk for CHD in both men and women. In this Framingham cohort, the relationship between serum cholesterol levels and all-cause, CHD, and non-CHD mortality as a function of age was evaluated. Elevated cholesterol levels were associated with high all-cause and CHD mortality at age 40 years, negligible at 50–70 years, and negative at 80 years. Similar results were observed with the relationship between low- and high-density lipoprotein cholesterol (LDL and HDL, respectively) and all-cause and CHD mortality in different age groups. Non-CHD mortality was significantly negatively related to cholesterol levels at age 50 years or older. The negative results at age 60 years or older for all-cause and CHD mortality may be due to the negative relationship with LDL levels rather than the protective effects of elevated HDL levels. This study demonstrated that clinicians should be cautious about starting lipid-lowering therapy in elderly men or women.

Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M. Mortality from CHD in subjects with type 2 diabetes and nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229–34.

Type 2 diabetes mellitus is a major risk factor for CHD, which is an independent risk factor (with both strength of epidemiologic association and biologic plausibility). Whether patients with

diabetes without previous CHD are at greater risk for myocardial infarction than those without diabetes who have CHD has been debated. A Finnish population-based study evaluated the 7-year rate of fatal and nonfatal myocardial infarction in 1059 patients with and 1373 patients without diabetes. The 7-year rate of myocardial infarction in patients with diabetes, with and without previous CHD, was significant at 45% and 20.2%, respectively ($p < 0.001$). However, in those without diabetes, with and without previous CHD, the rate was 18.8% and 3.5%, respectively ($p < 0.002$). The hazard ratio (HR) of death after adjustment for age, sex, total cholesterol level, hypertension, and smoking was close to 1.0. This study suggests that patients with and without diabetes (with previous CHD) should be treated aggressively.

Lipids and Lipoprotein Metabolism

Genest J. Lipoprotein disorders and cardiovascular risk. *J Inherit Metab Dis* 2003;26:267–87.

The pharmacotherapy for patients with lipid disorders requires a firm understanding of lipoprotein metabolism and underlying genetic defects. This article is an excellent review of lipoprotein composition and structure, lipoprotein transport and lipid metabolism, and genetic disorders leading to dyslipoproteinemia.

Brewer HB. Increasing HDL cholesterol levels. *N Engl J Med* 2004;350(15):1491–4.

Although LDL remains the primary target for reducing the risk of CHD, the focus on potential targets for raising HDL has increased in recent years. This report reviews the role of HDL in reverse cholesterol transport, with a focus on a recently identified sterol transporter, the adenosine 5'-triphosphate (ATP)-binding cassette transporter 1 (ABCA1). In addition, potential modalities for raising HDL levels are reviewed, such as genetically engineered apolipoprotein A-I Milano (discussed in the Angiographic or Surrogate End Point Trials section) and inhibitors of cholesterol ester transfer protein. The author concludes that drugs being developed to increase HDL levels hold great promise for reducing the risk of cardiovascular disease.

Oram JF, Lawn RM. ABCA1: the gatekeeper for eliminating excess tissue cholesterol. *J Lipid Res* 2001;42:1173–9.

The cellular ATP-binding cassette transporter ABCA1 mediates the initial steps in reverse cholesterol transport. Genetic mutations in ABCA1 cause severe HDL deficiency. This article reviews the role of ABCA1 in removing excess cholesterol from peripheral cells, gene mutation, regulation, and tissue expression of ABCA1. The authors conclude that ABCA1 is the gatekeeper for modulating cholesterol efflux from peripheral tissue and is an attractive target for drug development.

Phan CT, Tso P. Intestinal lipid absorption and transport. *Front Biosci* 2001;6:D299–319.

Inhibition of cholesterol absorption is an important strategy for reducing serum cholesterol levels. This review is an update of our current knowledge of the digestion, uptake, and transport of dietary lipid. The authors discuss the role of intestinal lipid transporters in the uptake of lipids by the enterocytes, how chylomicrons are formed and packaged for export into the lymphatic system through exocytosis, and clinical disorders as they relate to lipid absorption.

Atherogenesis

Libby P. Molecular basis of the acute coronary syndromes. *Circulation* 1995;91:2844–50.

Research in vascular biology has surged in recent years. Advances have led to significant insights into the treatment of atherosclerosis. This article reviews the basic regulatory mechanisms underlying vascular biology. In addition, it reviews research developments that have resulted in the paradigm shift from a focus on high-grade stenosis and revascularization to the vascular biology of the arterial wall and noncritically stenotic plaques (“vulnerable plaques”). These plaques are actually more prone to rupture, leading to acute coronary syndromes (ACS). The author concludes that increased understanding of cellular and molecular mechanisms of the vascular wall in patients with atherosclerosis will lead to novel therapies aimed at stabilizing these vulnerable plaques.

Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med* 1999;340:115–26.

The pathologic process of atherogenesis is mediated and propagated by a variety of inflammatory mediators. This article reviews

factors such as lipids and lipoproteins, homocysteine, hypertension, and infectious microorganisms that induce and promote inflammation. The nature of the inflammatory response and its role in plaque instability and rupture are discussed. The author concludes that atherosclerosis is clearly an inflammatory disease not always associated with hypercholesterolemia. Targeting the various components of the inflammatory process should result in promising new therapies to reduce the risk of cardiovascular disease.

Guidelines and Position Statements

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Third 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) final report. *Circulation* 2002;106:3143-421.

The cholesterol guidelines, issued by the third adult treatment panel (ATP III) of the NCEP in May 2001, reflect the extension of the knowledge base since the ATP II guidelines were issued in 1993. The main focus of the 2001 recommendations is to lower LDL further than recommended previously. The optimum LDL goal decreased from 130 to 100 mg/dl. Although the optimum total cholesterol goal remained the same, lower than 200 mg/dl is considered desirable; HDL level should be at least 40 mg/dl, as compared with 35 mg/dl in the earlier guidelines. Other changes involve treating patients with diabetes who have elevated cholesterol levels more aggressively, testing first for high total cholesterol levels, determining a new level at which low HDL becomes a major risk factor for CHD, intensifying the use of changes in nutrition, increased physical activity, and weight control (therapeutic lifestyle changes), identifying the metabolic syndrome of risk factors linked to insulin resistance, paying more attention to elevated triglyceride levels, and advising against hormone replacement therapy as an alternative to lipid-lowering drugs.

The 2001 guidelines also introduced the concept of the Framingham risk score, or the probability of having a CHD event within 10 years. The score is computed based on age, sex, tobacco use, and high blood glucose level. This score should be calculated for any patient with hyperlipidemia and two or more risk factors for CHD. For a patient whose 10-year risk is greater

than 20%, the LDL goal would be less than 100 mg/dl. All the changes translate to aggressive treatment for patients with diabetes or certain risk factor clusters, and for elderly patients, with lipid-lowering agents as adjunct therapy for a healthier diet and increased physical activity. The 2001 guidelines will increase the use of lipid-lowering agents.

Grundy SM, Cleeman JI, Bairley Merz CN, et al, for the Coordinating Committee of the National Cholesterol Education Program Endorsed by the National Heart, Lung and Blood Institute, American College of Cardiology Foundation, and American Heart Association. Update implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Circulation* 2004;110:227-39.

This update is based on results from the five clinical trials of statin treatment conducted since the release of the NCEP ATP III guidelines in 2001. Endorsed by the American College of Cardiology Foundation, American Heart Association, and National Heart, Lung and Blood Institute (ACC/AHA/NHLBI), this update offers options for more aggressive lowering of LDL levels for individuals at high and moderate risk for CHD. This update emphasizes that therapeutic lifestyle changes remain the cornerstone of treatment for lowering cholesterol levels. For high-risk patients, the goal LDL level is still less than 100 mg/dl; one therapeutic option sets the goal at less than 70 mg/dl for patients at very high risk. The update recommends consideration of lipid-lowering agents as an adjunct to therapeutic lifestyle changes in high-risk patients with an LDL level 100 mg/dl or greater, and consideration of drug treatment as an option for patients whose LDL level is less than 100 mg/dl. For patients at moderately high risk, the update recommends keeping the overall LDL goal of less than 130 mg/dl. One therapeutic option for patients whose LDL level is 100-129 mg/dl is to set the LDL goal below 100 mg/dl, with drug treatment. The update advises that the intensity of LDL-lowering drug treatment in patients at high risk or moderately high risk be sufficient to achieve at least a 30% decrease in LDL level. Finally, for patients at moderate or low risk, the update does not modify the ATP III recommendations.

Pasternak RC, Smith SC Jr, Bairley-Merz CN, et al. ACC/AHA/NHLBI advisory on the use and

safety of statins. *J Am Coll Cardiol* 2002;40:568–73.

These guidelines from the ACC/AHA/NHLBI committee are the first recommendations specifically directed toward health care professionals regarding the use and safety of statins. The committee defined and summarized the current understanding of statin use, including cautions, contraindications, and safety monitoring for statin therapy. More specifically, the committee provides information regarding myopathy compiled by the United States Food and Drug Administration (FDA), clinical trials, and a brief summary from ATP III. These guidelines were released in response to the voluntary withdrawal of cerivastatin from the U.S. market on August 8, 2001, by the manufacturer, in agreement with the FDA. The withdrawal of cerivastatin prompted concerns on the part of physicians and patients regarding the safety of statin therapy. Of note, statins are the most commonly prescribed lipid-lowering agents worldwide, often cited as over 25 million prescriptions. Because of the life-saving potential of statins, the committee's purpose was to enhance the prescribing of statins and dispel any misunderstanding about the safety of these agents.

Haffner SM; American Diabetes Association. Dyslipidemia management in adults with diabetes. *Diabetes Care* 2004;27(suppl 1):S68–71.

The recommendations in this article are based on the earlier American Diabetes Association technical review, Management of Dyslipidemia in Adults with Diabetes, by the same authors (*Diabetes Care* 2003;26(suppl 1):S83–6). That article was a concise review of relevant literature focusing on both drug and nondrug therapy for patients with type 2 diabetes, a disease associated with a 2–4-fold excess risk of CHD. This 2004 article presents screening and diagnoses based on expert opinions. Treatment-goal recommendations based on levels of evidence (A, B, and C) are summarized.

Meta-Analyses of Clinical Trials

LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;282:2340–6.

Although reducing LDL levels lowers the risk of recurrent CHD in middle-aged men, whether

this is true with women and elderly individuals is less certain. The goal of this meta-analysis was to determine the risk reduction of CHD and all-cause mortality associated with statin therapy in women and the elderly. Studies included in the analysis involved patients who were randomized to treatment with a statin or control for at least 4 years; primary outcome was death or a major clinical event. Overall, statin treatment reduced the risk of major clinical events by 31% and all-cause mortality by 21%. No difference in risk reduction of major clinical events was noted between men and women, or between patients aged 65 years or older and those younger than 65 years. The authors concluded that statin therapy for at least 5 years provides risk reduction for middle-aged and elderly men and women.

Amarenco P, Labreuche J, Lavalley P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* 2004;35:2902–9.

Previous studies had shown that statin therapy reduces the risk of stroke; however, the effects of reducing LDL levels on stroke occurrence were not clear. These authors provided a systematic review and meta-analysis of all randomized trials evaluating statin therapy before August 2003. The primary goal of this analysis was to determine the effects of statins and LDL level reduction on stroke occurrence in more than 90,000 patients. The authors evaluated the effect of statins on type and rate of stroke as well as carotid atherosclerosis, measured by intimal medial thickness according to LDL level reduction. Relative risk reduction for stroke was 21%, with no heterogeneity between trials, and with reduction in fatal stroke and no increase in hemorrhagic stroke. Each 10% reduction in LDL level was associated with relative risk reduction of 15.6% and carotid intimal medial thickness of 0.73%/year. Results from this analysis suggest that statin therapy, by decreasing LDL levels, may reduce the rate of stroke. In addition, the results indicate that LDL level reduction is strongly correlated with progression of carotid intimal medial thickness.

Goldberg AC. A meta-analysis of randomized controlled studies on the effects of extended-release niacin in women. *Am J Cardiol* 2004;94:121–4.

The aim of this meta-analysis was to determine the LDL-lowering effects of extended-release

niacin in women compared with men. In five trials involving 432 patients, the difference in LDL level reductions were significantly greater in women than men at all evaluated dosages of extended-release niacin 1000–2000 g/day. In addition, effects on triglyceride level reduction were greater in women and reached significance with 1500 g/day. No difference was noted between men and women regarding lipoprotein(a) and HDL levels. Although the NCEP ATP III does not recommend different guidelines for women and men, HDL and triglyceride levels appear to be stronger risk factors in women than in men. Hence, the metabolic syndrome may be of special concern in women. This is compounded by the fact that LDL and total cholesterol levels as risk predictors are as powerful in women as in men. Niacin is unique in that it substantially improves all major lipid parameters, and the extended-release formulation has been associated with fewer episodes of flushing. This meta-analysis confirms that women respond well to extended-release niacin, which is safe for treatment of mixed hyperlipidemia.

Balk EM, Lau J, Goudas LC, et al. Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. *Ann Intern Med* 2003;139:670–82.

The clinical benefits of statins are largely due to lipid-lowering effect; however, these benefits also are due to nonlipid effects on endothelial function, inflammation, thrombosis, and smooth muscle proliferation (often collectively called pleiotropic effects). These effects have been identified in numerous experiments, and changes have reportedly occurred within weeks or months of the start of therapy. The authors provide a systematic review in an attempt to evaluate the effects of statins on nonlipid serum markers, particularly with lipid levels and CHD outcomes. When appropriate, a meta-analysis was performed. Among the nonlipid markers evaluated, only high-sensitivity C-reactive protein (hs-CRP) levels were significantly lowered by statin therapy. However, no correlation was observed between statin effects on hs-CRP and lipid levels or CHD outcomes. Of note, hs-CRP level was independently associated with premature development of CHD. The findings from this trial, along with those from other clinical trials, indicate that screening for hs-CRP level is appropriate in those at high risk for CHD and that statin therapy may provide an

antiinflammatory effect, potentially contributing to reduction of CHD outcomes.

Corvol JC, Bouzamondo A, Sirol M, Hulot JS, Sanchez P, Lechat P. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. *Arch Intern Med* 2003;163:669–76.

A number of risk factors for first stroke can be addressed, such as having experienced myocardial infarction. The incidence of stroke after myocardial infarction is 1–2%/year, with the greatest risk in the first month. Although antiplatelet therapy (e.g., aspirin) is the mainstay of treatment, trials have suggested that statin therapy may reduce the risk of stroke after myocardial infarction. The authors evaluated 38 trials involving a total of 83,161 patients, with follow-up of about 5 years. The meta-analysis showed a significant relative risk reduction (17%) of stroke with lipid-lowering agents, without significant heterogeneity between trials and between subgroups, according to type of patient or lipid-lowering agent. Statins showed a significant relative risk reduction (26%) in the rate of stroke. This analysis demonstrated that lipid-lowering therapy, particularly statins, reduces the occurrence of stroke in patients with CHD when their total cholesterol level is lowered to less than 232 mg/dl. These results further support statin therapy, along with aspirin, to reduce the occurrence of stroke after myocardial infarction in patients with previous high cholesterol levels.

Prospective Primary Prevention Trials

Statins

Downs JR, Clearfield M, Weis S, et al, for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA* 1998;270:1615–22.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was the first landmark statin trial to show reduction of CHD morbidity and mortality in a cohort of generally healthy individuals without clinical evidence of coronary artery disease (CAD). This randomized, double-blind, placebo-controlled trial investigated the benefits of long-term lovastatin therapy in men and women with average LDL and total cholesterol levels, and

lower-than-average HDL levels. The study randomized 6605 participants to receive either placebo or lovastatin 20 mg/day, which could be titrated to 40 mg/day to maintain LDL levels of 110 mg/dl or lower. Baseline mean total cholesterol and LDL levels were 221 and 150 mg/dl, respectively. The primary end point was a composite of sudden cardiac death, fatal and nonfatal myocardial infarction, and unstable angina. Participants receiving lovastatin experienced a 37% relative risk reduction for the first acute major coronary event compared with those receiving placebo (Cox proportional hazards model, 95% confidence interval [CI] 21–50%, $p < 0.001$). Also, AFCAPS/TexCAPS showed that benefit with lovastatin therapy extended to Hispanics, African-Americans, and older persons. This study was the first large-scale primary prevention trial to include a substantial number of women and to include unstable angina in the primary end point.

Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–7.

The West of Scotland Coronary Prevention Study (WOSCOPS) was the first landmark trial to demonstrate the benefit and safety of lipid-lowering therapy with a statin in patients with hypercholesterolemia for prevention of CHD. The authors evaluated the effectiveness of pravastatin in preventing coronary events in men with moderate hypercholesterolemia, a baseline LDL level of 155 mg/dl or greater, and no history of myocardial infarction. The study randomized 6595 men aged 45–64 years to receive either placebo or pravastatin 40 mg every evening. The combined primary end point was the occurrence of nonfatal myocardial infarction or death from CHD as a first event. Other end points were the effect of treatment on death from cardiovascular causes, death from any cause, and frequency of coronary revascularization procedures. Pravastatin produced a 31% risk reduction of the combined primary end point (95% CI 17–43%, $p < 0.001$) compared with placebo after 4.9 years of follow-up. This study also showed that pravastatin reduced the risk of coronary angiography, percutaneous transluminal coronary angiography, coronary artery bypass grafting, and death from all cardiovascular causes.

Sever PS, Dahlof B, Poulter NR, et al. Prevention

of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian cardiac outcomes trial–lipid lowering arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149–58.

This study reported the results from the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA), a multicenter, randomized trial comparing two antihypertensive treatment strategies for primary prevention of CHD. Results showed that adding statins to antihypertensive therapy reduced CHD risk in patients with hypertension and moderate cardiovascular risk who were not conventionally considered to have dyslipidemia. The ASCOT-LLA results support the benefit of early treatment of patients at high risk of cardiovascular events. In this double-blind, two-by-two factorial comparison, 10,305 patients with hypertension from ASCOT were randomized to receive atorvastatin 10 mg/day or placebo. Study patients had total cholesterol levels of 250 mg/dl or lower and at least three risk factors for cardiovascular disease. The primary end point was the combination of nonfatal myocardial infarction, silent myocardial infarction, and fatal CHD.

The study was terminated early on recommendation of the data safety monitoring board because atorvastatin therapy had resulted in a highly significant reduction in the primary end point of CHD events and in the rate of stroke compared with placebo. Relative risk of the primary end point was reduced by 36% (HR 0.64, 95% CI 0.50–0.83, $p = 0.0005$) after 1 year of follow-up. Four of the secondary end points (total cardiovascular events, total coronary events, and fatal or nonfatal stroke) and the primary end point (except for silent myocardial infarction) were also significantly reduced. Other than the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), ASCOT-LLA was the only trial to study the effects of lipid-lowering therapy specifically in patients with hypertension. The results support the trend to treat numerous cardiovascular risks in patients with hypertension because statin therapy conveyed benefits in addition to good blood-pressure control.

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic,

hypertensive patients randomized to pravastatin vs usual care: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT). *JAMA* 2002;288:2998–3007.

This randomized, nonblinded trial was the lipid-lowering component of ALLHAT. The purpose of the study was to determine the effects of pravastatin versus usual care in a subset of patients with hypertension, moderate hypercholesterolemia, and at least one other CHD risk factor. The study also assessed CHD reduction and other benefits in populations that have been excluded or underrepresented in previous trials, such as older patients, women, and racial and ethnic minority groups. The study randomized 10,355 participants to receive pravastatin 40 mg/day or usual care, which was at the discretion of primary care physicians. The primary end point was all-cause mortality, the secondary outcome a composite of fatal or nonfatal CHD events.

After a mean of 4.8 years, calculated LDL levels decreased by 27.7% and 11.0% in the pravastatin and usual-care groups, respectively. The primary end point of all-cause mortality was not significantly different between the two groups (relative risk [RR] 0.99, 95% CI 0.89–1.11, $p=0.88$), nor was the secondary end point (RR 0.91, 95% CI 0.79–1.04, $p=0.16$). Failure to detect mortality and morbidity benefits with pravastatin was attributed to several reasons. One reason was a decline in adherence to the prescribed treatment over time; another was a high rate of crossover of patients from the usual-care group to the pravastatin group, and a third was a modest differential in total cholesterol levels (9.6%) between the pravastatin and usual-care groups. In a subgroup analysis, however, pravastatin significantly reduced CHD events in African-Americans. The authors suggested that achieving larger reductions in total cholesterol and LDL levels is needed to achieve reduced CHD risk.

Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–96.

The Collaborative Atorvastatin Diabetes Study (CARDS) was the first primary prevention study to show reduction of major cardiovascular events in a population with type 2 diabetes and a

moderate LDL level. This randomized, double-blind, placebo-controlled study investigated the effectiveness of atorvastatin versus placebo in the primary prevention of cardiovascular disease in patients with type 2 diabetes. The study enrolled 2838 men and women aged 40–75 years with type 2 diabetes and at least one of the following other risk factors: hypertension, retinopathy, macroalbuminuria, microalbuminuria, or smoking. Study patients had baseline LDL levels of 160 mg/dl or lower and triglyceride levels of 600 mg/dl or lower. Eligible patients were randomized to receive either atorvastatin 10 mg/day or placebo, but investigators were allowed to prescribe treatment in addition to the study drug if further lipid-lowering therapy was needed. Additional treatment could include atorvastatin 10 mg/day, simvastatin up to 40 mg/day, pravastatin up to 40 mg/day, fluvastatin up to 80 mg/day, and cerivastatin 0.3 mg/day. The primary end point was a composite of an acute CHD event, coronary revascularization procedures, and stroke. Atorvastatin treatment was associated with a 37% reduction in occurrence of the primary end point (HR 0.63, 95% CI 0.48–0.83, $p=0.001$). Separate assessment of each component revealed reductions of 36% in acute coronary events, 31% in coronary revascularization events, and 48% in stroke. Overall, CARDS was the first trial to study the effects of a statin exclusively in patients with diabetes, unlike other studies that performed only subgroup analyses of patients with diabetes.

Fibrates

World Health Organization Committee of Principal Investigators. WHO cooperative trial on primary prevention of ischaemic heart disease with clofibrate to lower serum cholesterol: final mortality follow-up. Report of the committee of principal investigators. *Lancet* 1984;2:600–4.

This is the final report of the World Health Organization (WHO) cooperative trial that investigated the effects of clofibrate versus placebo on ischemic heart disease (IHD) in healthy men without evidence of heart disease. The study compared a high-risk group of men receiving clofibrate with a high-risk control group and a low-risk control group. The results, first published in 1978, showed a 25% reduction ($p<0.05$) in nonfatal myocardial infarction among men with plasma cholesterol levels in the upper third of the distribution who were given clofibrate. However, mortality from all causes

and causes other than IHD was significantly higher in the clofibrate group. The first posttrial follow-up report showed 25% more deaths in the clofibrate group than in the high-cholesterol control group ($p < 0.01$).

This warranted a follow-up of mortality for an additional 4 years. After an average of 13.2 years from time of study entry to the end of the final follow-up, 1788 deaths occurred in 208,000 patient-years of observation. A total of 720 deaths (8.6/1000 patients/yr) occurred from all causes in the clofibrate group, 650 (7.9/1000/yr) in the high-risk control group, and 418 (5.7/1000/yr) in the low-risk control group. Differences in the total numbers and rates/1000 patients/year of deaths between the clofibrate group and the high-risk control group were not statistically significant. Excess deaths in the clofibrate group were more numerous during the treatment phase than after treatment ended. The final report of the WHO cooperative study showed an excess mortality in patients treated with clofibrate, but this was confined to the clofibrate treatment period and did not continue during follow-up. Clofibrate reduced the occurrence of nonfatal myocardial infarction, but not mortality, from IHD.

Frick MH, Elo O, Haapa K, et al. Helsinki heart study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237–45.

The Helsinki Heart Study was the first primary prevention trial to show that lipid-lowering treatment with gemfibrozil reduces the risk of CHD in men with dyslipidemia. This double-blind, placebo-controlled trial investigated the effects of gemfibrozil on fatal and nonfatal myocardial infarction and cardiac death. The study randomized 4081 middle-aged men without CAD, and whose non-HDL (defined as total cholesterol minus HDL) level was 200 mg/dl or greater, to receive either gemfibrozil 600 mg twice/day or placebo. In the gemfibrozil group, HDL levels increased by 10%, whereas LDL, non-HDL, total cholesterol, and triglyceride levels were reduced by 10%, 14%, 11%, and 43%, respectively. After a mean follow-up of 60.4 months, 56 cardiac events had occurred in the gemfibrozil group compared with 84 in the placebo group ($p < 0.02$). This represents a reduction of 34.0% (95% CI 8.2–52.6) in cardiac end points. The greatest reduction was seen in

the rate of nonfatal myocardial infarction. The gemfibrozil group experienced 45 nonfatal myocardial infarctions compared with 71 ($p < 0.02$) in the placebo group (37% reduction, $p < 0.05$). Kaplan-Meier curves for occurrence of definite cardiac end points showed that the curves began to separate after the first 2 years of treatment, and continued to decrease in the gemfibrozil group. However, no differences between the two groups were noted regarding mortality.

In the safety analysis, the gemfibrozil group experienced a higher rate of moderate-to-severe upper gastrointestinal symptoms (11.3% vs 7.0% in placebo group, $p < 0.0001$). Overall, the Helsinki Heart Study—the one major study evaluating gemfibrozil in patients undergoing primary preventive treatment—demonstrated that gemfibrozil reduced the risk of fatal and nonfatal myocardial infarction and sudden death, but not overall mortality.

Keech A, Simes RJ, Barter P, et al, for the FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849–61.

The Fenofibrate Intervention and Event Lowering in Diabetes study, a prospective, randomized, placebo-controlled trial, was the first to investigate the effects of a fibrate on cardiovascular events in patients with type 2 diabetes with and without previous myocardial infarction. A total of 9795 patients aged 50–75 years not receiving statin therapy at study entry were randomized to receive micronized fenofibrate 200 mg/day (4895 patients) or matching placebo (4900 patients) for 5 years, after a fenofibrate and placebo run-in phase. The primary outcome was coronary events (CHD death or nonfatal myocardial infarction). The outcome for prespecified subgroup analyses was total cardiovascular events (a composite of cardiovascular death, myocardial infarction, stroke, and coronary and carotid revascularization).

Mean baseline LDL, HDL, and triglyceride levels were 118.7, 42.5, and 153.3 mg/dl, respectively. Coronary events were not significantly reduced (5.9% of patients receiving placebo, 5.2% of those receiving fenofibrate; relative reduction 11%, $p = 0.16$). However, nonfatal myocardial infarctions were significantly reduced (24%, $p = 0.010$), as were revascularization procedures (21%, $p = 0.003$). Total

cardiovascular mortality and overall mortality were not significantly reduced. Significant increases in the rate of pancreatitis (0.5% with placebo vs 0.8% with fenofibrate, $p=0.031$) and pulmonary embolism (0.7% vs 1.1%, $p=0.022$) were seen in the fenofibrate group.

The authors concluded that because a number of patients in the placebo group started receiving statin therapy, the benefits of fenofibrate may have been masked. In addition, baseline triglyceride and HDL levels were not in ranges in which benefits from fibrate therapy would typically be seen. The FIELD study further emphasizes that statins should be primary therapy and that fibrates could be administered in selected patients with atherogenic dyslipidemia. The incremental benefits of a fibrate added to statin therapy are being investigated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

Resins

Lipid Research Clinics Coronary Primary Prevention Trial Investigators. The lipid research clinics coronary primary prevention trial results: the relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 1984;251:365–74.

The lipid research clinics coronary primary prevention trial (LRC-CPPT) was one of the first studies to show that lipid-lowering therapy reduces risk of CHD in men with primary hypercholesterolemia. This multicenter, double-blind, clinical trial randomized 3806 men aged 35–59 years, without signs of CHD and with plasma cholesterol levels 256 mg/dl or greater, to receive either cholestyramine 24 g/day or placebo. The primary end point was the combination of definite CHD-related death and/or definite nonfatal myocardial infarction. Other end points were all-cause mortality, positive exercise test result, angina pectoris, atherothrombotic brain infarction, peripheral vascular disease, and transient cerebral ischemic attack.

After 7 years of follow-up, average plasma total cholesterol and LDL level reductions were 13.4% and 20.3%, respectively, in the cholestyramine group; these levels were significantly greater ($p<0.001$) than in the placebo group. The cholestyramine group experienced risk reductions of 24% for CHD death and 19% for the primary end point of CHD death or nonfatal myocardial infarction ($p<0.05$). Cholestyramine

also resulted in reductions of 20% ($p<0.01$) in the frequency of development of angina, 25% ($p<0.001$) in the development of a positive exercise test result, and 21% ($p=0.06$) in the frequency of coronary artery bypass surgery. The rate of all-cause mortality was not statistically different between the two groups.

Additional analysis of data from LRC-CPPT provided more information regarding the relationship between lipid lowering and occurrence of CHD. An 18.8% reduction in occurrence of CHD corresponded to decreases of 7.9% in total cholesterol level and 10.8% in LDL level. A clear dose-response relationship was noted between lipid changes and reported cholestyramine intake. Also, analysis showed that increased HDL levels were independently related to reduced CHD occurrence in the cholestyramine group.

Overall, LRC-CPPT was the first primary prevention study to conclusively show reduction in CHD risk with cholestyramine resin treatment. Other major trials conducted at the time of LRC-CPPT were either secondary prevention trials or studies evaluating diet intervention. The LRC-CPPT authors concluded that the degree of lipid lowering achieved with cholestyramine 24 g/day potentially reduces CHD risk by nearly 50%.

Secondary Prevention Trials

Statins

Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994;344:1383–9.

The Scandinavian Simvastatin Survival Study was the first landmark statin trial and the first to demonstrate a statistically significant reduction in overall mortality secondary to lipid intervention. The study also answered questions as to whether statin therapy could improve survival because of increases in non-CHD deaths seen in other studies. The study was a double-blind trial that randomized 4444 men and women with CHD to receive simvastatin 20–40 mg/day or placebo. The primary end point was total mortality, and the secondary end point was time to major coronary events. After a median follow-up of 5.4 years, 256 (12%) patients in the placebo group had died, compared with 182 (8%) in the simvastatin group. Relative risk of total mortality with simvastatin was 0.70 (95% CI

0.58–0.85, $p=0.0003$). Relative risk of major coronary events, also lower in the simvastatin group, was 0.88 (95% CI 0.59–0.75, $p<0.0001$). Benefits of simvastatin were seen in both sexes and in all age groups; no significant between-group differences were noted in noncardiovascular deaths.

Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels: cholesterol and recurrent events trial investigators. *N Engl J Med* 1996;335:1001–9.

The Cholesterol and Recurrent Events trial (CARE) trial was the first secondary prevention study to evaluate the effectiveness of lipid lowering in a population with average plasma lipid levels. This double-blind study randomized 4159 patients with previous myocardial infarction to receive either pravastatin 40 mg/day or placebo. The primary end point was CHD death or a symptomatic, nonfatal myocardial infarction. Mean LDL level at baseline was 139 mg/dl, and the pravastatin group experienced an LDL level reduction of 32%. Compared with the placebo group, pravastatin-treated patients had lower LDL (28%), total cholesterol (20%), and triglycerides (14%) levels; HDL level was higher (5%; $p<0.001$ for all comparisons). The frequency of the primary end point was 24% lower with pravastatin than placebo ($p=0.003$). Rates of nonfatal myocardial infarction, coronary artery bypass surgery, angioplasty, and stroke were all significantly lower with pravastatin than placebo. No between-group difference in CHD mortality was noted. Baseline LDL level influenced the extent of CHD risk reduction in the pravastatin group. Patients with higher LDL levels at baseline had greater reduction in major coronary events with pravastatin, whereas those with lower LDL levels at baseline had smaller, if any, reduction. Among the notable adverse effects observed, significantly more breast cancer developed in the pravastatin group than in the placebo group. The CARE trial demonstrated that lowering cholesterol levels in patients with typical or average LDL levels reduced the risk of recurrent coronary events.

Heart Protection Study Collaborative Group. MRC/BHF Heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22.

The Medical Research Council/British Heart Foundation Heart Protection Study (HPS) evaluated the benefits of lipid-lowering therapy in high-risk patients largely underrepresented in other clinical trials, such as those with diabetes or noncoronary occlusive arterial disease, elderly or female patients, and those with below average cholesterol levels. Also, the HPS provided more information regarding the effects of statins on site-specific cancers. The study enrolled over 20,000 patients, the largest number in a statin trial. Study patients had a substantial 5-year risk of death due to history of coronary disease, noncoronary occlusive arterial disease, diabetes, or treated hypertension. Patients were randomized to a 2 x 2 factorial design consisting of simvastatin 40 mg/day or matching placebos, as well as antioxidant vitamins or matching placebos. Primary outcomes were total, coronary, and noncoronary mortality; secondary outcomes were major coronary and vascular events, such as stroke.

After a mean follow-up of 5 years, reductions in the simvastatin group were 17% in all-cause mortality ($p<0.0001$), 18% in coronary death ($p=0.0005$), and 16% in death from other vascular causes ($p=0.07$). In addition, simvastatin significantly reduced the relative risk of major coronary events by 27%, stroke by 25%, and any revascularization by 24% ($p<0.0001$ for all). Benefit from simvastatin therapy was seen in all age subgroups, including 75–85 years, and all baseline LDL level subgroups, even patients with baseline LDL levels less than 116 mg/dl. Risk reduction with simvastatin was independent of treatment with angiotensin-converting enzyme (ACE) inhibitors, β -blockers, and aspirin. No significant differences were noted in rate or type of cancer between the two groups.

The HPS demonstrated that lowering cholesterol levels with statin therapy substantially reduced the frequency of coronary and noncoronary vascular events in a wider range of high-risk patients than had been demonstrated before. The study enrolled a large number of patients from subgroups, such as those with diabetes, cerebrovascular disease, or peripheral arterial disease. High-risk patients with relatively low baseline LDL levels (< 116 mg/dl) also benefitted from simvastatin therapy, which contributes to the NCEP optional LDL level goal of less than 70 mg/dl for patients at highest risk.

Long-Term Intervention with Pravastatin in Ischemic 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 levels. *N Engl J Med* 1998;399:1349–57.

The LIPID study investigated the effects of pravastatin on CHD death in patients with a history of myocardial infarction or unstable angina and a broad range of cholesterol levels. This study differs from the 4S and CARE studies in that it involved patients with lower initial cholesterol levels and evaluated the primary end point of CHD death alone instead of a composite end point. Over 9000 patients with a history of myocardial infarction or unstable baseline and total cholesterol levels of 155–271 mg/dl were randomized to receive pravastatin 40 mg/day or matching placebo. The primary end point, death from CHD, was further subclassified into categories. Secondary outcomes included all-cause mortality, myocardial infarction, stroke, and coronary revascularization. After a mean follow-up of 6 years, a 24% relative risk reduction in the primary outcome of CHD death was noted with pravastatin therapy compared with placebo (95% CI 12–35%, $p < 0.001$). Overall rate of mortality was 22% lower (95% CI 13–31%, $p < 0.001$) and mortality from cardiovascular causes 25% lower ($p < 0.001$) in the pravastatin group. Fewer patients died of cancer, trauma, or suicide in the pravastatin than placebo group, but the differences were not statistically different.

Results from the LIPID study extend the benefits of statin therapy to high-risk patients with low baseline LDL levels and to all patients with CHD, including those with a history of unstable angina or stroke. This study also showed that pravastatin reduces CHD mortality and all-cause mortality without increasing the risk of death due to trauma, suicide, or cancer.

Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–504.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE IT–TIMI) 22 study demonstrated that intensive lipid level reduction of LDL to a target level of approximately 70 mg/dl in patients with recent ACS provides additional CHD risk reduction beyond standard lipid level reduction to an LDL goal of approximately 100 mg/dl. The study randomized

4162 patients hospitalized within the preceding 10 days for unstable angina or acute myocardial infarction to receive either pravastatin 40 mg/day, considered standard lipid-lowering therapy, or atorvastatin 80 mg/day, considered intensive lipid-lowering therapy. (Patients were also randomized to receive gatifloxacin or placebo in a 2 x 2 factorial design, but those results are reported elsewhere.) The primary efficacy end point of PROVE IT–TIMI 22 was time to the first occurrence of a composite of all-cause mortality, myocardial infarction, unstable angina requiring rehospitalization, revascularization, or stroke. The secondary end point was risk of CHD death, nonfatal myocardial infarction, or revascularization. At the time of randomization, median LDL level was 106 mg/dl for both groups. The pravastatin group achieved a median LDL level of 95 mg/dl during treatment, whereas this level was 62 mg/dl in the atorvastatin group ($p < 0.001$).

After 2 years, the event rate in the standard-therapy pravastatin group was 26.3% versus 22.4% in the intensive-therapy atorvastatin group, representing a 16% hazard ratio reduction with atorvastatin (95% CI 5–26%, $p = 0.005$). The secondary end point was reduced by 14% in the atorvastatin group as well ($p = 0.029$). The benefit of high-dose atorvastatin was consistent across the prespecified subgroups, which included men and women, patients with unstable angina, those with myocardial infarction, and those with and without diabetes. However, patients with baseline LDL levels above 125 mg/dl had greater reductions in hazard ratio than those with baseline LDL levels below 125 mg/dl. In terms of safety, the atorvastatin group had a significantly greater rate of elevated alanine aminotransferase level (3.3%) than the pravastatin group (1.1%, $p < 0.001$).

Overall, the PROVE IT–TIMI 22 study showed that intensive therapy with a high-dose statin to lower LDL level to approximately 70 mg/dl reduced the risk of another cardiovascular event compared with standard therapy with a moderate-dose statin to lower LDL level to approximately 100 mg/dl. This study demonstrated that patients with recent ACS may benefit from further lipid-lowering therapy beyond the standard LDL goal of less than 100 mg/dl.

De Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute

coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;292:1307–16.

Phase Z of the Aggrastat to Zocor (A to Z) Trial evaluated the benefits of intensive simvastatin treatment started soon after an ACS event compared with conservative simvastatin treatment started in a delayed manner. A second component of the study, phase A, compared enoxaparin and unfractionated heparin in patients with ACS treated with tirofiban and aspirin; the results were published elsewhere. In phase Z, patients with non-ST-elevation ACS or ST-elevation myocardial infarction and a total cholesterol level less than 250 mg/dl were randomized to receive either simvastatin 40 mg/day for 30 days and then simvastatin 80 mg/day, or placebo for 4 months and then simvastatin 20 mg/day. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke. Secondary end points were revascularization, all-cause mortality, new-onset heart failure, and others.

After a median follow-up of 721 days, rates of primary end point events did not differ significantly between the two groups. The simvastatin-plus-placebo group incurred 343 cases (in 16.7% of patients) of cardiovascular death, myocardial infarction, readmission for ACS, and stroke, compared with 309 (14.4%) in the simvastatin-only group (HR 0.89, 95% CI 0.76–1.04, $p=0.14$). Among the secondary end points, only cardiovascular death and new-onset heart failure were significantly lower in the simvastatin-only than placebo-plus-simvastatin group. In terms of safety and tolerability, the simvastatin-only treatment group had greater rates of aspartate aminotransferase and alanine aminotransferase elevations and myopathy with creatine kinase elevations.

Overall, starting intensive simvastatin therapy soon after ACS did not reduce the composite primary end point compared with delayed start of conservative simvastatin therapy. However, rates of cardiovascular death and new-onset heart failure were lower. The failure to detect between-group differences in primary outcome could have been caused by less statistical power than predicted and by a small between-group difference in LDL levels. Compared with the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, a larger population in the A to Z trial received glycoprotein IIb-IIIa inhibitor therapy or had

planned revascularization procedures, which may have competed with statin therapy to reduce cardiovascular events. In addition, patients in the A to Z trial were randomized several days earlier than those in the PROVE IT-TIMI 22 study, representing a less stable and higher risk patient group. These explanations could contribute to understanding why the intensive-treatment group did not experience benefits over the conservative-treatment group, as seen in other studies.

Schwartz GG, Olsson AG, Ezekowitz MD, et al, for the Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285:1711–18.

The MIRACL study was the first to investigate whether statin therapy begun soon after recent unstable angina or non-Q-wave acute myocardial infarction reduces deaths and recurrent ischemic events. Previously, these high-risk patients were excluded from large trials. The MIRACL study randomized 3086 patients with ACS to receive either atorvastatin 80 mg/day or placebo for 16 weeks, with treatment starting 24–96 hours after hospitalization. The primary combined end point was death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia. Secondary end points were the occurrence of each primary end point component plus nonfatal stroke, new or worsening heart failure, worsening angina requiring hospitalization, or other cardiovascular end points.

During the study, no statistically significant difference was noted between the two groups in primary end point. There were 228 occurrences (14.8% of patients) of primary end point events in the atorvastatin group and 269 (17.4%) in the placebo group (RR 0.84, 95% CI 0.70–1.00, $p=0.48$). Of the primary end point components, only recurrent symptomatic myocardial ischemia was reduced in the atorvastatin group. Regarding secondary outcomes, atorvastatin significantly reduced the risk of fatal and nonfatal stroke but not of other outcomes, such as coronary revascularization or worsening angina. In addition, more patients in the atorvastatin than placebo group had elevated liver transaminase levels (2.5% vs 0.6%, $p<0.001$).

Overall, the MIRACL study showed that treatment with atorvastatin 80 mg/day started

soon after a coronary event reduced recurrent ischemic events. However, the study did not show statistically significant benefits in reducing the risk of death or the combined primary end point after ACS in atorvastatin-treated patients. The study duration may have been too short to detect such a difference.

Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease: atorvastatin versus revascularization treatment investigators. *N Engl J Med* 1999;341:70–6.

This study tested the hypothesis that lipid-lowering treatment with atorvastatin can delay or prevent the need for revascularization without increasing the risk of ischemic events in patients with one- or two-vessel CAD, relatively normal left ventricular function, and no severe symptoms of angina pectoris. The study randomized 341 patients with stable CAD who had been recommended for percutaneous revascularization to receive either lipid-lowering treatment with atorvastatin 80 mg/day or the recommended revascularization procedure (angioplasty) followed by usual care. The primary end point was ischemic events, defined as death from cardiac causes, resuscitation after cardiac arrest, nonfatal myocardial infarction, cerebrovascular accident, coronary artery bypass graft, angioplasty, or worsening angina.

After 18 months of follow-up, 22 (13%) patients in the atorvastatin group and 37 (21%) in the angioplasty group had ischemic events ($p=0.048$). However, this difference did not reach a level of significance after adjustment for interim analysis. In addition, fewer revascularization procedures were performed in the atorvastatin than angioplasty group (20 [12%] vs 29 [16%] patients). Treatment with atorvastatin was also associated with a significantly longer time to a first ischemic event ($p=0.03$). However, angina symptoms improved in a significantly larger percentage of angioplasty patients, although this may have been due to increased administration of nitrates in this group.

Overall, this study found a lower frequency of ischemic events over 18 months and a longer time to a first event in patients receiving intensive lipid-lowering therapy than in those who underwent angioplasty. Fewer atorvastatin-treated patients were hospitalized with worsening angina or underwent bypass surgery or angioplasty during the follow-up period. The

authors concluded that aggressive treatment with atorvastatin appears to be as safe and effective as angioplasty and usual care in reducing ischemic events in patients with stable one- or two-vessel CAD.

Athyros VG, Mikhailidis DP, Papageorgiou AA, et al, for the GREACE Study Collaborative Group. Relationship between LDL-c and non-HDL-C levels and clinical outcome in the greek atorvastatin and coronary-heart-disease evaluation (GREACE) study. *Curr Med Res Opin* 2004;20:1385–92.

The GREACE study was performed because of the controversy surrounding the relationship between baseline LDL level and the extent of cholesterol reduction. Some studies demonstrated a linear relationship, whereas others demonstrated a threshold or no relationship. The GREACE study sought to determine whether cholesterol levels and the extent of LDL level reduction have a direct relationship on the primary outcomes of coronary mortality and nonfatal myocardial infarction. The study enrolled men and women younger than 75 years recently hospitalized for an ACS event, with baseline LDL levels below 100 mg/dl and triglyceride levels below 400 mg/dl. Patients were randomized either to usual care or to structured care with atorvastatin 10 mg/day titrated until achievement of an LDL level below 100 mg/dl.

In the usual-care group, a direct relationship was noted between the primary end points and baseline LDL levels ($R=0.273$, $p<0.0001$) or LDL levels during the study ($R=0.318$, $p<0.0001$). A trend toward greater CHD event rates was observed in the higher baseline LDL level quartiles. However, in the structured-care group, no relationship was noted between LDL or non-HDL levels and the primary end points. Patients in the upper two quartiles according to baseline LDL levels needed greater atorvastatin dosages to achieve LDL levels lower than 100 mg/dl and had disproportionately higher relative risk reductions than patients in the lower two quartiles. Overall, the GREACE study demonstrated a linear relationship between LDL levels and cardiovascular outcomes. It also showed that patients with the highest baseline LDL levels benefitted the most from reductions to less than 100 mg/dl in cardiovascular events. Therefore, a target-oriented strategy for lowering cholesterol may be better than a single-dose strategy for all patients.

Serruys PW, de Feyter P, Macaya C, et al, for the Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;287:3215–22.

The LIPS was the first prospective trial to evaluate the effects of a statin on clinical end points in patients undergoing their first percutaneous coronary intervention (PCI). This study investigated whether fluvastatin versus placebo prolongs survival time free of cardiac disease after successful completion of first PCI, with or without stenting. This double-blind trial included 1677 men and women after PCI of one or more lesions in native coronary arteries; their total cholesterol levels were 135–170 mg/dl. Patients were randomized to receive either fluvastatin 40 mg twice/day or placebo for 3–4 years. The primary outcome was a composite of cardiac death, nonfatal myocardial infarction, and a reintervention procedure (defined as coronary artery bypass graft, repeated PCI, or PCI for a new lesion).

After a median follow-up of 3.9 years, survival time free of cardiac events was significantly longer in the fluvastatin group (first quartile of time to first event 1558 days) than in the placebo group (1227 days, $p=0.01$). Also, 21.4% of the fluvastatin group and 26.7% of the placebo group had at least one primary end point, resulting in a significant risk reduction of cardiac events (RR 0.78, 95% CI 0.64–0.95, $p=0.01$). Overall, LIPS showed that early lipid-lowering therapy with fluvastatin 80 mg/day after PCI reduced absolute risk of fatal and nonfatal cardiac events by 5.3%, and relative risk by 22%. In addition, results from LIPS also suggest that benefits are equal and significant regardless of baseline cholesterol levels, unlike the CARE study. This adds support to the use of aggressive approaches to lowering cholesterol levels and treating patients based on risk instead of baseline cholesterol levels.

LaRosa JC, Grundy SM, Waters DD, et al, for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425–35.

The TNT study investigated whether intensive lipid-lowering therapy with atorvastatin 80 mg/day is associated with better outcomes than moderate lipid-lowering therapy with atorvastatin 10 mg/day in patients with stable nonacute CHD.

This double-blind, parallel-group study randomized 10,001 patients to the two treatment groups. The primary outcome was occurrence of a major cardiovascular event, defined as CHD death, nonfatal myocardial infarction, and fatal and nonfatal stroke. Mean LDL levels during the study were 77 and 101 mg/dl for patients receiving atorvastatin 10 and 80 mg/day, respectively. Total cholesterol and triglyceride levels were also significantly lower with atorvastatin 80 mg/day, but HDL levels were similar in the two groups. The event rate of the composite primary outcome was 8.7% and 10.9% with atorvastatin 80 and 10 mg/day, respectively, representing a 22% relative risk reduction (HR 0.78, 95% CI 0.69–0.89, $p<0.001$). Although no between-group difference was noted in all-cause mortality, patients receiving atorvastatin 80 mg/day experienced significant risk reductions for any major coronary event, a cerebrovascular event, any cardiovascular event, and any coronary event. However, significantly more adverse events occurred in patients receiving atorvastatin 80 mg/day, including more atorvastatin discontinuations and cases of persistently elevated liver enzyme levels. The rate of treatment-related myalgia was similar between the groups.

Overall, the TNT study demonstrated that more aggressive treatment of hypercholesterolemia to target levels below the current NCEP ATP III guidelines provided additional clinical benefit over moderate treatment to a goal of less than 100 mg/dl. Just as the PROVE IT–TIMI 22 study helped lower LDL level goals for patients with ACS, the TNT study may provide evidence that lower LDL level goals could be beneficial for patients with stable CHD.

Pedersen TR, Faergeman O, Kastelein JJ, et al, for the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;294:2437–45.

The IDEAL study is one of the few final studies testing the hypothesis that there is further benefit of reducing LDL levels to less than 100 mg/dl. This prospective, randomized, open-label study randomized 8888 adults with a history of acute myocardial infarction to receive atorvastatin 80 mg/day or simvastatin 20 mg/day. The primary outcome measure was a major coronary event

(coronary death, confirmed nonfatal myocardial infarction, or cardiac arrest with resuscitation) at a median follow-up of 4.8 years. Mean baseline LDL level was 121 mg/dl in both groups and was reduced to 80.0 and 99.8 mg/dl in the atorvastatin and simvastatin groups, respectively. A major coronary event occurred in 411 (9.3%) atorvastatin patients and 463 (10.4%) simvastatin patients, resulting in a relative risk reduction of 11% ($p=0.07$). The rate of nonfatal myocardial infarction was reduced by 17% ($p=0.02$); however, rates of coronary deaths and all-cause mortality were similar in both treatment groups. Myalgia, liver function abnormalities, and adverse events resulting in permanent drug discontinuation were significantly higher in patients receiving atorvastatin. Although this study did not demonstrate a reduction in major coronary events with more aggressive lowering of LDL levels, several of the prespecified end points did. The authors offered several reasons to explain why statistical significance was not reached for the primary end point. However, the important findings of this study show consistency with the total body of evidence that more aggressive lowering of LDL levels is beneficial. The increased risk of statin-associated adverse events with higher dosages also is consistent with findings of other similar studies.

Fibrates

Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol: Veterans Affairs high-density lipoprotein cholesterol intervention trial study group. *N Engl J Med* 1999;341:410–18.

The Veterans Affairs high-density lipoprotein cholesterol intervention trial (VA-HIT) was the first large-scale intervention trial to focus on patients with CHD and low levels of HDL but relatively normal LDL. This study demonstrated that increasing HDL levels and lowering triglyceride levels with gemfibrozil significantly reduces the risk of nonfatal myocardial infarction or coronary death. The VA-HIT randomized 2531 men with HDL levels of 40 mg/dl or less and LDL levels of 140 mg/dl or less to receive gemfibrozil 1200 mg/day or placebo. The primary outcome was the combined rate of nonfatal myocardial infarction and death from CHD. In the gemfibrozil group, mean HDL level was 6% higher than in the placebo group, mean

total cholesterol was 4% lower, and mean triglycerides were 31% lower. Mean LDL levels were not significantly different between the two groups. After a mean of 5 years of follow-up, gemfibrozil reduced the rate of the primary outcome by 22% (95% CI 7–35%, $p=0.006$). Gemfibrozil also significantly reduced the risk of transient ischemic attacks and carotid endarterectomy. Dyspepsia was the only adverse event to occur more often in the treatment group. Overall, VA-HIT demonstrated that increasing low HDL levels in patients with CHD without affecting LDL levels can reduce recurrent coronary events.

Bezafibrate Infarction Prevention Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the bezafibrate infarction prevention (BIP) study. *Circulation* 2000;102:21–7.

The BIP study evaluated whether bezafibrate reduces CAD mortality and nonfatal myocardial infarction in patients with established CAD, HDL level less than 45 mg/dl, and moderately elevated cholesterol levels. The study randomized 3090 men and women aged 45–74 years to receive either bezafibrate 400 mg/day or placebo. The primary end point was fatal or nonfatal myocardial infarction, or sudden death, occurring within 24 hours of symptom onset. Secondary end points were hospitalization for unstable angina, percutaneous transluminal coronary angiography, and coronary artery bypass grafting. After a mean duration of 6.2 years, bezafibrate therapy resulted in an 18% increase in HDL and a 21% reduction in triglyceride levels, whereas total cholesterol and LDL levels remained relatively unchanged. No statistically significant differences between the two groups were noted for the primary or secondary end points. The frequencies of the primary outcome were similar in the two groups: 211 (13.6%) events in the bezafibrate group and 232 (15%) in the placebo group ($p=0.26$). Rates of all-cause mortality and cardiac-related mortality also were similar in the two groups. However, in a post hoc analysis, a small group of patients with baseline triglyceride levels of 200 mg/dl or greater had a 39.5% reduction in the probability of a primary end point ($p=0.02$), whereas the reduction was not significant in patients with triglycerides less than 200 mg/dl. Unlike VA-HIT and the Helsinki Heart Study, the BIP study did not demonstrate an overall reduction in occurrence of myocardial

infarction or death with fibrate therapy. This may be due to differences in characteristics of the study populations as well as the lower frequency of the primary event in the BIP placebo group than in the VA-HIT placebo group. However, the BIP study identified a subgroup of patients with high triglyceride levels who may benefit from long-term therapy with bezafibrate.

Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;231:360–81.

The Coronary Drug Project was the only secondary prevention trial to demonstrate coronary risk reduction with niacin monotherapy. This double-blind study evaluated whether lipid-modifying agents could prevent new CHD events in patients with established CHD, and whether these interventions would be safe for long-term therapy. The study was discontinued before completion for three of the six original treatment groups (conjugated estrogens 2.5 mg/day, conjugated estrogens 5 mg/day, or dextro-thyroxine 1.8 g/day) due to excess mortality or morbidity. Only those randomized to receive niacin 3 g/day, clofibrate 1.8 g/day, or placebo completed the study. Participants were men aged 30–64 years with at least one previous myocardial infarction. The primary end point was total mortality; other major end points were cause-specific mortality and nonfatal cardiovascular events.

After 5 years, all-cause mortality and coronary mortality rates were similar in the clofibrate and placebo groups. Compared with the placebo group, the clofibrate group had higher rates of heart failure, new hypertension, new angina pectoris, intermittent cerebral ischemic attacks, pulmonary embolism, thromboembolism, thrombophlebitis, and atrial fibrillation. In addition, a higher percentage of clofibrate-treated patients were hospitalized. Overall mortality and coronary mortality did not differ significantly between the niacin and placebo groups, but the occurrence of nonfatal myocardial infarction alone and in combination with coronary death was significantly lower in the niacin than in the placebo group. Based on these data, clofibrate showed no benefit with regard to mortality or nonfatal cardiovascular events. Compared with placebo, however, niacin significantly decreased the risk of nonfatal myocardial infarction but not total mortality.

Group of Physicians of the Newcastle upon

Tyne Region. Trial of clofibrate in the treatment of ischaemic heart disease. *Br Med J* 1971;4: 767–75.

This double-blind trial evaluated the effects of clofibrate on morbidity and mortality in patients with ischemic heart disease. The study randomized 497 men and women with a history of angina or myocardial infarction to receive either clofibrate or placebo containing corn oil. The primary end point was death (defined as sudden death, fatal infarction, or death from heart failure) and nonfatal myocardial infarction (defined as angina or infarction). After at least 3.5 years of follow-up, the cardiac death rate was significantly lower in the clofibrate group than in the placebo group (11.1% and 19.0%, respectively, $p=0.02$). This difference was mostly attributable to the significantly fewer sudden deaths in the clofibrate group. The rate of nonfatal myocardial infarction was also lower in the clofibrate group than in the placebo group, but this difference did not reach statistical significance (11.9% and 18.2%, respectively, $p=0.055$). When the groups were further divided according to baseline cardiac history, patients with angina or both angina and myocardial infarction benefitted from clofibrate therapy, whereas those with a history of myocardial infarction (no angina) did not. In addition, these findings were independent of baseline lipid levels or extent of cholesterol reduction by clofibrate. This early study, performed when the impact of a lipid-lowering drug on long-term morbidity and mortality was unknown, demonstrated that clofibrate treatment could protect patients with CHD from sudden death and future ischemic events.

Research Committee of the Scottish Society of Physicians. Ischaemic heart disease: a secondary prevention trial using clofibrate. *Br Med J* 1971;4:775–84.

Similar to the Newcastle study, this Scottish study evaluated whether reducing serum lipid levels with clofibrate would affect mortality and morbidity in patients with established ischemic heart disease. The study included 717 patients with a history of myocardial infarction, angina, or both. Patients were divided into a double-blind group, which included those not receiving anticoagulants, and an anticoagulant group, which included a small subgroup of patients also receiving warfarin. In both groups, patients were randomized to receive clofibrate or placebo (olive

oil capsules). Study end points were sudden death, fatal myocardial infarction, and nonfatal definite or probable myocardial infarction.

After 6 years of follow-up, no significant overall differences in rates of morbidity and mortality were noted between the clofibrate group and the placebo group in either the double-blind group or the anticoagulant group. However, a trend was noted in favor of clofibrate. A subgroup analysis showed that significantly more fatal infarctions occurred in men in the clofibrate group with a history of myocardial infarction only. Similar findings were also seen in the increased rates of sudden death and fatal infarction in the overall clofibrate group. In terms of nonfatal infarction, rates were similar in the clofibrate and placebo groups. The only benefit from clofibrate therapy seen in this study was reduced mortality in the subgroup of patients with a history of myocardial infarction and angina or angina alone at study entry. Overall, this Scottish study demonstrated that clofibrate reduced the rate of fatal CHD events in patients with a history of angina, which is similar to the Newcastle study results. In the Scottish study, the benefits of clofibrate did not extend to the overall group, especially patients with a history of myocardial infarction.

Carlson LA, Rosenhammer G. Reduction in mortality in the Stockholm ischaemic heart disease secondary prevention study by combined treatment with clofibrate and nicotinic acid. *Acta Med Scand* 1988;223:405–18.

The Stockholm Ischaemic Heart Disease Secondary Prevention Study evaluated the effects of combination lipid-lowering therapy with clofibrate plus nicotinic acid on IHD in patients discharged from a Stockholm hospital after treatment for myocardial infarction. This open-label study randomized 555 patients into either the clofibrate–nicotinic acid group or the control group. At the end of 5 years, in the clofibrate–nicotinic acid group, mean serum cholesterol level was lowered by 13% ($p < 0.001$) and triglyceride level by 19% ($p < 0.001$). Also in the clofibrate–nicotinic acid group, the rate of total mortality was reduced by 26% ($p < 0.05$) and IHD mortality by 36% ($p < 0.01$). In addition, major nonfatal cardiovascular events were reduced by 33%. The benefits of lipid-lowering therapy were confined to patients with fasting triglyceride levels greater than 1.5 mmol/L (133 mg/dl) since no treatment effect was observed in patients with triglyceride levels of 1.5 mmol/L (133 mg/dl) or

lower. In addition, the effects seemed to be related to degree of triglyceride level reduction but not to cholesterol reduction. In patients with at least 30% reduction in triglyceride levels, IHD-related mortality was 9.9% compared with 26.4% in the control group, which reflects a 60% risk reduction ($p < 0.01$). Overall, the Stockholm IHD study demonstrated morbidity and mortality benefits of clofibrate–nicotinic acid combination therapy in patients after myocardial infarction. Most of the benefit was seen in patients with elevated baseline triglyceride levels and those who achieved larger reductions in triglyceride levels due to the lipid-lowering therapy.

Niacin

Canner PL, Berge GK, Wenger NK, et al. Fifteen-year mortality in coronary drug project patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986;18:1245–55.

This study was the 15-year follow-up to the Coronary Drug Project (discussed in the previous section); it was conducted to detect any long-term adverse effects of the study interventions. The primary objective was to determine the vital status of all 8341 patients in the Coronary Drug Project nearly 9 years after termination of the study. The total mortality rate in patients randomized to high- and low-dose estrogen, dextrothyroxine, and clofibrate was 57.0–59.7% compared with 58.2% in the placebo group, and in each of these treatment groups, no statistical difference in mortality was noted compared with placebo. Only the niacin treatment group had a statistically significant lower mortality rate (52.0%) than the placebo group (56.2%; $p = 0.004$). Niacin-treated patients also had a longer median survival time from entry into the study (11.40 vs 13.03 yrs, $p = 0.0012$). This survival benefit was primarily due to the reduction of deaths from CHD. Overall, this follow-up study showed no evidence of long-term adverse effects in patients treated with estrogens, dextrothyroxine, or clofibrate beyond the study time frame. More important, the study demonstrated that the mortality rate in the niacin group was lower than in the placebo group after a mean follow-up of 6.2 years even though it was slightly higher at the termination of the Coronary Drug Project. This delayed benefit took place even after niacin was discontinued; life table curves showed that the niacin group began to diverge in the beneficial direction at month 72. This finding of long-term survival benefit may be

due to the greater cholesterol level reductions seen in niacin-treated patients compared with the other interventions, or an improved survival rate after myocardial infarction in these patients.

Surgical Methods

Buchwald H, Varco RL, Matts JP, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia: report of the program on the surgical control of the hyperlipidemias (POSCH). *N Engl J Med* 1990;323:946–55.

The Program on the Surgical Control of the Hyperlipidemias (POSCH) study was the only prospective, randomized, secondary prevention trial to use partial ileal bypass as the method of reducing cholesterol levels. This study evaluated whether the resulting lipid level changes would affect CHD morbidity and mortality. Patients with a history of one myocardial infarction were randomized to either the control group (i.e., treated with diet instruction) or the surgery group (treated with diet instruction plus partial ileal bypass). The primary end point was all-cause mortality; secondary end points were cause-specific death or other cardiovascular and atherosclerotic events.

The trial ended after a mean follow-up of 9.7 years (range 7.0–14.8 yrs). Five years after randomization, total cholesterol levels in the surgery group were 23.3% lower than in the control group, LDL levels 37.7% lower, HDL levels 4.3% higher, very low-density lipoprotein cholesterol (VLDL) levels 8.3% higher, and triglyceride levels 19.8% higher. Surgery reduced total mortality by 21.7% and CHD mortality by 28.0% compared with controls, but this was not statistically significant. However, patients in the surgery group had significantly lower rates of CHD mortality and nonfatal myocardial infarction combined, peripheral vascular disease, coronary artery bypass grafting, percutaneous transluminal coronary angiography, and disease progression as determined by coronary arteriography. Patients in the surgery group also had more adverse events, such as diarrhea, kidney stones, gallstones, and bowel obstruction. Overall, POSCH provided strong evidence that large, sustained decreases in cholesterol levels resulted in significant reduction of nonfatal CHD events as well as reduced atherosclerotic progression on sequential coronary arteriography.

Buchwald H, Varco RL, Boen JR, et al. Effective

lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH: program on the surgical control of the hyperlipidemias. *Arch Intern Med* 1998;158:1253–61.

This study was a 5-year follow-up study to POSCH. After the formal completion of POSCH, patients consented to annual follow-up by telephone interview. Mean follow-up for this study was 14.7 years (range 12.2–20 yrs) from original randomization. Five years after formal trial closure, 12.1% of the surgery group and 34.8% of the control group were taking cholesterol-lowering agents, but patients in the surgery group still had significantly lower total cholesterol levels than controls. Of 421 patients assigned to undergo partial ileal bypass, 23 underwent reversal of the surgery due to intolerable diarrhea or recurrent nephrolithiasis. At the 5-year follow-up, 106 (25.4%) control patients had died compared with 84 (20%) surgery patients (RR 0.75, 95% CI 0.56–1.00, $p=0.49$). In terms of deaths from CHD, 70 (16.8%) control and 49 (11.6%) surgery patients died (RR 0.66, 95% CI 0.46–0.96, $p=0.03$). When nonfatal myocardial infarction and other clinical end points were combined with mortality, risk reduction in the surgery group was significant as well. Overall, this follow-up study showed that lipid-lowering intervention with partial ileal bypass 5 years after the trial resulted in statistically significant reductions in total deaths, CHD deaths, and nonfatal cardiovascular events, thus providing evidence of long-term benefits in the management of CHD.

Buchwald H, Williams SE, Matts JP, Nguyen PA, Boen JR. Overall mortality in the program on the surgical control of the hyperlipidemias. *J Am Coll Surg* 2002;195:327–31.

This was a follow-up study to POSCH after patients had been followed for a mean of 18 years (range 15.5–23.0 yrs). Investigators followed patients through 1998, and analysis showed that the overall mortality rate in the control group exceeded that in the surgery group (who had undergone partial ileal bypass). During the follow-up period, overall mortality increased in both groups but was consistently lower in the surgery group (120 deaths, 28.5%) than in the control group (144, 34.4%; $p=0.05$). Risk was reduced by 20% due to surgical intervention compared with control (RR 0.799, 95% CI

0.628–1.018, $p=0.07$). The authors calculated a gain of 2.7 years in life expectancy in the surgery group. This follow-up study to POSCH confirmed that lipid-lowering therapy decreased overall mortality and increased life expectancy.

Angiographic or Surrogate End Point Trials

Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med* 1997;336:153–62.

This study tested two hypotheses: that aggressive LDL level reduction to a goal of 60–85 mg/dl is more effective in delaying progression of atherosclerosis in grafts than moderate reduction to 130–140 mg/dl, and that low-dose anticoagulation reduces obstruction of bypass grafts. The study randomized 1351 patients to receive either lovastatin 2.5–5 mg/day with or without cholestyramine 8 g/day (moderate-treatment group) or lovastatin 40–80 mg/day with or without cholestyramine 8 g/day (aggressive-treatment group) for a mean duration of 4.3 years. Evaluation was by quantitative coronary angiography (QCA). The primary end point was the per-patient percentage of initially patent major grafts showing substantial progression (defined as a decrease of ≥ 0.6 mm in lumen diameter) at the site of greatest change noted at follow-up. Most patients were Caucasian men with a mean age of 61.5 years. After 1 year of follow-up, mean LDL level was 93 mg/dl in the aggressive-treatment group versus 136 mg/dl in the moderate-treatment group. The aggressive-treatment group achieved 37–40% reduction in LDL concentration during the study versus 13–15% in the moderate group. Therefore, this study actually compared LDL levels below 100 mg/dl with those below 140 mg/dl. A statistically significant decrease was seen in the primary outcome of per-patient percentage of grafts with substantial disease progression (27% with aggressive treatment vs 39% with moderate treatment, $p<0.001$). No significant benefit was seen with warfarin versus placebo. This study indicates that patients treated with a statin with or without cholestyramine to achieve an LDL level less than 100 mg/dl have significantly less progression of atherosclerosis as measured by QCA compared with those who achieve more modest LDL level reductions.

Blankenhorn DH, Azen SP, Krams DM, et al. Coronary angiographic changes with lovastatin therapy: the monitored atherosclerosis regression study (MARS). *Ann Intern Med* 1993;119:969–76.

This was the first angiographic trial to investigate the effects of a statin, lovastatin 40 mg twice/day, versus placebo on progression of coronary atherosclerosis. Inclusion criteria were age younger than 70 years, total cholesterol level 190–295 mg/dl, and CAD in at least two segments, with at least one segment having a diameter stenosis of 50% or more. Patients with diabetes and candidates for coronary artery bypass grafting were excluded. The study randomized 270 patients, mostly men, of whom 247 had follow-up angiography at 2 years. Assessment was by QCA. The primary end point was the average per-patient change from baseline in percent diameter stenosis in all lesions that showed 20% stenosis at baseline or follow-up. Secondary end points were average per-patient change in minimum lumen diameter, the global change score, and the proportion of patients with disease progression or regression (defined as a change in diameter stenosis of $\geq 12\%$).

Mean baseline LDL level in the lovastatin group was 151 mg/dl, which decreased 38% \pm 12.3% to 93 mg/dl; LDL level in the placebo group decreased by only 0.9% \pm 13.8%. Lovastatin caused a modest increase in HDL level (8.5% \pm 10.3%). The primary end point did not reach statistical significance; mean per-patient diameter stenosis increased in both groups (lovastatin 1.6% \pm 6.7% vs placebo 2.2% \pm 6.8%, $p>0.20$). The only statistically significant difference between groups was in lesions with stenosis of 50% or greater at baseline; lovastatin caused a mean decrease of 4.1% \pm 11.0% versus an increase of 0.9% \pm 11.0% with placebo ($p=0.005$). Fewer patients demonstrated progression and more demonstrated regression with lovastatin, as measured by global change score and change in percent diameter stenosis; these differences were statistically significant. No statistically significant differences were noted in clinical events, although a trend toward fewer events was noted in the lovastatin group (22 events) versus the placebo group (31 events).

Brensike JF, Levy RI, Kelsey SF, et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI type II coronary intervention study. *Circulation* 1984;69:313–24.

This study from the National Heart, Lung and Blood Institute was the first published angiographic trial designed to determine whether lowering cholesterol levels by diet and drug therapy reduced the rate of progression of CAD. The study randomized 143 patients with type II hyperlipidemia and CAD to a low-cholesterol, low-fat diet with or without cholestyramine 24 g/day; dosage was adjusted for adverse effects. Assessment by coronary angiography, which was a relatively new research methodology at the time, was available for the 5-year follow-up in 116 patients (extended from the initially intended 2 yrs due to lower-than-expected rate of progression). Mean \pm SD LDL level was 251.5 \pm 4.3 mg/dl before the diet (at study entry) and 236 \pm 4.8 mg/dl after the diet; cholestyramine treatment resulted in an additional 26% LDL level reduction. Therefore, LDL levels remained quite elevated in most study patients. Although not statistically significant, a trend toward less progression was noted in the cholestyramine group. This study was small, and LDL level reduction from the drugs was limited; however, the study was important in that it provided some support for a beneficial effect of LDL lowering on atherosclerotic progression.

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;345:1583–92.

The hypothesis for the HDL–Atherosclerosis Treatment Study (HATS) was that lipid-altering and antioxidant therapy provide independent and additive benefits for patients with CAD and low HDL levels. Study patients were men younger than 63 years and women younger than 70 years with clinical coronary disease who had at least three stenoses 30% or greater or one stenosis 50% or greater of the lumen, HDL level less than 35 mg/dl in men or less than 40 mg/dl in women, LDL level 145 mg/dl or greater, and triglyceride level less than 400 mg/dl. A total of 160 patients were randomized to receive one of four treatments: simvastatin 10 mg/day, adjusted to an LDL level less than 90 mg/dl and greater than 40 mg/dl, plus sustained-release niacin 2.0 g/day, adjusted to an HDL level increase by changing to a crystalline product if necessary and increasing the dosage to 3–4 g/day; antioxidants (vitamins A and C, β -carotene, and selenium); simvastatin-niacin combination plus antioxidants; or placebo (niacin placebo was active, with 50 mg/tablet). Placebo patients could be treated with

simvastatin 10 mg/day to maintain an LDL level of 130 mg/dl or less.

The primary end point was the mean per-patient change from initial to final arteriogram in the percent stenosis caused by the most severe lesion in each of the nine proximal coronary segments. Average age of the patients was 53 years, 13% were women, 55% had a previous myocardial infarction, and 16% had diabetes. Mean \pm SD doses were simvastatin 13 \pm 6 mg/day and niacin 2.4 \pm 2.0 g/day. Mean LDL level during treatment in the simvastatin-niacin group was 75 mg/dl, representing a 43% reduction, versus 116 mg/dl in the placebo group. Antioxidant therapy reduced the cardioprotective HDL2 fraction by 15% when given alone and blunted the expected HDL level increase when given with simvastatin-niacin. The vitamins had no effect on the other lipoprotein fractions. The simvastatin-niacin group demonstrated a decrease from baseline in mean percent stenosis, which was significantly different from that of the placebo group. The simvastatin-niacin-antioxidant group did not demonstrate atherosclerotic regression, although progression was less than in the placebo group. A significant decrease in composite clinical event rate was evident with simvastatin-niacin treatment (90% reduction vs placebo, $p=0.03$). Risk in other treatment groups did not differ significantly from that in the placebo group.

This study demonstrated a significant benefit in atherosclerotic regression and a lack of progression with aggressive LDL reduction and HDL elevation by low-dose simvastatin combined with moderate-dose niacin therapy. Consistent with large-scale studies of antioxidant vitamins, no benefit was seen when these agents were administered alone; in fact, they appeared to blunt the beneficial effects of the lipid-lowering regimen.

Crouse JR III, Byington RP, Bond MG, et al. Pravastatin, lipids, and atherosclerosis in the carotid arteries (PLAC-II). *Am J Cardiol* 1995;75:455–9.

Designed to test whether pravastatin would retard progression of carotid intimal medial thickness, this was the first trial to use B-mode ultrasonography to monitor intimal medial thickness progression as a surrogate for coronary disease. Enrolled patients had coronary disease, LDL levels in the 60th–90th percentile for age, and at least one extracranial carotid lesion with an intimal medial thickness of 1.3 mm or greater.

Pravastatin 10–40 mg/day, adjusted to maintain an LDL level of 90–110 mg/dl, was compared with placebo, and ultrasound assessments were performed at 6-month intervals beginning at 1 year of follow-up and ending at 3 years. The primary end point was growth or progression of the mean maximum intimal medial thickness. Data were adjusted for baseline cardiovascular risk factors, mean intimal medial thickness, and reader effects because a change was demonstrated in reading patterns by some readers over time.

No significant difference was found between groups in mean intimal medial thickness for all segments or those at the bifurcation or internal carotid artery. A statistically significant reduction in progression was noted at the common carotid artery (reduction of 0.0161 mm/yr with pravastatin vs placebo, $p=0.03$). A 61% decrease in the combined end point of any coronary event and any death was seen in the pravastatin group ($p=0.04$). This study is of interest because of the methodology used, which is less invasive than coronary angiography and predicts coronary atherosclerosis progression. Although the degree of angiographic change was of questionable clinical significance, a decrease in coronary events was demonstrated.

Frick MH, Syvanne M, Nieminen MS, et al. Prevention of angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. Lipid coronary angiography trial (LOCAT) study group. *Circulation* 1997;96:2137–43.

This trial studied the effect of treating men with a history of coronary bypass surgery whose primary lipid abnormality was a low HDL level. Three hundred ninety-five men aged 70 years or younger with an HDL level of 42.5 mg/dl or lower, LDL level 174 mg/dl or lower, and triglyceride level 354 mg/dl or lower were randomized to slow-release gemfibrozil 1200 mg/day or placebo. Those with diabetes or who smoked more than 20 cigarettes/day were excluded. Change in average diameter of segments from baseline to follow-up angiogram and mean luminal diameter were assessed; changes in primary segments (unaffected and graft-dependent native coronary segments) were the main end point of the study. All patients had an exercise tolerance test at baseline and at follow-up angiography at a mean of 32 months. Fewer than one third of patients in each group demonstrated ischemic signs. In the gemfibrozil

group, mean \pm SD HDL level increased 21% from baseline to 38 ± 7 mg/dl, triglyceride level decreased 36% to 92 ± 34 mg/dl, and LDL level decreased 4.5% to 130 ± 21 mg/dl. In the placebo group, mean \pm SD HDL level increased 7% from baseline to 34 ± 6 mg/dl, triglyceride level increased 4.6% to 154 ± 62 mg/dl, and LDL level increased 5.3% to 148 ± 23 mg/dl. All differences were statistically significant. No statistically significant difference was noted in the primary end point; however, significantly less progression was seen in segments unaffected by or influenced by grafts than in graft-dependent segments. No between-group differences in clinical event rates were noted. Although HDL was increased in this study, the levels remained low, and LDL levels during treatment remained elevated.

Haskell WL, Alderman EL, Fair JM, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and cardiac events in men and women with coronary artery disease: the Stanford coronary risk intervention project (SCRIP). *Circulation* 1994;89:975–90.

This study tested the hypothesis that intensive multiple risk factor reduction over 4 years significantly reduces the rate of progression of atherosclerosis in the coronary arteries of men and women compared with patients randomly assigned to the usual care provided by their physician. Three hundred patients (259 men, 41 women, mean \pm SD age 56 ± 7.4 yrs) with angiographically defined coronary atherosclerosis were randomized to receive intensive multifactor risk reduction or usual care. The risk reduction intervention consisted of individualized programs involving a low-fat and low-cholesterol diet, exercise, weight loss, smoking cessation, and drug therapy to favorably alter lipoprotein profiles. Patients were started with a bile acid-binding resin (colestipol) and, depending on response, other drugs, such as niacin, gemfibrozil, lovastatin (available only during second half of the study), and probucol were added or substituted. The LDL target level was 110 mg/dl instead of the 130 mg/dl advocated by the NCEP at the time.

At baseline, 6.3% and 12.6% of patients in the usual care and risk reduction groups, respectively, were taking lipid-lowering agents. At the 4-year follow-up, these percentages rose to 22.6% and 89.9% of patients, respectively. The main angiographic outcome was the rate of change in the minimal diameter of diseased segments at 4

years, as measured by computer-assisted QCA. Intensive risk reduction resulted in significant improvements in LDL (-22%), apolipoprotein B (-22%), HDL (+12%), plasma triglycerides (-20%), body weight (-4%), exercise capacity (+20%), and intake of dietary fat (-24%) and cholesterol (-40%) compared with relatively small changes in the usual-care group. The mean \pm SD change in minimal coronary artery diameter was smaller in the risk reduction group than in the usual-care group (-0.024 ± 0.066 vs -0.045 ± 0.073 mm/yr, $p < 0.02$). The risk reduction group had 25 hospitalizations due to clinical cardiac events compared with 44 in the usual-care group (rate ratio 0.61, 95% CI 0.4–0.9, $p = 0.05$). This study is of interest in that it incorporated aggressive risk factor modification other than lipid lowering. However, it was unable to differentiate among interventions to determine which were most effective in improving angiographic outcomes and reducing risk of coronary events.

Jukema JW, Bruschke AVG, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated cholesterol levels: the regression growth evaluation statin study (REGRESS). *Circulation* 1995;91:2528–40.

This study assessed the effects of pravastatin on progression and regression of coronary atherosclerosis after 2 years of treatment in men with normal to moderately elevated cholesterol levels. The study enrolled 885 patients with a total cholesterol level of 155–310 mg/dl. Patients included had clinical evidence of CAD and a coronary arteriogram showing at least one lesion that narrowed the lumen diameter by at least 50%. Patients with diabetes were excluded; those who were to undergo percutaneous transluminal coronary angiography or coronary artery bypass grafting were allowed to participate. Primary outcome, assessed by QCA, was the per-patient change in mean segment diameter and mean minimum obstruction diameter. Mean \pm SD LDL level at baseline was 167 ± 30 mg/dl for both groups; at 24 months, it was 127 ± 34.8 and 172 ± 33.6 mg/dl in the pravastatin and placebo groups, respectively. Both groups showed progression in that mean segment and minimum obstruction diameters at follow-up were smaller than at baseline. Statistically significantly less change was seen in the pravastatin group, but the difference was small, with a mean segment

diameter decrease of 0.10 and 0.06 mm in the placebo and pravastatin groups, respectively ($p = 0.019$). The frequency of clinical events did not differ between groups, except for a nonscheduled percutaneous transluminal coronary angiography that was needed in 47 and 20 placebo and pravastatin-treated patients, respectively ($p = 0.004$). No difference in primary outcome was noted in patients who received pravastatin and underwent coronary artery bypass grafting or percutaneous transluminal coronary angiography or were medically managed.

Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ. Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. *JAMA* 1990;264:3007–12.

This 2-year study of 72 men and women investigated the effect of LDL level reduction on regression of coronary atherosclerosis. Patients were randomized to receive colestipol up to 30 g/day and niacin up to 7.5 g/day; when lovastatin became available, it was added to the regimen. The control group was offered colestipol up to 15 g/day. Assessment was by QCA, and progression and regression were defined as a 10% change in lesion diameter stenosis. Mean \pm SD LDL levels at baseline were 275 ± 52 and 283 ± 58 mg/dl in the control and treatment groups, respectively, and during the study were 243 ± 67 and 172 ± 63 mg/dl (38.1% decrease from baseline). In the treatment group, HDL levels increased 28%. The mean per-patient change in percent area stenosis was +0.80 in the control group versus -1.53 in the treatment group (95% CI -4.55 to -0.11, $p = 0.039$). These changes were consistent in men and women. Of note, LDL levels in the treatment group remained relatively high during the study.

Watts GF, Lewis B, Brunt JN, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' atherosclerosis regression study (STARS). *Lancet* 1992;339:563–9.

This study assessed the effects of a “practicable” lipid-lowering diet on coronary atherosclerosis, and the effects of greater cholesterol level reduction with diet plus cholestyramine. Ninety men older than 66 years with total cholesterol levels greater than 240 mg/dl (mean 280 mg/dl) were randomized to receive usual care, diet (total fat intake 27% of dietary energy, saturated fats

8–10%, cholesterol 100 mg/1000 kcal, omega-6 and omega-3 polyunsaturated fats 8%, and increased plant-derived soluble fiber), or diet plus cholestyramine 8 g twice/day. Overweight patients were prescribed 1000–1200 kcal/day to achieve a body mass index of 25 kg/m². The primary outcome was change in mean absolute width of segments as determined by angiography. At a mean of 39 months, angiograms of 74 patients were suitable for analysis. Patients' LDL levels decreased 16.2% in the diet group and 35.7% in the diet-drug group; triglyceride levels decreased significantly in the diet group but were unchanged in the diet-drug group. Change in mean absolute width of segments was -0.201 mm in the usual-care group, +0.003 mm in diet group, and +0.103 mm in the diet-drug group ($p < 0.012$ for trend). Overall progression was less in the diet and diet-drug groups, and regression occurred significantly more often in these groups. Similar results were seen in the frequency of clinical events. The lipid-lowering diet in STARS resulted in improvement in angiographic measurements compared with usual care, and addition of cholestyramine to this diet improved angiographic outcomes further.

Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: arterial biology for the investigation of the treatment effects of reducing cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intimal medial thickness. *Circulation* 2002;106:2055–60.

This study was a prospective, randomized, open-label comparison of the effects of pravastatin 40 mg/day or atorvastatin 80 mg/day on carotid intimal medial thickness. Eligible patients were adults who met the NCEP ATP II criteria for pharmacologic lipid lowering. The primary end point was change in mean common carotid intimal medial thickness after 1 year, and the secondary end point was a composite of clinical cardiovascular events. Investigators randomized 161 patients to the two treatment groups. Mean patient age was 60 years, 71.4% were men, 46% had known cardiovascular disease, and mean \pm SD baseline LDL level was 152 \pm 34 mg/dl. During therapy, mean \pm SD LDL level was 76 \pm 23 mg/dl in the atorvastatin group (48.5% decrease from baseline) versus 110 \pm 30 mg/dl in the pravastatin group (27.2% decrease, $p < 0.001$). Mean carotid intimal medial thickness was stable in the pravastatin group (mean \pm SD change from baseline 0.025 \pm 0.017 mm) versus

regression in the atorvastatin group (-0.034 \pm 0.021 mm). This study is of interest in that it compared two levels of LDL level reduction, and added to the evidence supporting lower LDL goals. However, since the study used two different drugs, it also raised the question of whether the variability seen was due solely to degree of LDL level reduction versus other effects that differed between drugs.

Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial biology for the investigation of the treatment effects of reducing cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 2004;110:3512–17.

This study investigated the effect on carotid intimal medial thickness of extended-release niacin 1 g/day or placebo added to statin monotherapy in patients with known CHD. Eligible patients had LDL levels less than 130 mg/dl and HDL levels less than 45 mg/dl; patients with diabetes or metabolic syndrome were included. The primary predefined end point was change in mean common carotid intimal medial thickness after 1 year. Mean age of the 167 randomized patients was 67 years, and 91% were men. Mean \pm SD LDL level at baseline was 89 \pm 20 mg/dl, which remained unchanged during the study. Mean \pm SD baseline HDL level was 40 \pm 7 mg/dl, which increased significantly in the niacin group to 47 \pm 16 mg/dl but remained unchanged in the placebo group. Fasting glucose levels increased significantly in both groups. Increased carotid intimal medial thickness progression in the niacin group was not statistically significant (from 0.892 \pm 0.259 mm at baseline to 0.907 \pm 0.235 mm, $p = 0.23$). In the placebo group, however, carotid intimal medial thickness increased significantly from 0.868 \pm 0.207 to 0.912 \pm 0.202 mm ($p < 0.001$). About 25% of patients had diabetes and 50% had metabolic syndrome. An interesting nonprespecified subgroup analysis suggested that the beneficial effect of niacin was somewhat lessened in patients with diabetes or metabolic syndrome. No difference in clinical coronary outcomes was noted between treatment groups. This study indicated that adding a low dose of extended-release niacin to the statin monotherapy of patients with moderately low HDL and desirable LDL levels can reduce progression of atherosclerosis as measured by carotid intimal medial

thickness. However, the study did not intend to establish the beneficial effect on clinical outcomes.

Nissen SE, Tuzcu EM, Schoenhagen P, et al, for the REVERSAL Investigators. The effect of atorvastatin 80 mg vs pravastatin 40 mg on the progression of coronary atherosclerotic lesions as measured by intravascular ultrasound. *JAMA* 2004;291:1071–80.

This study, called the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, compared the effects of aggressive LDL level reduction with atorvastatin 80 mg/day, with those of moderate reduction with pravastatin 40 mg/day, on the rate of atherosclerotic disease progression as measured by intravascular ultrasound over 18 months. Study patients were men and women aged 30–75 years who had an LDL level of 125–210 mg/dl and required coronary angiography for clinical reasons. Mean patient age was approximately 56 years, more than 70% were men, and most patients were Caucasian. Mean LDL level at baseline was 150 mg/dl; final mean LDL was 110 mg/dl (25% reduction) in the pravastatin group and 79 mg/dl (46% reduction) in the atorvastatin group ($p < 0.001$). The primary outcome was the percent change in atheroma volume. The pravastatin group demonstrated an increased volume of 2.7% (95% CI 0.24–4.67, $p < 0.001$), whereas the atorvastatin group demonstrated no progression (change -0.4%, 95% CI -2.35–1.49).

In the subsegment with the greatest disease burden, both treatment groups showed statistically significant regression compared with baseline; a statistically significantly greater decrease in atheroma volume was noted in patients treated with atorvastatin than with pravastatin. This study is of interest because it compared two intensities of LDL level reduction. However, it tested two different drugs, so the question remains as to whether the effect was due to drug therapy versus LDL level reduction, or whether higher doses of pravastatin (not available at the start of the study) would have demonstrated responses similar to those seen with high-dose atorvastatin. In addition, intravascular ultrasound is a relatively new analytic method, and its correlation with clinical outcomes has not been established.

Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant apo A-I Milano on coronary atherosclerosis in patients with acute coronary

syndromes: a randomized controlled trial. *JAMA* 2003;290:2292–300.

This randomized, double-blind, multicenter, parallel-treatment study assessed the effect of two different doses of recombinant apolipoprotein A-I Milano–phospholipid complex (ETC-216) versus placebo on coronary atheroma volume as measured by intravascular ultrasound. Patients who were within 14 days of ACS and required diagnostic coronary angiography were treated with infusions of saline placebo or ETC-216 15 or 45 mg/kg/week for 5 weeks. This was a pilot study and was not powered to compare treatment groups; the primary outcome measure was the percent change in atheroma volume as measured by intravenous ultrasound in both treatment groups combined. Of 57 patients, 12 were randomized to placebo, 23 to low-dose ETC-216, and 22 to high-dose ETC-216. The combined treatment group demonstrated a mean \pm SD change in atheroma volume of $-1.06\% \pm 3.17\%$, median value 0.81% (95% CI -1.53–0.34%, $p = 0.02$ compared with baseline). Total atheroma volume in the combined treatment group decreased 14.1 mm³ ($p < 0.001$). The effect of ETC-216 was predominantly seen in the most severely diseased 10-mm subsegments. No change was noted in mean coronary luminal diameter as measured by coronary angiography. Two patients in the high-dose ETC-216 group were withdrawn from the study due to adverse drug effects. This trial suggests that ETC-216 may have a rapid effect on decreasing atherosclerotic disease burden in patients with recent ACS. However, larger studies with clinical outcomes are needed to determine the efficacy and safety of this approach.

Whitney EJ, Krasuski RA, Personius BE, et al. A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events. *Ann Intern Med* 2005;142:95–104.

To determine the effect on coronary atherosclerosis of combination drug therapy with gemfibrozil 600 mg twice/day plus niacin 3 g/day plus cholestyramine up to 16 g/day, this study increased HDL level in patients with fairly normal LDL and low HDL levels. Fairly normal LDL level was defined as up to 160 mg/dl, low HDL level was below 40 mg/dl. The study was performed in 1993, when using a placebo control was still permissible; however, all patients were prescribed the AHA step II diet. Patients with

diabetes were excluded from participation. The primary outcome was percent change in global angiographic stenosis from baseline to the end of treatment, as assessed by QCA at baseline and 30 months. The secondary outcome was a composite measure of clinical events.

Mean age of the 143 randomized patients was 63 years, and more than 90% of the patients were men. Mean \pm SD LDL level was 126 ± 28.7 mg/dl in the treatment group and 130.5 ± 24 mg/dl in the control group. Mean HDL level in both groups was approximately 34 mg/dl at baseline. Relative to the control group, the treatment group experienced reductions of 26.4% in LDL level, 49.8% in triglycerides, and 4% in weight, and increases of 35.9% in HDL and 9.5% in fasting glucose. Mean \pm SD global stenosis decreased from $54.5\% \pm 6.8\%$ to $53.7\% \pm 5.9\%$ in the treatment group and increased from $53.4\% \pm 7.3\%$ to $54.8\% \pm 7.1\%$ in the placebo group. Of the treatment patients, 70% were unchanged or improved versus 50% of placebo patients ($p=0.03$). Major cardiovascular end points (death, hospitalization for angina, revascularization procedure, and cardiovascular accident or transient ischemic attack) occurred in 26.4% of placebo patients versus 12.7% of treated patients (difference of 13.7%, 95% CI 0.9–26.5%, $p=0.04$). Flushing, rash, and abdominal symptoms were more common in the treatment group. Fasting glucose levels increased significantly more in the treatment group, but no additional diagnoses of diabetes were made. Although the study purported to show that the benefits seen were due primarily to increasing the HDL level, LDL reduction of almost 22% in the treated group would have resulted in a mean LDL level during treatment of just under 100 mg/dl.

Pasternak RC, Brown LE, Stone PH, et al. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and “normal” cholesterol levels: a randomized, placebo-controlled trial. Harvard atherosclerosis reversibility project (HARP) study group. *Ann Intern Med* 1996;125:529–40.

This portion of the Harvard Atherosclerosis Reversibility Project (HARP) study reports the lipid-lowering efficacy and tolerability of multidrug therapy to improve LDL and HDL levels in patients with CHD and average lipid levels. Stepped-care therapy with pravastatin 40 mg/day, slow-release nicotinic acid 1.5–3.0 g/day, cholestyramine resin 4–24 g/day, and gemfibrozil 600–1200 mg/day was sequentially added until

the treatment goal of total cholesterol less than 160 mg/dl and an LDL:HDL ratio less than 2.0 were reached. If LDL reached 80 mg/dl or less, subsequent steps were not introduced. The study randomized 91 patients to treatment or placebo. The patients (primarily men, mean age 60 yrs) had CHD, a total cholesterol level below 250 mg/dl at baseline, and a total cholesterol:HDL ratio greater than 4.0 at baseline. Mean lipid levels at baseline were total cholesterol 214 mg/dl, LDL 140 mg/dl, HDL 42 mg/dl, and triglycerides 159 mg/dl.

With pravastatin, changes in lipid levels from baseline were -22% for total cholesterol, -32% for LDL, +8% for HDL, and -15% for triglycerides ($p<0.001$ for all comparisons). With the addition of 1.5 g of nicotinic acid, further lipid level changes were -6% for total cholesterol ($p<0.002$), -11% for LDL, +8% for HDL, and -10% for triglycerides ($p<0.001$ for all comparisons). With nicotinic acid 2.25–3.00 g, lipid changes were -7% for total cholesterol ($p=0.007$), -14% for LDL ($p<0.001$), +6% for HDL ($p=0.02$), and -13% for triglycerides ($p=0.03$). With cholestyramine, total cholesterol and LDL levels were unchanged from the previous step; lipid level changes were -8% for HDL ($p=0.03$) and +46% for triglycerides ($p<0.001$). With gemfibrozil, additional lipid changes were LDL +12% ($p=0.09$), HDL +12% ($p=0.03$), and triglycerides -37% ($p<0.001$). In 50% of patients whose baseline LDL levels were greater than 130 mg/dl, pravastatin decreased LDL level to 100 mg/dl or less by 6 weeks, but maintained that level in only 30% of patients. Eventually, 70% of patients needed combination therapy to reach this goal during the 2.5 years of the study. Adding nicotinic acid to pravastatin produced LDL levels of 100 mg/dl or less in 15 more of these 35 patients; thus, 94% of the patients receiving these two drugs reached this goal. Although small, this study is useful in that it evaluated the sequential effects of adding drugs that were the standard therapies at the time. Also, it demonstrated that many patients need combination drug therapy to reach the LDL goal of less than 100 mg/dl.

Serum Lipid, Lipoprotein, and Apolipoprotein Levels: Role in Cardiovascular Risk

Triglycerides

Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen male study. *Circulation* 1998;97:1029–36.

To assess the potential of triglyceride levels to function as an IHD risk factor, this Danish study measured fasting lipid levels and assessed risk factors for IHD in 2906 Caucasian men. The men did not have IHD at baseline; at their assessment 8 years later, 229 first IHD events had occurred. The study population was divided into three tertiles according to triglyceride concentration. Triglyceride levels were 1.09 mmol/L (96.5 mg/dl) or less in the first tertile, 1.10–1.59 mmol/L (97–141 mg/dl) in the second, and 1.60 mmol/L (142 mg/dl) or greater in the third. Starting with the low triglyceride concentration tertile and increasing through the middle and high tertiles, the three groups demonstrated significant ($p < 0.001$) trending increases in total cholesterol level, LDL level, physical inactivity, body mass index, systolic and diastolic blood pressure, percentage of patients in low social class, age, and percentage of patients with hypertension, non-insulin-dependent diabetes mellitus, and glucosuria. Also noted was a significant trending decrease in HDL level with the increasing triglyceride tertile concentrations. Within each triglyceride tertile, patients were separated across HDL level tertiles to minimize the confounding role of HDL level in determining the risks attributed to triglyceride concentrations. The HDL level tertile categories were 1.18 mmol/L (45 mg/dl) or less, 1.19–1.47 mmol/L (46–56.5 mg/dl), and 1.48 mmol/L (57 mg/dl) or greater. After controlling for potential confounders, including alcohol consumption and tobacco use, an increase was noted in IHD risk with increasing triglyceride levels in each HDL level tertile. In the high triglyceride concentration tertile (mean 2.45 mmol/L [217 mg/dl]), the IHD frequency was 12.2%, 9.5%, and 12.5% in the low, middle, and high HDL level tertiles, respectively.

The authors hypothesized that perhaps HDL loses its protective effect in the setting of high triglyceride levels. Fasting hypertriglyceridemia was associated with an increased IHD risk regardless of HDL concentration, even though levels were not greatly elevated according to contemporary guidelines (the NCEP ATP II guidelines called for triglyceride levels less than 200 mg/dl). Therefore, fasting triglyceride level is an important screening parameter in patients at risk of IHD. However, the fact that patients with high triglyceride levels also had more risk factors for IHD (and metabolic syndrome) should still be considered, even though this was adjusted for in

the analysis. Two criteria that were absent and significant—fasting serum glucose level and LDL pattern size—also may have contributed to IHD development, especially in patients with high triglyceride levels.

Austin MA, McKnight B, Edwards KL, et al. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: a 20-year prospective study. *Circulation* 2000;101:2777–82.

This study, which assessed the effects of familial forms of hypertriglyceridemia on cardiovascular disease mortality, was based on two studies from the 1970s that involved 101 families. In the study cited, first-degree relatives of the families were study subjects and spouses were controls for familial combined hyperlipidemia (FCHL, 287 relatives, 195 spouses) and familial hypertriglyceridemia (FHTG, 148 relatives, 88 spouses). From 1993–1997, vital status and cause of death were determined among the study subjects. Although the rate of total mortality increased 40% in the FCHL group and decreased 12% in the FHTG group, no statistically significant changes were noted. The FCHL group had a statistically significant increase in cardiovascular mortality of 70% ($p = 0.02$). The FHTG group also had a 70% increase in cardiovascular mortality but this did not achieve statistical significance ($p = 0.39$), probably because of this group's lower number of cardiovascular-related deaths (21 patients). Triglyceride level was an independent risk factor of 20-year cardiovascular disease mortality among first-degree relatives for FHTG (RR 2.7, 95% CI 1.7–5.2, $p = 0.02$) but not for FCHL (RR 1.5, 95% CI 0.87–2.4, $p = 0.16$). Therefore, FCHL relatives had a higher frequency of cardiovascular mortality, but only the FHTG relatives had triglyceride concentration as an independent predictor of cardiovascular disease mortality. This may be because patients with FCHL have overproduction of apolipoprotein B and formation of small, dense LDL particles, which may contribute to cardiovascular mortality.

Brown DF, Kinch SH, Doyle JT. Serum triglycerides in health and in ischemic heart disease. *N Engl J Med* 1965;273:947–52.

This 4-year follow-up study assessed the effects of serum cholesterol or triglyceride concentration on frequency of IHD in 1851 men. Of these men, 140 were known to have IHD. Mean triglyceride levels were not significantly different between

healthy subjects and patients with IHD. As triglyceride concentrations increased, IHD rates increased as well. The same was true with cholesterol levels, and determining an independent effect of triglyceride or cholesterol level was difficult. Patients with high cholesterol (> 246 mg/dl) and triglyceride levels (> 541 mg/dl) had the highest IHD rates. A major finding was that patients with high triglyceride levels had high IHD rates, until total cholesterol levels reached 275 mg/dl or greater. At that point, IHD rates were similar despite triglyceride concentration. Secondary to this finding, the authors determined that fasting triglyceride concentrations were not useful in predicting IHD events in this study, but that more investigation should be conducted to further characterize this phenomenon. The hypothesis that elevated triglyceride level is linked to insulin and carbohydrate metabolism was also discussed in this study.

Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). *Am J Cardiol* 1992;70:733–7.

This prospective study assessed the incidence of CAD over a 6-year period in 4559 men aged 40–65 years with no history of myocardial infarction or stroke. Over the 6 years, 186 events were recorded: 134 definite nonfatal myocardial infarctions, 31 fatal myocardial infarctions, and 21 sudden cardiac deaths. The groups who experienced CAD had significantly elevated total cholesterol, LDL, and triglyceride levels, as well as significantly elevated blood pressure and body mass index, and a high percentage of cigarette smokers. The group with CAD also had significantly lower HDL levels. After controlling for multivariate risk factors, low HDL level remained a significant predictor of CAD, whereas triglyceride level did not. However, hypertriglyceridemia (triglyceride level \geq 200 mg/dl) was associated with more CAD events in subgroups with elevated total cholesterol, LDL, and LDL:HDL ratio, and in men with decreased HDL levels. In those with LDL levels 160 mg/dl or greater, concomitant hypertriglyceridemia increased the frequency of CAD 2.5-fold. Although a statistical correlation was not proven through multivariate analyses, hypertriglyceridemia remains a risk for CAD in patients with concomitant lipid abnormalities.

High-Density Lipoprotein Cholesterol

Gotto AM Jr, Brinton EA. Assessing low levels of high-density lipoprotein cholesterol as a risk factor in coronary heart disease: a working group report and update. *J Am Coll Cardiol* 2004;43:717–24.

This article is based on the meeting of the Working Group who discussed the latest research on decreased HDL levels as a risk factor for CAD. The group concluded that increasing HDL levels can reduce the frequency of CAD, and that more research is needed to identify ways to improve our ability to increase HDL levels. Data suggest that for every 1-mg/dl increase in HDL level, CAD risk decreases 2–3%. Currently, the best way to raise HDL levels is by administration of niacin or fibric acids. In a head-to-head study of extended-release niacin versus gemfibrozil, niacin raised HDL and apolipoprotein A-I levels more significantly than gemfibrozil. Apolipoprotein A-I is a major protein component of HDL. Statins may raise HDL levels to varying degrees, and more research is needed to differentiate which statins are preferred for raising HDL levels. Other possible therapies for raising HDL levels are omega-3 fatty acids, which are found in fish oils, grape-seed oil, and thiazolidinediones (glitazones). Newer therapies on the horizon are recombinant apolipoprotein A-I Milano, which stimulates apolipoprotein A-I production; cholesteryl ester transfer protein inhibitors, which block cholesteryl ester efflux from HDL particles to very low-density lipoprotein and low-density lipoprotein particles in exchange for triglycerides; and targeted gene therapy, which involves using macrophages to induce apolipoprotein A-I production.

Brousseau ME, Schaefer EJ, Wolfe ML, et al. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. *N Engl J Med* 2004;350:1505–15.

This single-blind, placebo-controlled study assessed the effects of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in 19 subjects. Nine of the 19 subjects received concomitant atorvastatin 20 mg/day; all 19 were given placebo for 4 weeks followed by torcetrapib 120 mg/day. Six subjects not receiving atorvastatin went on to receive torcetrapib 120 mg twice/day. No serious adverse events or withdrawals due to adverse events occurred. Minor-to-moderate adverse events, such as

headache, dyspepsia, and sweating, were reported during the study. Cholesteryl ester transfer protein activity was significantly reduced in both groups of subjects (i.e., those receiving and not receiving atorvastatin), and across both dosing regimens of torcetrapib versus placebo. Torcetrapib 120 mg/day increased HDL levels in subjects receiving concomitant atorvastatin (61% increase, $p < 0.001$) and in those not receiving atorvastatin (46% increase, $p = 0.001$). In subjects who went on to receive torcetrapib 120 mg twice/day, HDL levels were increased 106% ($p < 0.001$). Apolipoprotein A-I levels were also increased in all groups. Torcetrapib alone did not produce significant decreases in either triglyceride or LDL levels. The HDL2 subclass was significantly increased in all groups. Levels of large low-density lipoprotein particles were significantly increased in the torcetrapib monotherapy groups, but not in the atorvastatin group. Therefore, trials with hard clinical end points are needed to further characterize the effects of raising HDL levels on atherosclerosis.

Yokota H, Hashimoto Y, Okubo S, et al. Apolipoprotein A-I deficiency with accumulated risk for CHD but no symptoms of CHD. *Atherosclerosis* 2002;162:399–407.

This case study describes a 69-year-old Japanese woman with extremely low HDL levels (0.10–0.18 mmol/L [3.9–7.0 mg/dl]) and no detectable apolipoprotein A-I (< 0.6 mg/dl). Apolipoprotein A-I is a major protein of HDL particles that carries HDL, and both apolipoprotein A-I and HDL are inversely related with occurrence of CHD. Despite low levels, the patient described did not develop CHD despite numerous risk factors, such as elevated LDL levels, hypertension, and impaired glucose tolerance. Perhaps CHD development was avoided due to concomitant treatment with pravastatin 10 mg/day, consumption of about 30 ml of wine/day, or HDL particles rich in apolipoprotein E. Of 22 patients with homozygous deficiencies in apolipoprotein A-I, only nine developed CHD. More research is needed to determine what types of apolipoprotein A-I mutations confer a higher risk for CHD.

Weverling-Rijnsburger AW, Jonkers IJ, van Exel E, Gussekloo J, Westendorp RG. High-density vs low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age. *Arch Intern Med* 2003;163:1549–54.

This study assessed how well total cholesterol, LDL, and HDL levels served as a predictor of CAD in 599 subjects during a 4-year follow-up period after they reached 85 years of age. Subjects in the lowest tertile of total cholesterol (median 179 mg/dl), LDL (median 106 mg/dl), and HDL (median 36 mg/dl) levels had higher mortality than those in the highest tertiles due to a 2.4–2.7-fold increased risk of infection. Increased risk of mortality due to CAD or stroke was not predicted by either total cholesterol or LDL level across the three strata. However, the lowest HDL level strata predicted CAD risk (RR 2.0, 95% CI 1.0–3.9, $p = 0.04$) and stroke (RR 2.6, 95% CI 1.0–6.6, $p = 0.05$). In these elderly subjects, therefore, only HDL level predicted cardiovascular events. Cholesterol-lowering therapy arguably is not necessary in the elderly since it may lead to increased risk of mortality due to infection; however, therapies that increase HDL level should be further studied in this population.

Non-High-Density Lipoprotein Cholesterol

Frost P, Havel R. Rationale for the use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. *Am J Cardiol* 1998;81:26B–31.

Measuring LDL level is the gold standard for estimating risk of cardiovascular disease. However, using LDL levels has limitations. Patients must be fasting, and LDL concentration determined by the Friedewald equation is not useful when triglyceride level exceeds 400 mg/dl. Also, measuring LDL level takes into account LDL, intermediate-density lipoprotein cholesterol, and lipoprotein(a), but not VLDL, which is atherogenic. Therefore, the authors proposed using non-HDL levels as an alternative to LDL levels for screening, risk assessment, and determining the effectiveness of therapy. Measuring non-HDL levels does not require the patient to be fasting, is useful when triglyceride level exceeds 400 mg/dl, and takes into account all atherogenic particles. Non-HDL level is calculated by subtracting HDL level from total cholesterol level. Correlation of non-HDL level with a wide variety of lipid components is better than with LDL level, and correlation with LDL level is low at an LDL concentration less than 160 mg/dl. This shows that non-HDL levels

provide additional information regarding risk compared with LDL levels alone. Measuring non-HDL levels is useful in patients for whom hypertriglyceridemia is a problem, such as those with diabetes. The recommended cutoff point is 30 mg/dl above a patient's LDL goal level.

Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med* 2001;161:1413–19.

This study assessed whether non-HDL level is a good predictor of cardiovascular disease risk, and how non-HDL level fared compared with LDL level in predicting risk in 2406 men and 2056 women. After follow-up for an average of 19 years, 234 men and 113 had died due to cardiovascular disease. Increases in non-HDL level (RR 2.14, 95% CI 1.50–3.04), LDL level (RR 1.77, 95% CI 1.22–2.59), and total cholesterol level (RR 2.07, 95% CI 1.39–3.08) significantly predicted cardiovascular disease risk. Increases in HDL level significantly reduced risk (RR 0.41, 95% CI 0.27–0.61). Only increases in non-HDL level and decreases in HDL level significantly predicted cardiovascular disease risk in women. Every 30-mg/dl increase in non-HDL and LDL levels translated to an increased risk of 19% and 11%, respectively, in men, 15% and 8% in women. A 10% increase in HDL level led to a decreased risk of 23% in both men and women. Non-HDL level was also a significant predictor of all-cause mortality at levels exceeding 220 mg/dl, whereas LDL level did not predict all-cause mortality. Thus, non-HDL level may be better than LDL level as a predictor of cardiovascular disease and all-cause mortality.

Ballantyne CM, Andrews TC, Hsia JA, Kramer JH, Shear C, for the ACCESS Study Group. Atorvastatin comparative cholesterol efficacy and safety study. Correlation of non-high-density lipoprotein cholesterol with apolipoprotein B: effect of 5 hydroxymethylglutaryl coenzyme A reductase inhibitors on non-high-density lipoprotein cholesterol levels. *Am J Cardiol* 2001;88:265–9.

This 54-week study randomized 3916 patients to receive one of five statins: atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin. The purpose was to determine how well non-HDL level correlated with apolipoprotein B concentrations versus LDL level. Apolipoprotein B is a marker of all the atherogenic lipoproteins

and has been a better marker of CHD than LDL level. Non-HDL level correlated better with apolipoprotein B than LDL level at baseline and at 54 weeks, although both were statistically significant. As triglyceride concentrations increased, non-HDL level correlated better across all triglyceride concentration strata as opposed to LDL level; the greatest difference was seen in patients with triglyceride levels exceeding 250 mg/dl ($r=0.908$ for non-HDL, $r=0.855$ for LDL). Also, patients with CHD showed better correlation between apolipoprotein B and non-HDL levels ($r=0.929$) versus LDL levels ($r=0.810$). Thus, non-HDL level may be a better marker of CHD risk than LDL level since it correlates more closely with apolipoprotein B. Atorvastatin reduced non-HDL and LDL levels more significantly than the other statins, and more patients taking atorvastatin reached their respective goals. However, dosages used in this study were not equally potent, which may have affected the outcomes.

von Muhlen D, Langer RD, Barrett-Connor E. Sex and time differences in the associations of non-high-density lipoprotein cholesterol versus other lipid and lipoprotein factors in the prediction of cardiovascular death (the Rancho Bernardo study). *Am J Cardiol* 2003;91:1311–15.

This study analyzed the effects of total cholesterol, triglyceride, LDL, HDL, and non-HDL levels, as well as total cholesterol:HDL ratio in predicting CHD mortality or cardiovascular mortality in 1094 men and 1386 women. After 10 years, 310 men and 268 women had died; similar proportions of the deaths in each group were due to CHD and cardiovascular mortality. Also after 10 years, total cholesterol:HDL ratio ($p=0.01$), triglyceride levels ($p=0.01$), and non-HDL levels ($p=0.05$) predicted CHD and cardiovascular mortality ($p=0.04$, 0.05 , and 0.05 , respectively) after adjusting for age. However, after adjusting for all other risk factors, the associations were lost in all lipid indexes. In women, no predictors of mortality were noted in 10 years, and only total cholesterol:HDL ratio predicted CHD mortality at 3 years ($p=0.001$) and 5 years ($p=0.005$), and predicted cardiovascular mortality only at 3 years ($p=0.05$) after adjusting for age and for other risk factors ($p=0.001$, 0.01 , and 0.02 , respectively). Total cholesterol level predicted cardiovascular mortality at 5 years and at no other time point. Thus, non-HDL level was not superior to other

lipid indexes in predicting CHD mortality or cardiovascular mortality in this study.

Small, Dense Low-Density Lipoprotein

Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype: a proposed genetic marker for coronary heart disease risk. *Circulation* 1990;82:495–506.

This study described the differences between two distinct phenotypes (A and B) of LDL in 301 subjects from 61 nuclear families. The LDL particle diameter of phenotype A was greater than 255 angstroms (large, buoyant LDL), and of phenotype B was generally 255 angstroms or less (small, dense LDL). Compared with subjects expressing phenotype A, those with phenotype B were associated with increased total cholesterol ($p<0.001$), triglyceride ($p<0.001$), LDL ($p<0.05$), and apolipoprotein B levels ($p<0.001$); increased VLDL mass ($p<0.001$); smaller low-density lipoprotein particles ($p<0.001$); and decreased HDL ($p<0.001$), apolipoprotein A-I ($p<0.05$), and HDL2 mass ($p<0.001$). In a study assessing phenotype B, subjects expressing that phenotype had an odds ratio (OR) of 3.0 for development of myocardial infarction. Thus, phenotype B is also known as the atherogenic lipoprotein phenotype.

Griffin BA, Freeman DJ, Tait GW, et al. Role of plasma triglyceride in the regulation of plasma low-density lipoprotein (LDL) subfractions: relative contribution of small, dense LDL to coronary heart disease risk. *Atherosclerosis* 1994;106:241–53.

This study assessed the effects of triglyceride levels on small, dense LDL (LDL-III) as well as the effects of LDL-III on the rates of CAD in four groups of patients: patients with CAD, patients without CAD, patients with previous myocardial infarction, and healthy controls. At triglyceride concentrations below 1.5 mmol/L (133 mg/dl), LDL-III was not significantly correlated with triglyceride levels, but larger, more buoyant LDL (LDL-II) was significantly correlated ($r=0.51$, $p<0.001$). The largest LDL subclass (LDL-I) also was not significantly correlated. However, once triglyceride concentrations exceeded 1.5 mmol/L (133 mg/dl), both LDL-I and LDL-II were significantly negatively correlated with triglyceride levels ($p<0.001$), and LDL-III was significantly positively correlated with triglyceride levels ($r=0.54$, $p<0.001$). Thus, triglyceride concentrations play an important role

in the formation of small, dense LDL. Two proposed mechanisms are the increase in production of large, triglyceride-rich VLDL or increased triglyceride-rich VLDL exchanging triglycerides for cholesteryl esters with LDL through cholesteryl ester transfer protein. This study also found a 4-fold risk of developing CAD with LDL-III and a 6-fold risk of experiencing myocardial infarction with LDL-III. Thus, small, dense LDL not only is related to triglyceride levels but is highly atherogenic as well.

Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men: prospective results from the Quebec cardiovascular study. *Circulation* 1997;95:69–75.

Of 2103 men in the Quebec Cardiovascular Study, 114 developed IHD during the 5-year follow-up period. These 114 patients were matched to healthy controls for age, body mass index, smoking habits, and alcohol intake. Small, dense LDL was defined as having a peak particle diameter (PPD) of 25.64 nm or less. Patients in the first LDL-PPD tertile (≤ 25.64 nm) had an increased risk of IHD compared with those in the third LDL-PPD tertile (> 26.05 nm) (RR 3.6, 95% CI 1.5–8.8). Therefore, the small, dense LDL phenotype translated to an increased risk of IHD. Also, apolipoprotein B concentrations were the strongest predictor of IHD risk. Patients with an apolipoprotein B concentration less than 120 mg/dl had no increased risk of IHD regardless of LDL-PPD. However, patients with an apolipoprotein B concentration 120 mg/dl or greater had an increased risk of IHD if LDL-PPD was greater than 25.64 nm (OR 2.0) and an even greater risk if LDL-PPD was 25.64 nm or less (OR 6.2, $p<0.001$). Thus, increasing LDL-PPD reduced the risk of IHD, but lowering total apolipoprotein B concentration to less than 120 mg/dl was more important and provided greater risk reduction.

Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA* 1996;276:875–81.

This nested, case-control study assessed the ability of small, dense LDL particles to predict CAD in 124 matched pairs (90 men, 34 women). Between the two groups (cases and controls), the patients with CAD (cases) had an LDL particle

size 0.51 ± 1.37 nm smaller than that of controls ($p < 0.001$). When LDL particle size was broken down into quintiles, 61% of the cases were in the two lowest quintiles. The significance of the difference in LDL particle size for cases and controls remained after controlling for other lipid parameters, systolic blood pressure, smoking, and body mass index. However, the difference was no longer statistically significant after adjusting for total cholesterol:HDL ratio. Triglyceride concentrations and body mass index had an impact on LDL particle size. The increase in CAD occurrence with decreased LDL particle size lends further evidence to the hypothesis that small, dense LDL particles predict CAD risk.

Apolipoproteins

Bhatnagar D, Durrington PN. Clinical value of apolipoprotein measurement. *Ann Clin Biochem* 1991;28:427–37.

This article reviews all the major apolipoproteins, their main functions, and their possible clinical relevance. Apolipoprotein B is associated with chylomicrons, VLDL, intermediate-density lipoprotein, and LDL. Each chylomicron, VLDL, intermediate-density lipoprotein, and LDL contains one apolipoprotein B molecule. Chylomicrons express an apolipoprotein B having 48% the molecular weight of normal; thus, two apolipoprotein B molecules exist: apolipoprotein B48 and apolipoprotein B100. The LDL accounts for 90% of the total apolipoprotein B100, except in patients with severe hypertriglyceridemia. Apolipoprotein(a), also known as lipoprotein(a), is homologous to plasminogen and links to apolipoprotein B through a disulfide bond. It has contributed to CAD, usually in the setting of increased LDL levels. Many isoforms of apolipoprotein(a) exist, making it difficult to quantify. Apolipoprotein A-I is the main apolipoprotein on HDL and may be responsible for reverse cholesterol transport. Also, apolipoprotein A-I stimulates lecithin:acyl transferase, which brings cholesterol into the HDL particle. Not much is known about apolipoprotein A-II except that it is also associated with HDL. Apolipoprotein C-II activates lipoprotein lipase, which is essential for utilizing triglycerides. Apolipoprotein E is associated with polymorphisms that may increase cardiovascular risk. Most patients express E3-E3 or E2-E3 genotypes, which are common and unremarkable. However, E2-E2 or E4-E4 genotypes may be associated with increased CAD risk.

Lamarche B, Moorjani S, Lupien PJ, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow up of men in the Quebec cardiovascular study. *Circulation* 1996;94:273–8.

This study assessed the ability of apolipoprotein B and apolipoprotein A-I to predict the frequency of IHD in 2155 men over a 5-year period. At the end of the study, 116 patients developed IHD. Compared with those who did not develop IHD, significant increases were noted in age and systolic blood pressure, and in the frequency of patients with diabetes and smokers. Significant predictors of IHD were increased apolipoprotein B, total cholesterol, and HDL levels, as well as total cholesterol:HDL ratio. Elevated apolipoprotein A-I level did not significantly predict IHD, and no significant differences were noted between survival probabilities among the three tertiles of apolipoprotein A-I concentration. Survival was significantly higher ($p < 0.0005$) in the lowest tertile of apolipoprotein B concentration than in the highest tertile. Increased apolipoprotein B level remained a significant predictor of IHD despite controlling for total cholesterol, LDL, HDL, and apolipoprotein A-I levels, as well as total cholesterol:HDL ratio. Patients with elevated apolipoprotein B concentrations and total cholesterol:HDL ratio were at the highest risk for IHD. Thus, patients with elevated apolipoprotein B levels are clearly at high risk for IHD development, whereas elevated apolipoprotein A-I levels did not significantly predict IHD.

Tomkin GH, Owens D. Abnormalities in apo B-containing lipoproteins in diabetes and atherosclerosis [review]. *Diabetes Metab Res Rev* 2001;17:27–43.

This article reviewed the interrelationship of diabetes and atherosclerosis and identified causes of increased atherosclerosis in patients with diabetes. One potential mechanism is the overexpression of apolipoprotein C-III in patients with type 1 diabetes mellitus. Apolipoprotein C-III inhibits activity of lipoprotein lipase, leading to hypertriglyceridemia. Also, apolipoprotein C-III interferes with apolipoprotein E binding to the apolipoprotein B-E receptor, which clears atherogenic particles from the circulation. Accumulation of atherogenic particles leads to an increased risk of atherogenesis. Insulin also suppresses the release of free fatty acids from adipose tissue. When free fatty acids are

released, they are taken to the liver and used for promotion of VLDL assembly. The VLDL particles are potentially atherogenic, so patients with decreased insulin production demonstrate an increase of atherogenic particles. Patients with diabetes also have increased total fatty acids in their LDL particles, which may increase the susceptibility of LDL to oxidation. Oxidized LDL particles are more readily taken up by macrophage scavenger receptors and may lead to atherogenesis.

Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 2001;358:2026–33.

The AMORIS study assessed the power of apolipoprotein B, apolipoprotein A-I, and the apolipoprotein B:apolipoprotein A-I ratio in predicting fatal myocardial infarction. Information about smoking, hypertension, diabetes, and concomitant diseases or treatments were not recorded or adjusted for. Low-density lipoprotein level was calculated using a new equation that was highly correlated with the Friedewald equation ($r=0.97-0.99$). In this study, 98,722 men and 76,831 women experienced 864 and 359 fatal myocardial infarctions, respectively (a 2.5-fold increase in risk for men). The highest rate of fatal myocardial infarction was in men aged 60–69 years and women aged 70–79 years. The apolipoprotein B:apolipoprotein A-I ratio was the strongest predictor of risk in men and women in univariate analysis. Increased apolipoprotein B level was the strongest predictor of risk in men and women in multivariate analyses that included other lipid indexes (RR 1.43, $p<0.0001$ in men, RR 1.34, $p=0.0033$ in women); increased apolipoprotein A-I also had strong predictive value. Thus, apolipoprotein B and apolipoprotein A-I levels are important in assessing risk for myocardial infarction, possibly because the apolipoprotein B:apolipoprotein A-I ratio measures the number of atherogenic particles divided by the number of antiatherogenic particles.

Lipoprotein(a)

Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease: meta-analysis of prospective studies. *Circulation* 2000;102:1082–5.

This meta-analysis of 27 published prospective studies assessed the association of lipoprotein(a) with 5436 cases of CHD death or nonfatal myocardial infarction. The weighted mean follow-up was 10 years. In 18 population-based study cohorts, increased lipoprotein(a) level was associated with a significant 70% increase in CHD death or nonfatal myocardial infarction ($2p<0.00001$) when comparing patients in the third tertile of lipoprotein(a) concentration with those in the first tertile. Using the same method of comparison, a significant 30% increase was seen in CHD death or nonfatal myocardial infarction ($2p<0.001$) in the nine studies involving patients with previous disease. Unfortunately, cutoff numbers were not reported, nor were the concentrations of classic lipid indexes. Lipoprotein(a) concentration has not been correlated with other classic lipid level risk factors and thus may provide information about independent risk for CHD. This meta-analysis showed a strong association between elevated lipoprotein(a) level and CHD, but more research is needed to determine causality.

Moliterno DJ, Jokinen EV, Miserez AR, et al. No association between plasma lipoprotein(a) concentrations and the presence or absence of coronary atherosclerosis in African-Americans. *Arterioscler Thromb Vasc Biol* 1995;15:850–5.

This study assessed the association between lipoprotein(a) and CAD in 140 African-American patients (62 men, 78 women). Patients were defined as CAD-negative if coronary angiography showed less than 10% diameter stenosis of one or more major epicardial arteries, and as CAD-positive if greater than 70% diameter stenosis. There were no major differences between the two groups regarding age, sex, estrogen replacement supplements, or other atherosclerotic risk factors. The CAD-positive group had significantly increased total cholesterol ($p=0.02$), triglyceride ($p<0.001$), VLDL ($p<0.001$), and LDL levels ($p=0.02$), and significantly decreased HDL levels ($p<0.001$). Lipoprotein(a) was not significantly different between the two groups with regard to concentration across the total groups (CAD-negative 54 ± 47 mg/dl vs CAD-positive 52 ± 38 mg/dl) or various subsets, or with regard to lipoprotein(a) allele size. Lipoprotein(a) was not a significant predictor of CAD risk, but age, total cholesterol level, and HDL level were. This study was consistent with two other studies that reported no increased risk of CAD due to elevated lipoprotein(a) levels in African-

American patients. Therefore, lipoprotein(a) level may not be useful for risk assessment in this population.

Shlipak MG, Simon JA, Vittinghoff E, et al. Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. *JAMA* 2000;283:1845–52.

This subset of the Heart and Estrogen/Progestin Replacement Study (HERS) assessed the value of lipoprotein(a) concentration for predicting CHD, and the ability of estrogen-progestin therapy to lower lipoprotein(a) levels and reduce future CHD risk. Lipoprotein(a) levels were available for 2759 women at baseline and at 1 year. When the baseline data were stratified to quartiles of lipoprotein(a) concentrations, patients in the highest quartile had significantly higher LDL ($p < 0.001$) and HDL levels ($p = 0.01$), and significantly lower triglyceride levels ($p < 0.001$) and rates of smoking ($p = 0.03$). Women in the highest lipoprotein(a) concentration quartile were at a significantly increased risk of 54% for primary CHD events and 61% for revascularization procedures compared with the lowest quartile. Estrogen-progestin therapy significantly reduced lipoprotein(a) levels compared with placebo ($p < 0.001$), but there was no overall effect of this therapy on primary CHD events. Estrogen-progestin resulted in fewer primary CHD events in women in the two highest quartiles. Mortality increased in year 1 of the study, but decreased in years 2–5. Lipoprotein(a) levels predicted CHD events in women. The effect of estrogen-progestin on decreasing lipoprotein(a) levels to reduce future CHD events was not strong in all women. Therefore, this therapy should not be considered for those with elevated lipoprotein(a) levels, especially in light of the Women's Health Initiative data.

Ariyo AA, Thach C, Tracy R, for the Cardiovascular Health Study Investigators. Lp(a) lipoprotein, vascular disease, and mortality in the elderly. *N Engl J Med* 2003;349:2108–15.

This study assessed the ability of lipoprotein(a) to predict vascular events in 3972 patients (2375 women) aged 65 years or older with no baseline history of CHD. Lipoprotein(a) was divided into equal quintiles, and results were reported as the highest versus lowest quintile. Men were more likely than women to smoke tobacco and have diabetes, whereas women were more likely to

have elevated lipid indexes, except for triglyceride levels, and were more likely to have a family history of myocardial infarction. Lipoprotein(a) was a significant predictor of stroke (RR 3.00, 95% CI 1.59–5.65, $p = 0.003$), death from vascular causes (RR 2.54, 95% CI 1.59–4.08, $p = 0.004$), and death from all causes (RR 1.76, 95% CI 1.31–2.36, $p = 0.01$). Lipoprotein(a) did not predict CHD events in men. Of interest, lipoprotein(a) did not significantly predict any events in women. Thus, lipoprotein(a) is an independent predictor of stroke risk, death due to vascular causes, and death from all causes, in men but not in women.

von Eckardstein A, Schulte H, Cullen P, Assmann G. Lipoprotein(a) further increases the risk of coronary events in men with high global cardiovascular risk. *J Am Coll Cardiol* 2001;37:434–9.

This prospective study assessed lipoprotein(a) as a coronary risk factor in 820 men aged 35–65 years who were followed for 10 years. The men were divided into two groups: those with and those without a history of major coronary events (MCE+ and MCE-, respectively). The group with major coronary events had significantly increased age; cholesterol, LDL, and triglyceride levels; systolic blood pressure; fasting blood glucose levels; history of angina; history of smoking; they had significantly lower HDL levels. The group with major coronary events also had significantly increased lipoprotein(a) levels ($p = 0.001$). When lipoprotein(a) concentrations were divided into quintiles, patients in the highest quintile (≥ 0.2 g/L) had a significantly increased rate of major coronary events compared with those in the lowest quintile (RR 2.7, 95% CI 1.4–5.2). Elevated lipoprotein(a) levels were associated with an increased risk for a major coronary event in patients with hypertension, elevated LDL levels, and low HDL levels. Lipoprotein(a) levels predicted the occurrence of major coronary events in the two highest quintiles, which accounted for 83% of total coronary events. Therefore, lipoprotein(a) level is an important independent coronary risk factor.

Kim C, Gau GT, Allison TG. Relation of high lipoprotein(a) to other traditional atherosclerotic risk factors in patients with coronary heart disease. *Am J Cardiol* 2003;91:1360–3.

This study assessed lipoprotein(a) level as a cardiovascular risk factor in 200 patients after an

index CHD event. The patients were stratified into two groups: those with lipoprotein(a) levels greater than 30 mg/dl and those with lipoprotein(a) levels 30 mg/dl or less. Patients with the higher lipoprotein(a) level at the time of their index CHD event had significantly more coronary angioplasty ($p=0.027$) and stent procedures ($p=0.002$). The higher lipoprotein(a) group also had significantly fewer patients with hypertension ($p=0.002$) or dyslipidemia ($p=0.018$), and significantly more patients with a family history of premature CHD ($p=0.001$). Lipid indexes were not significantly different between the two groups except for triglyceride level ($p=0.041$), which was lower in the elevated lipoprotein(a) group. Patients in the elevated lipoprotein(a) group had significantly fewer traditional CHD risk factors than those in the lower lipoprotein(a) group (1.53 ± 0.88 vs 2.12 ± 0.96 , $p=0.0001$). Thus, lipoprotein(a) level is an independent risk factor for CHD and may precipitate CHD events in patients with few traditional risk factors.

Maher VM, Brown BG, Marcovina SM, Hillger LA, Zhao XQ, Albers JJ. Effects of lowering elevated LDL on the cardiovascular risk of lipoprotein(a). *JAMA* 1995;274:1771–4.

Lipoprotein(a) concentration has been associated with an increased risk of CAD in patients with elevated LDL levels. This post hoc analysis of the Familial Atherosclerosis Treatment Study (FATS) assessed the effects of LDL lowering on the atherogenicity of lipoprotein(a). The 120 patients involved had a history of CAD, elevated apolipoprotein B concentration, and a family history of premature cardiovascular events. Patients were divided into groups for minimal ($\leq 10\%$) and substantial ($> 10\%$) LDL lowering. Twenty-nine patients had lipoprotein(a) concentrations above the 90th percentile (46.2 mg/dl). Lipoprotein(a) concentration was the most significant correlate of CAD from baseline in univariate ($p<0.001$) and multivariate ($p<0.005$) analyses. Patients with lipoprotein(a) concentration in the 90th percentile had a 3.1% increase in percent stenosis in proximal segments with minimal LDL level reduction versus a 0.6% decrease in percent stenosis in proximal segments with substantial LDL level reduction ($p<0.05$). Also, patients with lipoprotein(a) concentration in the 90th percentile had 77% decreased frequency of clinical events in the substantial versus minimal

LDL level lowering groups (9% vs 39%, $p<0.05$). Thus, lipoprotein(a) concentration is strongly associated as a risk factor for CAD, but lowering LDL level can minimize the effects of lipoprotein(a) concentration on the coronary vasculature and CAD events.

van Wissen S, Smilde TJ, Trip MD, de Boo T, Kastelein JJ, Stalenhoef AF. Long term statin treatment reduces lipoprotein(a) concentration in heterozygous familial hypercholesterolemia. *Heart* 2003;89:893–6.

Lipoprotein(a) concentrations were assessed in 325 patients with heterozygous familial hypercholesterolemia who received either atorvastatin 80 mg/day (160 patients) or simvastatin 40 mg/day (165 patients) for 2 years. The two treatment groups were similar at baseline except for lipoprotein(a) concentrations (327 and 531 mg/L for atorvastatin- and simvastatin-treated patients, respectively, $p=0.032$). After 2 years, lipoprotein(a) concentration was significantly reduced by both atorvastatin (to 263 mg/L, $p<0.001$), and simvastatin (to 417 mg/L, $p<0.001$); however, lipoprotein(a) levels were not significantly different between the two groups ($p=0.53$). Baseline lipoprotein(a) concentration was not correlated significantly with LDL level, prevalent cardiovascular disease, age, baseline intimal medial thickness, or change in intimal medial thickness at any time point. Also, change in lipoprotein(a) concentration was not correlated significantly with change in intimal medial thickness but was significantly (although weakly) correlated with change in LDL concentrations ($r=0.20$, $p=0.001$). Thus, long-term statin treatment reduced lipoprotein(a) concentrations in patients with heterozygous familial hypercholesterolemia over a 2-year period, but lipoprotein(a) concentration was not correlated with the presence or change of cardiovascular disease, so its utility is limited.

Luc G, Bard JM, Arveiler D, et al. Lipoprotein(a) as a predictor of coronary heart disease: the PRIME study. *Atherosclerosis* 2002;163:377–84.

This study assessed lipoprotein(a) concentration as a risk factor for CHD, as a predictor of hard CHD or angina, and as possibly interacting with other lipid indexes in 9133 French and Northern Irish men aged 50–59 years with no history of CHD. Over a 5-year follow-up period, 288 CHD events occurred. The group of patients who experienced an event had significantly more

smokers, diabetes, hypertension, and elevated lipid indexes, except for significantly decreased HDL levels. Lipoprotein(a) concentration significantly predicted CHD after controlling for numerous lipid and nonlipid variables ($p < 0.002$). Also, the highest quartile of lipoprotein(a) concentration significantly predicted more CHD events than the lowest quartile (RR 1.56, 95% CI 1.10–2.21, $p = 0.01$). The highest lipoprotein(a) quartile also predicted more events, such as fatal and nonfatal myocardial infarction and angina compared with the lower quartiles ($p < 0.05$). Relative risk of CHD was significantly increased across LDL level quartiles; patients in the highest LDL level quartile and the quartile with greater lipoprotein(a) concentration (≥ 33 mg/dl) had the highest risk (RR 3.95, 95% CI 2.42–6.42). This risk decreased across the lower quartiles of LDL level. Thus, increased lipoprotein(a) concentration is an independent risk factor of CHD and is useful for predicting CHD events. Also, it appears that CHD risk with lipoprotein(a) concentration increases with increasing LDL concentration. Since it is difficult to lower lipoprotein(a) concentration with conventional therapy, perhaps aggressively lowering LDL level is a reasonable strategy.

Cantin B, Gagnon F, Moorjani S, et al. Is lipoprotein(a) an independent risk factor for ischemic heart disease in men? The Quebec cardiovascular study. *J Am Coll Cardiol* 1998;31:519–25.

This 5-year prospective follow-up study in 2156 men aged 47–76 years without clinical evidence of IHD determined whether lipoprotein(a) concentration is a risk factor for IHD and how it relates to other lipid indexes. During the follow-up period, 116 IHD events occurred. Results indicated that increased lipoprotein(a) concentration was not an independent predictor of IHD; however, the traditional risk factors (advanced age, smoking, hypertension, elevated total cholesterol and LDL levels, and decreased HDL level) were predictors. Lipoprotein(a) concentration significantly correlated with total cholesterol, LDL, and apolipoprotein B levels ($p < 0.0001$ for each correlation). Lipoprotein(a) concentration was divided into low (< 30 mg/dl) and high (≥ 30 mg/dl) categories. Higher lipoprotein(a) concentrations increased the risk of IHD in traditional risk factors, such as total cholesterol, LDL, and apolipoprotein B levels, and removed

the protective effect of HDL. Thus, increased lipoprotein(a) concentration is not an independent predictor of IHD risk but seems to increase the risk associated with traditional risk factors.

Nonlipid Serum Markers Associated with Cardiovascular Disease

Hackam DG, Anand SS. Emerging risk factors in atherosclerotic vascular disease: a critical review of the evidence [review]. *JAMA* 2003;290:932–40.

This review identified 373 articles, including randomized controlled trials, prospective cohort studies, systematic overviews, case-control studies, cross-sectional trials, and mechanistic studies that evaluated C-reactive protein, lipoprotein(a), fibrinogen, and homocysteine as risk factors for atherosclerotic vascular disease. The authors provided a concise overview of each risk marker and the available evidence. Information regarding C-reactive protein is, to a degree, somewhat dated. However, the article is still useful for understanding the risk associated with the markers discussed and the evidence supporting their use as risk markers.

Balk EM, Karas RH, Jordan HS, Kupelnick B, Chew P, Lau J. Effects of statins on vascular structure and function: a systematic review. *Am J Med* 2004;117:775–90.

This literature review evaluated the effects of statins on coronary artery stenosis, carotid intimal medial thickness, and endothelial function. In addition, the authors attempted to determine whether the effects of statins on vascular structure and function are a class effect, and whether a correlation exists between these effects and lipid concentrations. Meta-analyses were performed when appropriate. This article provides a good overview and discussion regarding the effects of statins on these surrogate markers.

Oxidation and Antioxidants

Heinecke JW. Oxidants and antioxidants in the pathogenesis of atherosclerosis: implications for the low oxidized low-density lipoprotein hypothesis [review]. *Atherosclerosis* 1998;141:1–15.

Oxidation of the LDL molecule is thought to be an important factor in the development and progression of atherosclerosis. This review

article examines the mechanisms of LDL oxidation and the potential role of antioxidants. Mechanisms the author explored were LDL oxidation by metal ions, superoxide, thiols, lipoxygenase, reactive nitrogen species, and myeloperoxidase. Review of the role of antioxidants, especially animal data, was also examined. The strength of this review, for the most part, is the proposed mechanisms of LDL oxidation.

Yusuf S, Dagenais G, Pogue J, et al. Vitamin E supplementation and cardiovascular events in high-risk patients: the heart outcomes prevention evaluation study investigators. *N Engl J Med* 2000;342:154–60.

Oxidation of the LDL molecule is thought to be an important factor in the development and progression of atherosclerosis. Based on this rationale, antioxidants may be important in the treatment of cardiovascular disease. The Heart Outcomes Prevention Evaluation (HOPE) study evaluated the role of antioxidants (vitamin E) in patients at high risk for cardiovascular events. Observational studies have suggested benefit with vitamin E; however, results from randomized trials have been conflicting in part due to study limitations such as dosage, duration, and limited event rates. The HOPE study addressed these concerns. Study patients were aged 55 years or older and at high risk for cardiovascular events secondary to either cardiovascular disease or diabetes and one other risk factor. Patients were randomly assigned by a two-by-two factorial design to receive either vitamin E 400 IU/day or placebo, and either an ACE inhibitor or placebo. Primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular disease. Secondary outcomes were unstable angina, chronic heart failure, revascularization or amputation, death from any cause, complications of diabetes, and cancer. Vitamin E was given to 4761 patients and placebo to 4780.

After a mean follow-up of 4.5 years, no significant difference was noted in the primary end point (RR 1.05, 95% CI 0.95–1.16, $p=0.33$). In addition, no significant differences in secondary outcomes were observed. This study demonstrated that vitamin E 400 IU/day had no benefit based on the outcome parameters measured in patients at risk for cardiovascular events over a 4.5-year period. This relatively definitive trial demonstrated that vitamin E has

no apparent benefit in patients at high risk for cardiac events. The strengths of the trial include its large number of patients and sufficient power to detect differences in outcome. Also, the vitamin E dose was high, and the follow-up period probably was long enough for meaningful conclusions. Questions may remain regarding whether a higher dose of vitamin E or treatment with a combination of antioxidants would be beneficial, and whether a longer study period would have made a difference. This study does not address the issue of primary prevention.

Heart Protection Study Collaborative Group. MRC/BHF Heart protection study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:23–33.

Similar to the HOPE trial, this study evaluated the role of antioxidant therapy in patients at risk for cardiovascular events. A total of 20,536 patients were randomized to receive antioxidant vitamin supplementation with vitamin E 600 mg/day [*sic*], vitamin C 250 mg/day, and β -carotene 20 mg/day, or placebo. Patients were followed for a scheduled 5-year treatment period. Primary outcomes were major coronary events. Subcategory analysis included fatal and nonfatal vascular events. No significant differences were noted in the outcomes measured between antioxidants and placebo. Measured antioxidant levels were increased in the group that received the vitamin regimen. This study demonstrated that a daily antioxidant regimen had no benefit based on the outcome parameters measured in patients at risk for cardiovascular events over a 5-year period. This antioxidant regimen appeared to be safe. Results of this study mirror those of the HOPE study, confirming that antioxidant therapy in patients at high risk for cardiovascular events is unlikely to be beneficial. This study also addressed the question of whether combination antioxidant therapy would be beneficial compared with single-antioxidant therapy such as vitamin E. The study's strengths were its large number of patients and long-term follow-up; in addition, it demonstrated increased antioxidant levels.

Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the women's health study: a randomized controlled trial. *JAMA* 2005;294:56–65.

The overall purpose of this study was to determine whether long-term administration of vitamin E in healthy women would decrease the risk of cardiovascular disease or cancer. In a 2 x 2 factorial design, 39,876 women were randomized to receive either vitamin E 600 IU or placebo, and aspirin 100 mg or placebo every other day. Average follow-up was 10.1 years. Results demonstrated a nonsignificant 7% risk reduction (RR 0.93, 95% CI 0.82–1.05, $p=0.26$) for the primary composite end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. No significant reduction was noted for the individual components except for cardiovascular death (24% reduction, RR 0.76, 95% CI 0.59–0.98, $p=0.03$). However, no difference in total mortality was seen. A subgroup analysis indicated a 26% reduction in major cardiovascular events in women aged 65 years or older. Finally, no significant difference between groups was noted regarding frequency of cancer.

The authors concluded that this study does not support administration of vitamin E for primary prevention of cardiovascular disease or cancer in healthy women. Further studies may be warranted in women older than 65 years. Of note, this trial has a number of important aspects, such as the number of patients studied, long observation period, and relatively high dose of vitamin E administered. Based on these factors, this study is relatively definitive with regard to vitamin E and primary prevention of cardiovascular disease or cancer in women.

Lonn E, Bosch J, Yusuf S, et al, for the HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA* 2005;293:1338–47.

The HOPE trial demonstrated a neutral effect of vitamin E on cardiovascular outcomes over a 4.5-year period. This trial, HOPE–The Ongoing Outcomes (TOO), was an extension of the HOPE trial. The study investigated whether long-term vitamin E therapy would prevent cardiovascular events or cancer. Patients were randomized to receive either vitamin E 400 IU/day or placebo; median follow-up was 7.0 years. Study patients were older than 55 years and had a history of coronary or peripheral arterial disease, stroke, or diabetes, plus one other cardiovascular risk factor. Primary outcome for cardiovascular disease was a composite of myocardial infarction, stroke, and cardiovascular death. Secondary

outcomes were heart failure, unstable angina, and revascularization procedures. The results demonstrated no significant difference in the primary outcome variable (RR 1.04, 95% CI 0.96–1.14, $p=0.34$). However, the patients receiving vitamin E had a higher risk of heart failure (RR 1.13, 95% CI 1.01–1.26, $p=0.03$). Vitamin E also had no effect on occurrence of cancer. These results in a relatively high-risk patient population suggest that vitamin E supplementation should not be routinely prescribed; in fact, the risk of developing heart failure may be increased. The obvious strengths of this trial were its duration and dosage of vitamin E used. The mechanism behind increased occurrence of heart failure with vitamin E administration is not clear. Despite this, the study shows that the role of vitamin E in decreasing cardiovascular disease in this patient population is now relatively clear—it does not prevent the disease.

Monocyte Chemotactic Protein-1

Martinez-Gonzalez J, Alfon J, Berrozpe M, Badimon L. HMG-CoA reductase inhibitors reduce vascular monocyte chemotactic protein-1 expression in early lesions from hypercholesterolemic swine independently of their effect on plasma cholesterol levels. *Atherosclerosis* 2001;159:27–33.

This study investigated the role of statins on vessel wall expression of monocyte chemotactic protein-1 (MCP-1) and the inducible form of nitric oxide synthase beyond lipid reduction. The authors used an atherosclerotic pig model and equivalent doses of atorvastatin and pravastatin. Results demonstrated that MCP-1 expression was significantly reduced by both statins regardless of lipid-lowering effects and type of statin administered (lipophilic vs hydrophilic). No effect on nitric oxide synthase was noted. Results also demonstrated that statins may have an important effect on MCP-1, and this effect may be independent of degree of lipid reduction. Statins may be important in attenuating the inflammation process associated with atherosclerosis in part by affecting MCP-1 expression.

Parissis JT, Venetsanou KF, Kalantzi MV, Mentzikof DD, Karas SM. Serum profiles of granulocyte-macrophage colony-stimulating factor and C-C chemokines in hypertensive patients with or without significant hyperlipidemia. *Am J Cardiol* 2000;85:777–9.

This small but interesting study investigated whether certain markers thought to be associated with the atherosclerotic inflammatory process are elevated in patients with hypertension with and without significant hyperlipidemia. The study evaluated 46 patients with mild-to-moderate hypertension and 18 healthy volunteers. Of the 46 with hypertension, one group (22 patients) had total cholesterol levels greater than 240 mg/dl or LDL levels greater than 160 mg/dl (or both); the other group (24 patients) had total cholesterol and LDL levels lower than those of the first group. Results demonstrated that compared with healthy controls, patients with hypertension had higher serum concentrations of MCP-1, macrophage inflammatory protein-1 α , and granulocyte-macrophage colony-stimulating factor. In addition, these levels were higher in patients with the highest cholesterol levels. Both MCP-1 and granulocyte-macrophage colony-stimulating factor were significantly correlated with LDL level. These results suggest that these markers of inflammation may be useful for detection of the early inflammatory process associated with atherosclerosis, and that LDL level may play an important role in this process.

Chen YL, Chang YJ, Jiang MJ. Monocyte chemotactic protein-1 gene and protein expression in atherogenesis of hypercholesterolemic rabbits. *Atherosclerosis* 1999;143:115–23.

This study is significant in that it established in an animal model the relationship between cholesterol and MCP-1 expression and the pathophysiologic consequence of upregulation of MCP-1 expression. Specifically, MCP-1 may be a key player responsible for the initial development of atherosclerosis. This study's findings help validate the importance of MCP-1 in atherosclerosis and provide a premise for the importance of reducing cholesterol levels with regard to MCP-1.

Homocysteine

Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 2002;288:2015–22.

Debate continues regarding the significance of the relationship between homocysteine concentrations and cardiovascular disease. This study used meta-analysis statistics to determine the relationship between homocysteine concentration and vascular disease risk. The analysis

included 30 prospective or retrospective studies involving 5073 ischemic heart disease events and 1113 stroke events. Evaluation of blood concentrations of homocysteine indicated that the association with outcome variables was stronger in retrospective studies involving patients with disease than in prospective studies involving patients with no history of cardiovascular disease. A 25% lower homocysteine level was associated with 11% lower ischemic heart disease risk and 19% lower stroke risk. The authors suggested that an elevated homocysteine concentration may be a modest independent predictor of the outcomes measured in this study. Limitations of the study were those generally associated with meta-analyses; another limitation was that data only up to 1999 were included. However, the study provided evidence that an increased homocysteine concentration may be an important risk factor for cardiovascular disease, although the appropriate patient population at risk needs to be determined.

Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the vitamin intervention for stroke prevention (VISP) randomized controlled trial. *JAMA* 2004;291:565–75.

This double-blind, randomized, controlled trial evaluated the effect of high doses of folic acid, pyridoxine, and cobalamin to reduce the risk of events in 3680 patients with nondisabling cerebral infarction. Patients were randomized to receive a daily high-dose formulation of pyridoxine 25 mg, cobalamin 0.4 mg, and folic acid 2.5 mg (1827 patients), or a low-dose formulation of pyridoxine 200 μ g, cobalamin 6 μ g, and folic acid 20 μ g (1853 patients). Primary outcome was recurrent cerebral infarction; secondary outcomes were CHD events and death over a 2-year follow-up. The high-dose group had a 2- μ mol/L greater reduction in total homocysteine level than the low-dose group. No significant difference between the two groups was noted in events for the primary or secondary outcome measurements. However, baseline levels were still associated with risk. In this population, high-dose folic acid and vitamin therapy had no effect in reducing outcomes. However, the association seen between events and homocysteine levels warrants further investigation. Trials of longer duration are needed to further evaluate homocysteine therapy. In addition, the appropriate patient population, if

any, that would benefit from treatment with folic acid still needs to be determined.

Schnyder G, Roffi M, Pin R, et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *N Engl J Med* 2001;345:1593–1600.

This prospective, double-blind, randomized trial evaluated whether lowering plasma homocysteine levels affected restenosis rates after coronary angioplasty. Daily folate treatment with folic acid 1 mg, vitamin B₁₂ 400 µg, and pyridoxine 10 mg was compared with placebo in 205 patients after coronary angioplasty. Primary end point was restenosis within 6 months; secondary end point was a composite of major adverse cardiac events. Compared with placebo, folate treatment significantly reduced homocysteine levels, restenosis rates, and need for revascularization. Folate treatment as defined above may be an important therapy for patients undergoing percutaneous coronary angioplasty. The authors commented that this inexpensive therapy should be considered as an adjunct therapy for patients undergoing percutaneous coronary angioplasty. A similar number of patients received glycoprotein IIb-IIIa inhibitors and statin therapy. Dosages were not included, nor was the number of patients receiving aspirin, heparin, ticlodipine, or clopidogrel. In addition, due to the combination product administered, a question may remain as to whether the outcomes were due to lowering homocysteine levels or to other factors.

Ridker PM, Shih J, Cook TJ, et al, for the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) Investigators. Plasma homocysteine concentration, statin therapy, and the risk of first acute coronary events. *Circulation* 2002;105:1776–9.

This primary prevention trial, AFCAPS/TexCAPS, evaluated the ability of homocysteine concentration to predict coronary events in 5569 patients receiving either lovastatin or placebo. Results demonstrated that baseline homocysteine level was an independent predictor for a first acute coronary event. Patients at highest risk were those with elevated levels of both LDL and homocysteine. However, homocysteine concentration was not useful for predicting events in patients whose LDL level was below the median study level. This study questioned the utility of using homocysteine concentration as a marker to

identify initial cardiac events in low-risk patients as determined by LDL level. In other words, the data suggest that homocysteine levels should not be measured for primary prevention of first cardiovascular events in patients with normal LDL levels.

Anderson JL, Muhlestein JB, Horne BD, et al. Plasma homocysteine predicts mortality independently of traditional risk factors and C-reactive protein in patients with angiographically defined coronary artery disease. *Circulation* 2000;102:1227–32.

This prospective study evaluated risk associated with plasma homocysteine levels in 1412 patients with established CAD. Findings indicated that after a mean follow-up of 3 years, homocysteine level was a significant predictor of mortality and was independent of C-reactive protein and genotype status for folate metabolism. Patients in the tertile with the highest homocysteine levels had the greatest risk. This study is important because it further established elevated homocysteine concentration as an independent risk factor in patients with known CAD. However, the study did not address whether treatment that would lower this concentration would alter outcomes.

Liem A, Reynierse-Buitenwerf GH, Zwinderman AH, Jukema JW, van Veldhuisen DJ. Secondary prevention with folic acid: effects on clinical outcomes. *J Am Coll Cardiol* 2003;41:2105–13.

The effect of folic acid on outcomes in patients with stable CAD receiving statin therapy is not known. This open-label study evaluated the effect of folic acid 0.5 mg/day in 300 patients and 293 controls. Primary end point was all-cause mortality and a composite of vascular events; mean follow-up was 24 months. All patients had stable CAD and had been receiving statin therapy for a mean of 3.2 years. Mean \pm SD homocysteine levels were significantly decreased by 18% (from 12 ± 4.8 to 9.4 ± 3.5 µmol/L) in the folic acid group compared with controls. No significant differences were observed for the primary end point. Low-dose folic acid treatment and corresponding homocysteine level reduction were not effective in reducing clinical end points in this patient cohort. Results from this study call into question the usefulness of folic acid therapy for secondary prevention in patients with stable coronary disease receiving statin therapy. Of importance, baseline homocysteine levels

were in the range where risk to the patient is likely (Nygard O, Nordrehaug JE, Refsum H, et al. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med* 1997;337:230–6). Thus, the reduction seen in homocysteine levels should have demonstrated benefit. An obvious question from the trial is whether a greater reduction in homocysteine concentrations or higher baseline concentrations would have made a difference. In addition, results may have been different with a longer follow-up period.

Adhesion Molecules

Malik I, Danesh J, Whincup P, et al. Soluble adhesion molecules and prediction of coronary heart disease: a prospective study and meta-analysis. *Lancet* 2001;358:971–6.

This study investigated whether soluble adhesion molecules predict risk for CHD. Study patients were 643 men with CAD and 1278 controls; they were selected from a prospective study of 5661 men who were followed for 16 years. Serum concentrations of intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and P-selectin were measured. In addition, the authors performed a meta-analysis of other relevant studies. The ORs and 95% CIs for CHD after adjustment for other coronary risk factors and socioeconomic status were noted for ICAM-1 (OR 1.11, 95% CI 0.75–1.64), VCAM-1 (OR 0.96, 95% CI 0.66–1.4), E-selectin (OR 1.13, 95% CI 0.78–1.62), and P-selectin (OR 1.2 0.81–1.76). The authors concluded that measurement of these adhesion molecules probably is not useful for predicting risk beyond that of the more established risk factors. As presented in the article's discussion section, results of the meta-analysis appear to support their conclusion. These study data concern chronic disease and cannot be extrapolated to the acute coronary process. Of note, epidemiologic study samples may have been stored for nearly 20 years at -20°C . Whether degradation of the samples occurred and thus influenced the results is not known.

de Lemos JA, Hennekens CH, Ridker PM. Plasma concentration of soluble vascular cell adhesion molecule-1 and subsequent cardiovascular risk. *J Am Coll Cardiol* 2000;36:423–6.

This nested, case-control study investigated

whether soluble VCAM-1 is a marker for increased cardiovascular risk in men with confirmed myocardial infarction. Baseline plasma VCAM-1 samples were obtained from 474 men who experienced confirmed myocardial infarction during the 9-year follow-up period of the Physicians' Health Study. Their samples were compared with those obtained from a similar number of controls. No significant difference between the two groups was observed for median baseline VCAM-1 concentration. The data suggest that soluble VCAM-1 concentrations in apparently healthy men do not predict first coronary event. The study did not address secondary events.

Blankenberg S, Rupprecht HJ, Bickel C, et al. Circulating cell adhesion molecules and death in patients with coronary artery disease. *Circulation* 2001;104:1336–42.

This prospective study was conducted to determine whether soluble VCAM-1, ICAM-1, and E-selectin are risk markers for future cardiovascular events in patients with documented CAD. Baseline samples from a cohort of 1246 patients with CAD were obtained, and the rate of cardiovascular events was documented over a mean of 2.7 years. Baseline soluble VCAM-1, ICAM-1, and E-selectin predicted death from cardiovascular causes in these patients. When the data were controlled for other markers measured, such as C-reactive protein, only soluble VCAM-1 remained independently significant for fatal cardiovascular events (2.8-fold increase in risk, $p=0.003$). Circulating cell adhesion molecules predicted cardiovascular deaths in this patient population with documented CAD. Soluble VCAM-1 appeared to be the most predictive. Data concerning soluble adhesion molecules are sparse. Of note, this was a nonrandomized, observational study with inherent limitations. Based on the data from this trial, it appears that using soluble adhesion molecules as markers to predict events may be valuable in patients with established CAD.

Ridker PM, Buring JE, Rifai N. Soluble P-selectin and the risk of future cardiovascular events. *Circulation* 2001;103:491–5.

This study investigated whether P-selectin, a cell surface adhesion molecule, predicts cardiovascular events. Baseline plasma samples were obtained from 115 apparently healthy women who developed a cardiovascular event while

participating in the Women's Health Study. These samples were compared with those from 230 matched participants who remained event free during a 3.5-year follow-up period. Findings indicated that women who experienced a cardiovascular event had a higher mean P-selectin level than matched controls (83.2 vs 69.3 ng/ml, $p=0.003$). The greatest risk was observed at the highest quartile (2.2 times higher than that observed at the lowest quartile). The increased risk observed with increased P-selectin level was independent of traditional risk factors. This study demonstrated that elevated soluble P-selectin levels are a risk factor for primary vascular events in women.

High-Sensitivity C-Reactive Protein

Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973–9.

This early landmark study demonstrated the potential use of C-reactive protein as a risk marker for future cardiovascular events. This was an observational study based on 543 healthy men from the Physicians' Health Study who experienced a vascular event. These men were compared with 543 who did not experience a vascular event. The study found that increased C-reactive protein level was an independent predictor, with the greatest risk occurring at the highest quartile. Of interest, the effectiveness of aspirin for lowering the risk of first myocardial infarction was directly related to C-reactive protein level. This study helps establish increased C-reactive protein level as a potential risk factor for primary events in men.

Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998;97:2007–11.

Drawing from the Physicians' Health Study, the authors evaluated the role of C-reactive protein in concert with total cholesterol and HDL levels in predicting first myocardial infarction. This classic article demonstrated not only the independent value, but more important, the additive value of evaluating C-reactive protein and either total cholesterol level or total cholesterol:HDL ratio for determining risk of first myocardial infarction in healthy men. In other

words, this article showed that the risk is greatest when both total cholesterol and C-reactive protein levels are elevated.

Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836–43.

The previous studies by these authors demonstrated the value of C-reactive protein in predicting risk in apparently healthy men. In this study, the authors evaluated C-reactive protein and other markers of inflammation for predicting risk for first cardiovascular event in apparently healthy women. This was a prospective, nested, case-control study involving subjects from the Women's Health Study. Twelve markers were evaluated in 122 case subjects (women with cardiovascular events) and 244 control subjects (women free of cardiovascular disease). Results demonstrated that C-reactive protein was the strongest univariate predictor of risk, which was 4.4 times greater in the highest versus the lowest quartile. Other markers for risk were serum amyloid A, soluble ICAM-1, interleukin-6, homocysteine, total cholesterol, LDL, apolipoprotein B-100, HDL, and total cholesterol:HDL ratio. Prediction of risk was significantly improved in models that incorporated markers of inflammation in addition to lipids. Also, in a subgroup of patients with LDL levels below 130 mg/dl, increased C-reactive protein and serum amyloid A levels predicted risk. When the markers were evaluated by multivariate analysis, C-reactive protein and total cholesterol:HDL ratio were the only markers that independently predicted risk. Overall, this study demonstrated the importance of C-reactive protein in predicting risk of cardiovascular disease in apparently healthy women.

Ridker PM, Rifai N, Clearfield M, et al, for the Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in primary prevention of acute coronary events. *N Engl J Med* 2001;344:1959–65.

Previous data have shown that patients are at risk for coronary events when C-reactive protein levels are elevated even in those with lipid levels that may be considered normal. This study investigated whether statin therapy could reduce risk in patients with elevated C-reactive protein levels but without overt hyperlipidemia. C-reactive

protein levels were obtained at baseline and 1 year in 5742 patients enrolled in AFCAPS/TexCAPS. Results demonstrated that lovastatin was effective in patients with a total cholesterol:HDL ratio below the median and C-reactive protein level above the median. Similar results were seen for LDL level. The number needed to treat for 5 years to prevent one event was 43 and 48 patients for each respective analysis. The data also demonstrated that the changes in C-reactive protein level were probably unrelated to the changes in lipid levels. This study helps confirm previous studies demonstrating the importance of C-reactive protein to predict risk independently and when added to lipid levels. The study also demonstrated that, similar to pravastatin in the CARE trial, lovastatin also lowers C-reactive protein level, apparently independent of lipid level. Finally, these data suggest that patients may benefit from statin therapy, at least for primary prevention, when C-reactive protein level is elevated but lipid levels are normal.

Albert MA, Danielson E, Rifai N, Ridker PM, for the PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001;286:64–70.

Previous data suggest that lowering C-reactive protein level with statin therapy is independent of LDL level; this prospective trial investigated whether this is true with pravastatin in particular. Results demonstrated that pravastatin did, indeed, reduce C-reactive protein levels. Also, this study confirmed previous findings that no significant association exists between C-reactive protein and LDL levels. This suggests that statins may have both an antiinflammatory and a lipid-lowering effect. Clinically, this also suggests that the effects of statin therapy in preventing cardiovascular events may go beyond lipid lowering alone.

Ridker PM, Cannon CP, Morrow D, et al, for the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20–8.

This study investigated the relationship between LDL and C-reactive protein levels in reducing the risk of recurrent myocardial

infarction or death from coronary causes in 3745 patients with ACS. Study patients were drawn from the PROVE IT–TIMI 22 study. The authors evaluated the effect of atorvastatin 80 mg/day (intensive therapy) and pravastatin 40 mg/day (moderate therapy) on cardiovascular outcomes in patients with ACS. For this aspect of the study, the authors showed that when C-reactive protein level was decreased to less than 2 mg/L, event-free survival was improved. The improvement was seen with LDL levels less than 70 mg/dl and 70 mg/dl or greater. Also, less than 3% of the variation in C-reactive protein levels was explained by the variation seen in LDL level after statin therapy. The authors also found that once target levels were reached for C-reactive protein (< 2 mg/L) and LDL (< 70 mg/dl) levels, the type of statin administered did not seem important.

This study has a number of important implications. First, in patients with ACS, the authors confirmed findings from earlier primary prevention studies demonstrating the importance of C-reactive protein level in identifying risk. Also, they showed that lowering C-reactive protein levels with statin therapy is not directly associated with LDL level reduction. The results from this study may suggest a pathophysiologic role for C-reactive protein. In addition, with data from other trials, these results suggest that monitoring and treatment may be necessary for C-reactive protein as well as LDL levels. Finally, the results suggest that the type of statin administered may not be important, but the decrease in both LDL and C-reactive protein levels is important.

Interleukin-6

Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000;101:1767–72.

The authors used a prospective, nested, case-control design to draw patients from the Physicians' Health Study to determine whether interleukin-6 (IL-6) is a risk marker for myocardial infarction in apparently healthy men. A total of 202 patients who had a myocardial infarction were identified and matched with 202 subjects who did not have a myocardial infarction during a 6-year follow-up. Baseline median IL-6 levels were significantly higher in patients who had a myocardial infarction. Risk

increased with each increasing quartile ($p < 0.001$ for trend). Men in the highest quartile had a relative risk 2.3 times higher than those in the lowest quartile ($p = 0.005$). After adjusting for other cardiovascular risks, the relationship remained significant. These data indicate that increased IL-6 level is associated with an increased risk for myocardial infarction in apparently healthy men. The authors suggested that cytokine-mediated inflammation may play an important role in the development and progression of atherosclerosis.

Biasucci LM, Vitelli A, Liuzzo G, et al. Elevated levels of interleukin-6 in unstable angina. *Circulation* 1996;94:874–7.

This early study documented increased IL-6 levels in patients with unstable angina. Levels were measured in 38 patients with unstable angina and in 29 with stable angina. Interleukin-6 levels were detectable in 23 of 38 patients with unstable angina but in only 6 of 29 with stable angina. Significant correlation was seen between IL-6 and C-reactive protein levels. This study demonstrated significant increased IL-6 levels in patients with unstable versus those with stable angina. The data suggest that cytokine production and the resultant influence on acute-phase reactants contributed to cardiac events. Of note, the detection range was much less sensitive in this study than in a previous study by the same authors. This accounts for the finding that only six patients with stable angina had detectable IL-6 levels. The important finding in this study is the significant rise from a probably already activated cytokine state to an even higher state during an acute process such as unstable angina.

Matrix Metalloproteinase

Aikawa M, Rabkin E, Okada Y, et al. Lipid lowering of diet reduces matrix metalloproteinase activity and increases collagen content of rabbit atheroma: a potential mechanism of lesion stabilization. *Circulation* 1998;97:2433–44.

This study, in which experimental atheromas were induced in rabbits, tested whether lipid lowering by diet alters macrophage accumulation and matrix metalloproteinase (MMP) expression in atherosclerotic lesions. Results demonstrated that a lipid-lowering diet reduced macrophage content and MMP expression. In addition, interstitial collagen appeared to increase, suggesting greater stabilization of fibrous caps. This study establishes a mechanism by which

lipid lowering may prevent plaque rupture and subsequent cardiovascular events.

Aikawa M, Rabkin E, Sugiyama S, et al. An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrix metalloproteinase and tissue factor in vivo and in vitro. *Circulation* 2001;103:276–83.

This study investigated whether 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibition with cerivastatin decreases macrophage accumulation and MMP expression in a heritable hyperlipidemia rabbit model. Results demonstrated that HMG-CoA reductase inhibition decreased macrophage accumulation and MMP expression in this model. Further, these results demonstrate that lipid lowering with an HMG-CoA reductase inhibitor may prevent cardiovascular events by decreasing plaque instability through alterations in macrophage accumulation and MMP activity.

Plasminogen Activator Inhibitor-1

Bourcier T, Libby P. HMG CoA reductase inhibitors reduces plasminogen activator inhibitor-1 expression by human vascular smooth muscle and endothelial cells. *Arterioscler Thromb Vasc Biol* 2000;20:556–62.

This study investigated whether HMG-CoA reductase inhibitors affect the fibrinolytic system. Specifically, the authors evaluated the effect of HMG-CoA reductase inhibition on plasminogen activator inhibitor-1 and tissue plasminogen activator expression in cell cultures (inflammatory stimulated vascular smooth cells and endothelial cells). Results demonstrated that simvastatin inhibited the expression of plasminogen activator inhibitor-1 in both types of cells and increased expression of tissue plasminogen activator in endothelial cells. These data suggest that the benefit of HMG-CoA reductase inhibition may relate in part to an alteration in the fibrinolytic system that may have favorable outcomes, perhaps by reducing thrombotic risk after plaque rupture. The effect on the fibrinolytic system may be another mechanism beyond lipid lowering in which HMG-CoA reductase inhibitors may be beneficial in treating patients with CAD.

CD40 System

Garlachs CD, John S, Schmeisser A, et al. Upregulation of CD40 and CD40 ligand (CD154)

in patients with moderate hypercholesterolemia. *Circulation* 2001;104:2395–400.

Some researchers have suggested that the CD40 system located in part on endothelial cells or monocytes may promote expression of proinflammatory cytokines, adhesion molecules, and other factors that may contribute to atherosclerotic development and progression. This study investigated whether the CD40 system is upregulated in patients with hypercholesterolemia and whether HMG-CoA reductase inhibition affects this system. The study included 15 patients with hypercholesterolemia and 15 healthy matched subjects. At baseline and after 3 weeks of treatment with cerivastatin 0.3 mg/day in the hypercholesterolemia group, CD40, CD154, P-selectin, and MCP-1 were evaluated. Results demonstrated that at baseline, before cerivastatin therapy, platelets of CD154 and P-selectin were significantly increased and CD40 on monocytes was increased in the hypercholesterolemia group. Also, MCP-1 was elevated in a platelet cell model and in the serum of the hypercholesterolemia group. After cerivastatin therapy, CD40 was significantly downregulated and serum MCP-1 levels were decreased. Implications of this study include the possible role of the CD40 system to contribute to the pathophysiology of atherosclerosis. In addition, a possible mechanism for antiinflammatory effects of statins may be related to modulation of this system.

Noncholesterol Sterols

Miettinen TA, Gylling H, Strandberg T, Sarna S, for the Finnish 4S Investigators. Baseline serum cholestenol as predictor of recurrent coronary events in subgroup of the Scandinavian simvastatin survival study. *BMJ* 1998;316:1127–30.

Cholestenol, the 5- α -saturated derivative of cholesterol, is formed from endogenous cholesterol by enzymatic action. The cholestenol:cholesterol ratio, which is negatively related to cholesterol synthesis in humans, may help predict which patients may benefit from statin therapy in terms of coronary event reduction. This study assessed baseline cholestenol:cholesterol ratios in a Finnish subgroup of 868 patients from the Scandinavian Simvastatin Survival Study who were originally randomized to receive simvastatin or placebo. Patients were stratified into quartiles according to

their cholestenol:cholesterol ratio. In each quartile, relative risk of a major coronary event (coronary death, nonfatal myocardial infarction, revascularization procedure) were calculated for patients in both simvastatin and placebo patients. Risk reduction with simvastatin was seen with increasing quartiles of cholestenol:cholesterol ratios. The authors suggested that measurement of the cholestenol:cholesterol ratio may help in identifying patients who might not benefit from statin monotherapy.

Salem G, Horak I, Rothkopf M, et al. Lethal atherosclerosis associated with abnormal plasma and tissue sterol composition in sitosterolemia with xanthomatosis. *J Lipid Res* 1985;26:1126–33.

This report compared tissue sterol composition in two 18-year-old patients; one had severe atherosclerosis and died suddenly, the other had minimal atherosclerosis and died accidentally. The patient with severe atherosclerosis had increased levels in plasma and tissue of cholesterol, sitosterol, campesterol, and 5- α -saturated stanols; the patient who died accidentally had trace amounts of noncholesterol sterols. The authors endorsed cholestyramine treatment for reducing plant sterol concentration in patients with sitosterolemia. Cholestyramine enhances conversion of cholesterol and other sterols to bile acids, thereby reducing plasma concentrations.

Sudhop T, Gottwald BM, Bergmann KV. Serum plant sterols as a potential risk factor for coronary heart disease. *Metabolism* 2002;51:1519–21.

Patients with sitosterolemia have extremely elevated plant sterol levels and a high rate of premature CHD. This study investigated whether plant sterol concentrations were a risk factor for CHD in those without sitosterolemia. Baseline levels of campesterol, sitosterol, lathosterol, desmosterol, cholestenol, and serum lipid were determined in consecutive patients admitted for coronary bypass surgery. Compared with patients with no family history of CHD, those with this history had significantly higher concentrations of campesterol (0.5 ± 0.17 vs 0.38 ± 0.16 mg/dl, $p=0.011$) and sitosterol (0.4 ± 0.11 vs 0.31 ± 0.11 mg/dl, $p=0.004$). Other CHD risk factors were similar between the two groups. The authors concluded that plant sterols may be an additional CHD risk factor.

Myopathy, Hepatotoxicity, and Peripheral Neuropathy Associated with Lipid-Lowering Agents

Gaist D, Jeppesen U, Andersen M, Garcia Rodriguez LA, Hallas J, Sindrup SH. Statins and risk of polyneuropathy: a case-control study. *Neurology* 2002;58:1333–7.

This nested, case-control study of a patient registry in Denmark used outpatient visits or hospital discharges recorded from January 1, 1994–December 31, 1998, to identify the first-recorded cases of idiopathic polyneuropathy in a single county. Cases were excluded if diagnostic codes or testing indicated other possible causes of neuropathy (diabetes, renal insufficiency, excessive alcohol intake, hypothyroidism, cancer, monoclonal gammopathy of undetermined significance, acquired immunodeficiency syndrome, Lyme disease, connective tissue disease, heavy metal intoxication, cobalamine or folic acid deficiency, familial polyneuropathy, or chronic inflammatory idiopathic polyneuropathy). Only case patients with clinical data and electrophysiologic tests (abnormal conduction in at least two peripheral nerves, with at least one a leg nerve) confirming the diagnosis were included. A neurologist masked to drug exposure identified 166 cases with a first diagnosis of idiopathic polyneuropathy. Of these cases, 35 were classified as definite, with no other apparent cause of neuropathy; 54 as probable, with sufficient information to rule out excessive alcohol intake, diabetes, and renal insufficiency; and 77 as possible, with insufficient evidence to determine presence or absence of other exclusion criteria. Each case patient was matched with 25 controls based on age, sex, and calendar time. Prescription records were used to assess exposure to drugs and estimate the OR for administration of statins for both groups. Eight case patients were taking statins (five simvastatin, two pravastatin, one lovastatin, and one fluvastatin); one had taken lovastatin previously. The OR linking idiopathic polyneuropathy with statin therapy was 3.7 (95% CI 1.8–7.6) for all cases and 14.2 (95% CI 5.3–38.0) for definite cases. The OR in patients taking statins was 4.6 (95% CI 2.1–10.0) for all cases and 16.1 (95% CI 5.7–45.4) for definite cases, and 26.4 (95% CI 7.8–45.4) for those patients who had been taking statins for 2 or more years.

Hsu I, Spinler SA, Johnson NE. Comparative evaluation of the safety and efficacy of HMG-CoA

reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia. *Ann Pharmacother* 1995;29:743–59.

This comprehensive review compared the efficacy and safety of fluvastatin, lovastatin, pravastatin, and simvastatin in the treatment of primary hypercholesterolemia. Results from placebo-controlled and comparative studies of statin monotherapy are discussed; the comparative trials are summarized in Table 3 of the review. The safety evaluation section includes information on increased hepatic transaminase kinase concentration, increased creatine kinase and myopathy, lens opacity, and sleep disturbances. The authors concluded that the long-term safety of statin therapy has been established in clinical trials. The most common adverse events associated with statin therapy were asymptomatic increased hepatic transaminase and creatine kinase concentrations. However, symptomatic hepatic impairment and myopathy were rare. In the comparative trials, the adverse-effect profiles of statins were similar.

Omar, MA, Wilson DP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001;35:1096–107.

The authors provide an overview of rhabdomyolysis and the role of statins in patients with rhabdomyolysis. Case reports of statin-associated rhabdomyolysis were identified by a PubMed/MEDLINE search (January 1985–October 2000). This review has several useful tables. Table 1 compares pharmacokinetic properties of statins, Table 2 lists drugs associated with rhabdomyolysis due to interaction with statins, Table 3 provides the frequency of case reports associated with statin monotherapy and combination therapy, and Table 4 lists case reports of therapy. No information about rosuvastatin is provided.

Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288–95.

The authors identified 871 (601 unique) domestic and foreign cases of statin-associated rhabdomyolysis using the FDA's Adverse Event Reporting System (November 1997–March 2000). Outcome measures were the total number of reports (initial plus follow-up), the number of unique cases, patient age and sex, percentages of report codes and role codes, frequencies of concomitant interacting drugs that may have

precipitated rhabdomyolysis, outcome codes, and report source codes. Numbers and percentages of cases were associated with each statin as follows: 215 (35.8%) simvastatin, 192 (32.0%) cerivastatin, 73 (12.2%) atorvastatin, 71 (11.8%) pravastatin, 40 (6.7%) lovastatin, and 10 (1.7%) fluvastatin. No information was provided for rosuvastatin. Men had a higher rate of statin-associated rhabdomyolysis than women (51.2% vs 46.5%). The most commonly reported interacting drugs (more than 10 cases reported for each) were mibefradil, fibrates, cyclosporine, macrolide antibiotics, warfarin, digoxin, and azole antifungals. The most common outcome listed was hospitalization; 38 cases resulted in death. Statin therapy was the primary suspect of rhabdomyolysis in 72.0% of cases. The authors recognized the potential flaws in using the FDA reporting system to determine the frequency of statin-associated rhabdomyolysis.

Smith CC, Bernstein LI, Davis RB, Rind DM, Shmerling RH. Screening for statin-related toxicity: the yield of transaminase and creatine kinase measurements in a primary care setting. *Arch Intern Med* 2003;163:688–92.

These authors determined the frequency of screening of transaminase and creatine kinase levels in 1194 patients in a primary care practice in 1998. The patients were identified by use of a computerized medical record. During the study, 1014 (85%) patients had at least one monitoring test. Of these 1014 patients, 10 (1.0%) had a significant transaminase level elevation (> 120 U/L) and five (0.5%) had a moderate elevation (81–120 U/L); the elevations were not attributed to statin therapy. Six (0.9%) patients had at least one significantly abnormal creatine kinase level elevation (> 5 times the upper limit of normal); these elevations were attributed to statin therapy. Fourteen (2.1%) patients had moderate creatine kinase level elevations (2.5–5 times the upper limit of normal); two of these elevations were possibly related to statin therapy. The frequency of transaminase and creatine kinase level elevations was lower than that reported in the major statin trials. No documented adverse events were associated with any of the abnormal laboratory test results. Patients were taking atorvastatin (37%), lovastatin (23%), pravastatin (20%), and simvastatin (20%). This study included patients who would have been excluded from the major clinical trials due to preexisting medical conditions or concomitant drug

therapies. The authors questioned the need for routine monitoring of transaminase and creatine kinase levels.

Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis [letter]. *N Engl J Med* 2002;346:539–40.

The writers of this letter to the editor evaluated the frequency of fatal rhabdomyolysis associated with atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin using the Adverse Event Reporting System of the FDA and the National Prescription Audit Plus. The letter was written after Bayer voluntarily withdrew cerivastatin from the U.S. market. The reporting rate of rhabdomyolysis fatalities was less than 1 death/million statin prescriptions compared with 1.9 deaths/million prescriptions for cerivastatin monotherapy. Thirty-one deaths due to rhabdomyolysis were reported with cerivastatin. Of these, 19 were associated with monotherapy (12 and six patients with cerivastatin 0.8 and 0.4 mg, respectively; dose was not reported for one patient). Twelve fatalities were associated with combined cerivastatin and gemfibrozil. The authors urge clinicians to warn patients taking any statin to report symptoms of myopathy.

Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681–90.

This review article provides a clinical summary of statin-related myopathy and the frequency of statin-associated rhabdomyolysis. With a PubMed/MEDLINE search, articles concerning statin-related myopathy (through December 2002) and randomized, controlled clinical trials involving statins (through January 2003) were identified. Rates of myalgia in the placebo- and statin-treated groups in the clinical trials are reported in Table 1 of the article. Rates of myopathy in placebo- and statin-treated groups as reported in the randomized controlled statin trials are compared in Table 3. The authors report the type of patients, duration of study, statin dosage, number of patients, number with cases of rhabdomyolysis, number with cases of myositis, percentage of patients with elevated creatine kinase levels, and percentage with myalgia. The incidence of statin-associated rhabdomyolysis was determined using the FDA MedWatch database (January 1, 1990–March 31, 2002). In Table 2, rates of rhabdomyolysis with atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin are summarized

according to age groups and outcomes (death, disability, hospitalization, life-threatening disorder, other).

Hodel C. Myopathy and rhabdomyolysis with lipid-lowering drugs. *Toxicol Lett* 2002;128:159–68.

Using published literature and unpublished personal experiences with animal and clinical cases, this author provided a 30-year review of myopathy associated with fibrates and myopathy and rhabdomyolysis associated with statins. The mechanism of action of myopathy in humans and in the animal models for myopathy are discussed. The author suggests that electrophysiologic studies involving patients taking drugs known to be or suspected of being myotoxic will allow determination of the true incidence of drug-induced myopathy.

Huynh T, Cordato D, Yang F, et al. HMG-CoA reductase-inhibitor-related myopathy and the influence of drug interactions. *Intern Med J* 2002;32:486–90.

This article presents four case reports involving elderly women who developed rhabdomyolysis and severe, disabling myopathy. Patient no. 1 had been taking simvastatin 80 mg/day with gemfibrozil 600 mg twice/day for over 6 months. Rhabdomyolysis developed after roxithromycin was added to treat an upper respiratory infection. Patient no. 2, who had type 2 diabetes and chronic renal failure, developed rhabdomyolysis after taking simvastatin 20 mg/day for 3 months. Patient no. 3, who had chronic renal failure, had been taking simvastatin 40 mg/day for 5 years. Muscle biopsy confirmed necrotizing myopathy and the presence of inclusion bodies, which may indicate underlying muscle disease. Patient no. 4, who had diabetes, had been taking cerivastatin for 1 month before hospital admission. Muscle symptoms resolved in three patients; the exception was patient no. 3. These case reports illustrate the need to consider drug interactions and comorbid disease states when selecting lipid-lowering therapy.

Kiortsis DN, Nikas S, Hatzidimou K, Tsianos E, Elisaf MS. Lipid-lowering drugs and serum liver enzymes: the effects of both weight and baseline enzyme levels. *Fundam Clin Pharmacol* 2003;17:491–4.

This study examined the effects of statins and fibrates on liver enzyme levels in patients who

were obese, overweight, and lean, based on body mass index. Over 24 weeks, 263 men and women aged 31–74 years received atorvastatin 10–20 mg/day (62 patients), ciprofibrate 100 mg/day (44), micronized fenofibrate 200 mg/day (45), fluvastatin 40 mg/day (103), and gemfibrozil 900 mg/day (9). Serum transaminase concentrations were obtained at baseline, after 8 weeks of treatment, and at the end of the study; these levels were compared based on body mass index. At baseline, 8 weeks, and 24 weeks, more obese than lean patients had elevated transaminase levels; however, the differences were not statistically significant. No statistically significant changes in transaminase levels were observed in any patient group.

Punthakee Z, Scully LJ, Guindi MM, Ooi TC. Liver fibrosis attributed to lipid lowering medications: two cases. *J Intern Med* 2001;250:249–54.

Two case reports describe patients with chronic active hepatitis and liver fibrosis associated with statins and fibrates; other possible causes were ruled out. The first report describes a 39-year-old man originally treated inadequately with gemfibrozil and cholestyramine. His therapy was changed to lovastatin, which was discontinued after 9 months because of myalgia without creatine kinase level elevation. Nine months after lovastatin discontinuation, pravastatin therapy was started, and 9 months later the patient came to the hospital complaining of fever and asthenia. His elevated liver enzyme levels were consistent with acute liver injury; when these levels returned to normal, simvastatin therapy was started. After 22 months of simvastatin therapy, the patient returned to the hospital with the same symptoms and elevated liver enzyme levels. Simvastatin was stopped, and his elevated enzyme levels returned to the normal range. Findings from needle biopsy of the liver 2 weeks after simvastatin discontinuation were consistent with drug-induced chronic active hepatitis. Six years after the patient stopped taking simvastatin, hepatitis had not recurred.

The second case report describes an obese, 63-year-old woman whose transaminase concentrations were elevated to more than 11 times the upper limit of normal on routine monitoring. The patient had been taking fenofibrate for 2 years and simvastatin for 4 years at the time of her laboratory test. Liver enzyme concentrations returned to normal within 2 months after

discontinuation of the simvastatin and fenofibrate. Results of a liver biopsy 7 weeks after the patient stopped taking these drugs indicated that she had chronic active hepatitis with severe fibrosis.

Sinzinger H, Wolfram R, Peskar BA. Muscular side effects of statins. *J Cardiovasc Pharmacol* 2002;40:163–71.

This review article discusses the muscle-related side effects of statins. The authors did not describe their literature search or specify the period covered. Coenzyme Q₁₀ depletion and oxidation injury are presented as possible mechanisms of muscle symptoms. The article provides a general overview of pain (type, time of onset, duration, and localization), creatine kinase concentration, physical activity, statin dose-dependency, predisposing factors, risk associated with different statins, pathophysiology, and treatment.

van Puijenbroek EP, Du Buf-Vereijken PW, Spooren PF, van Doormaal JJ. Possible increased risk of rhabdomyolysis during concomitant use of simvastatin and gemfibrozil. *J Intern Med* 1996;240:403–4.

Two case reports describe rhabdomyolysis development during concomitant treatment with simvastatin and gemfibrozil. The first patient, a 62-year-old man with diabetes, atherosclerosis, and hyperlipidemia, was taking simvastatin 20 mg/day with gemfibrozil 600 mg/day. The second patient, a 50-year-old woman with diabetes, hyperlipidemia, chronic renal failure with nephrotic syndrome, and obesity, was taking simvastatin 80 mg/day with gemfibrozil 600 mg/day.

Wortmann RL. Lipid-lowering agents and myopathy. *Curr Opin Rheumatol* 2002;14:643–7.

This review article discusses the muscle-related side effects of statins, fibrates, and nicotinic acid. Clinical features, epidemiology, risk factors, and mechanisms are presented in short sections. In Table 4, drug-drug interactions resulting from cytochrome P450 (CYP) systems are listed by statin. Certain references are marked “of special interest” or “of outstanding interest.”

Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med* 2003;163:553–64.

This comprehensive review article focuses on

statin-associated myopathy. The authors identify drug-drug interactions as a potential cause of increased risk of myopathy. Statin-cyclosporine, statin-fibrate, statin-niacin, and statin-calcium channel antagonist interactions are discussed in subsections of the article. In Table 5, the authors list advisory statements as safety considerations in prescribing statins in primary care settings. This table could be easily posted in clinics or used by clinicians as a pocket-card reference. The bibliography for the article is much more extensive than for other review articles we present in this section.

Bannwarth B. Drug-induced myopathies. *Expert Opin Drug Saf* 2002;1:65–70.

This review article discusses drug-induced myopathies, including those associated with lipid-lowering therapy. Drug-induced myopathies are divided into five categories: necrotizing (mainly associated with lipid-lowering therapy), inflammatory, mitochondrial, corticosteroid, and various painless myopathies. Risk factors for statin-induced myopathy include high plasma concentrations of statin as a result of high doses or impaired metabolism; low levels of intestinal and hepatic CYP, particularly CYP3A4 subclass; and coadministration of CYP3A4 inhibitors. Other statin-related causes of rhabdomyolysis or potentiators of myotoxicity are certain viral infections; endocrine, metabolic, and electrolyte disturbances; major trauma; seizures; hypothermia; hypoxia; and misuse of amphetamines, cocaine, ecstasy, lysergide, or alcohol. Preventive measures against statin myopathy are listed. Table 1 in the article provides a partial list of drugs associated with myalgia. Certain references are marked “of special interest” or “of outstanding interest.”

Chazerain P, Hayem G, Hamza S, Best C, Ziza JM. Four cases of tendinopathy in patients on statin therapy. *Joint Bone Spine* 2001;68:430–3.

Four patients (three men, one woman) with statin-associated tendinopathy are described. Patient no. 1 was diagnosed with extensor tenosynovitis of the hands, patient no. 2 with tenosynovitis of the tibialis anterior tendon, and patients nos. 3 and 4 with Achilles tendinopathy. Two patients were taking atorvastatin, two simvastatin. In all four patients, symptoms resolved within 2 months of drug discontinuation. The only patient who showed possible statin causality was treated with a nonsteroidal

antiinflammatory drug and recovered within 2 weeks after atorvastatin discontinuation. Two patients had other risk factors for tendinopathy. One patient was rechallenged with a lower dose of simvastatin and experienced no recurrence of tendinopathy.

Federman DG, Hussain F, Walters AB. Fatal rhabdomyolysis caused by lipid-lowering therapy. *South Med J* 2001;94:1023–6.

This case report describes a 68-year-old man with fatal rhabdomyolysis caused by the combination of simvastatin and gemfibrozil. The patient had type 2 diabetes with diabetic nephropathy, hypertension, peripheral vascular disease, and dyslipidemia. His baseline serum creatinine level was 3.4 mg/dl. Four weeks before his hospital admission, gemfibrozil 600 mg twice/day was added to his drug regimen, which included simvastatin 80 mg/day. The patient's condition worsened, and he died on day 7 of his hospital stay. Autopsy showed significant myositis on microscopic examination. The authors warn against administration of high-dose statins in combination with fibrates in patients with renal insufficiency.

Kamaliah MD, Sanjay LD. Rhabdomyolysis and acute renal failure following a switchover of therapy between two fibric acid derivatives. *Singapore Med J* 2001;42:368–72.

Two case reports describe bezafibrate-induced rhabdomyolysis in two men with coronary artery disease and preexisting renal impairment. The patients were affected several days after their drug therapy was changed from gemfibrozil to bezafibrate. Both had been taking gemfibrozil 600 mg twice/day for a year; neither was receiving other lipid-lowering therapy. Both patients required dialysis. One patient developed an acute coronary event and died on day 7 of his hospital stay; the other recovered and was discharged. The authors suggest that fibrates may have different degrees of propensity for myotoxicities, and they urge clinicians to use caution when prescribing these drugs for patients with renal impairment.

Le Quintrec JS, Le Quintrec JL. Drug-induced myopathies. *Baillieres Clin Rheumatol* 1991;5: 21–38.

This article reviews major drug-induced generalized myopathies. Painless myopathies are categorized as those without neuropathy, with

neuropathy, and with abnormal neuromuscular transmission. Painful myopathies are categorized as those without neuropathy (polymyositis or other painful myopathies) and with neuropathy. Drug-induced myokymia and hypotonia are not discussed. Myopathy associated with lipid-lowering agents is described as painful myopathy without polymyositis. Clofibrate and its derivatives, fenofibrate, gemfibrozil, nicotinic acid, and statins have all been associated with myopathies. The authors note that combinations of fibrate-fibrate or fibrate-statin may be myotoxic. Clofibrate-induced myopathy is described in enormous detail: it occurs 36 hours–2 years after the start of therapy; patients with renal disease, low serum albumin levels, and hypothyroidism may be at greater risk than others; the myopathy has a syndrome of muscle pain, weakness and tenderness, and increased serum creatine kinase levels with normal results on reflex and sensory examination; electromyogram of the proximal upper and lower limb muscles shows a mixed myopathic picture; and muscle biopsy may show atrophy, degeneration, fragmentation, hyalinization, vacuolization, deranged mitochondria and phagocytosis by macrophages, without inflammatory infiltrates. The authors suggest the following criteria for associating myopathy with drug therapy: lack of preexisting muscular symptoms, a lag time between the start of treatment and start of symptoms, lack of other possible cause of myopathy, and partial or complete resolution of symptoms after the treatment drug is discontinued.

Mantel-Teeuwisse AK, Klungel OH, Herings RM, van Puijenbroek EP, Porsius AJ, de Boer A. Myopathy due to statin/fibrate use in the Netherlands. *Ann Pharmacother* 2002;36:1957–60.

This study compared the estimated number of expected cases of myopathy to the number of observed cases of myopathy due to statin or fibrate treatment in the Netherlands in 1 year. The expected number of cases was calculated by multiplying the total number of person-years of statin or fibrate treatment by the excess rate of myopathy due to those statins and fibrates as reported in the literature. The observed number of cases was obtained from PHARMO and the Dutch Pharmacovigilance Foundation Lareb. PHARMO links drug histories with hospital discharges, so it would not capture myopathy that did not require hospitalization. The Dutch Pharmacovigilance Foundation Lareb relies on reporting by health professionals, so it has the

same limitations as the Adverse Event Reporting System of the FDA. The number of observed cases was less than the estimated number of expected cases of myopathy.

Shanahan RL, Kerzee JA, Sandhoff BG, Carroll NM, Merenich JA. Low myopathy rates associated with statins as monotherapy or combination therapy with interacting drugs in a group model health maintenance organization. *Pharmacotherapy* 2005;25:345–51.

The authors determined the rate of statin-related myopathy in a group-model health maintenance organization (HMO) with approximately 360,000 members. Computer data were used to identify 468 patients with a diagnosis of myopathy during a 4-year period. Medical record review determined that 61 (13%) patients received statin therapy before their diagnosis of myopathy; 41 (67%) of the 61 had confirmed myopathy with creatine kinase level elevations above 1000 IU/L. Of the 41 patients, 17 (41%) had statin-related myopathy. Prevalence of statin-related myopathy was 0.12% with monotherapy and 0.22% when the statin was combined with interacting drugs; however, the difference was not statistically significant. None of the cases resulted in death. The authors noted that myopathy occurred more frequently in patients with a precipitating event (addition of an interacting drug, increased statin dose in the presence of an interacting drug, or other events not related to therapy) or concurrent risk factors. In this HMO, all patients prescribed a statin receive intensive education, which includes information about the possibility of increased risk of myopathy and rhabdomyolysis. This HMO's patients may be more motivated to report possible myopathy symptoms earlier than patients who do not receive this education. The authors urge practitioners to use caution in applying these results to health care settings that lack a structured program for monitoring patients.

Ziajka PE, Wehmeier T. Peripheral neuropathy and lipid-lowering therapy. *South Med J* 1998;91:667–8.

This case report describes a patient who experienced peripheral neuropathy that was induced and exacerbated by atorvastatin, lovastatin, pravastatin, simvastatin, and niacin. After taking lovastatin 20 mg/day for 4 years, the patient noted the start of symptoms (burning dysesthesia in both feet progressing to gait

disability); nerve conduction studies confirmed polyneuropathy. Lovastatin was discontinued and the symptoms improved. Twenty months later, the patient was prescribed pravastatin 20 mg/day. Symptoms worsened over the next 2 weeks, and the pravastatin therapy was changed to simvastatin 10 mg/day. The patient's neuropathic pain worsened over the next month. Simvastatin was discontinued and the symptoms improved. A brief trial of low-dose niacin 50 mg 3 times/day and then atorvastatin 10 mg/day also caused recurrence and worsening of neuropathic symptoms. In addition to this case report, the authors provide a brief review of other statin-associated peripheral neuropathy case reports. The authors speculate that the mechanism of statin-associated neuropathy may not be caused by ubiquinone depletion since niacin does not affect ubiquinone production.

Davidson M. Does differing metabolism by cytochrome P450 have clinical importance? *Curr Atheroscler Rep* 2000;2:14–19.

Drug metabolism by CYP enzyme is described. The impact of fibrates, cyclosporine, potent CYP3A4 inhibitors, and grapefruit juice on statin therapy is discussed only briefly since this information is available in the individual statin package inserts. Genetic polymorphisms of CYP isoenzymes are noted as possible causes of interindividual variation of drug effects. No evidence of CYP3A4 polymorphisms is cited; CYP2C9 has been associated with polymorphisms in Caucasians and African-Americans, but the clinical significance with fluvastatin therapy is not known.

Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. *Pharmacol Ther* 1999;84:413–28.

This comprehensive article discusses the possible direct effects statins may have on the arterial wall and explains drug interactions in terms of pharmacokinetic properties of statins. Table 2 provides a brief summary with references for possible mechanisms of the direct vascular action of statins. The bibliography is extensive.

Studies Assessing Alternate-Day Dosing

Graham MR, Lindsey CC, Kennedy JA. Maintenance of low-density lipoprotein goal with step-down pravastatin therapy. *Pharmacotherapy* 2002;22:21–6.

This prospective, randomized, open-label study involved 104 men who were taking pravastatin once/day and had maintained their NCEP ATP II goal LDL level for at least 3 months. Patients were randomized to two pravastatin treatment groups: 53 who received their original dose every other day and 51 who received half their original daily dose. Fasting lipid profiles and liver function were checked at baseline, 2 months, and 4 months; compliance was assessed. Only 49% of patients remained at their LDL goal (42% of those receiving their original dose every other day, 57% of those receiving half their original daily dose). Concentrations of LDL were statistically significantly higher at 2 and 4 months in the group receiving the original dose of pravastatin every other day. The authors concluded that giving pravastatin daily at half the original daily dose is more effective than giving the original dose every other day.

Copher HR, Stewart RD. Daily dosing versus alternate-day dosing of simvastatin in patients with hypercholesterolemia. *Pharmacotherapy* 2002;22:1110–16.

This nonrandomized, before-after comparison trial involved 15 men who were taking simvastatin once/day and had attained their NCEP ATP II goal LDL level. Efficacy of the original daily simvastatin dose was compared with alternate-day therapy at double the original daily dose. Laboratory values were obtained before and 8 weeks after the alternate-day therapy was started. All patients received an 8-week supply of prefilled pillboxes. Concentrations of LDL remained at goal in 12 of the 14 patients who completed the study. One patient, whose LDL level did not remain at goal, was not compliant with the alternate-day therapy. No statistically significant differences were noted between prestudy and poststudy levels of total cholesterol, LDL, HDL, triglycerides, liver transaminases, or creatine kinase. Therapy with double the original simvastatin dose every other day was as safe and effective as with the original dose taken daily.

Matalka MS, Ravnan MC, Deedwania PC. Is alternate daily dose of atorvastatin effective in treating patients with hyperlipidemia? The alternate day versus daily dosing of atorvastatin study (ADDAS). *Am Heart J* 2002;144:674–7.

This double-blind, placebo-controlled trial compared the efficacy of alternate-day dosing of

atorvastatin with once-daily dosing in 35 patients who met the NCEP ATP II guidelines for drug treatment. Patients were randomly assigned to receive atorvastatin 10 mg once/day or once every other day. Laboratory values were obtained at 6 and 12 weeks, and the atorvastatin dose was doubled if LDL was not at goal level. The initial dose of atorvastatin was doubled at the 6-week follow-up period in 17% of patients in the daily group and in 79% of those in the alternate-day group. At the end of the 12-week study period, the average atorvastatin dose was 12 mg in the daily group and 18 mg (9 mg/day) in the alternate-day group ($p < 0.001$). Target LDL goal was attained in 75% of the daily group and 43% of the alternate-day group; however, the alternate-day group had more secondary prevention patients. Both groups had similar LDL reductions (38% and 35% in the daily and alternate-day groups, respectively). The authors estimated that alternate-day therapy could reduce annual drug costs by 34%.

Studies Assessing Adherence to Guidelines

Stafford RS, Blumenthal D, Pasternak RC. Variations in cholesterol management practices of U.S. physicians. *J Am Coll Cardiol* 1997;29:139–46.

This study evaluated the cholesterol management practices of 2332 physicians during 1991–1992 based on data from the National Ambulatory Medical Care Surveys conducted by the National Center for Health Statistics. Randomly selected, office-based, patient care physicians reported specific clinical services provided during a sample of patient visits. Patient demographics, diagnoses, current drug therapies, physician characteristics, and visit characteristics were reported. Physicians also indicated whether they provided cholesterol counseling (which included any advice related to cholesterol) or ordered laboratory tests for either a cholesterol panel or total cholesterol level alone. The study evaluated the effects of independent variables—including physician specialty; patient sex, age, and race; presence of cardiovascular disease and its risk factors; expected payment source; and census region—on the odds that patients received cholesterol management services. The authors combined estimates from the National Ambulatory Medical Care Surveys with data from the third National Health and Nutrition Examination Survey (NHANES III) and the Atherosclerosis Risk in

Communities Study. In this manner, they demonstrated that 42 million (3.8%) of the 1.12 billion estimated visits to U.S. office-based physicians in 1991–1992 included cholesterol counseling (95% CI 40–45 million) and 49 million (4.4%) visits included cholesterol testing (95% CI 46–52 million). Study results showed that nonclinical, clinical, and demographic factors—such as physician specialty, presence of cardiovascular disease or risk factors, and payment source—strongly influenced patterns of cholesterol management. Overall, this study demonstrated that rates of hyperlipidemia screening and treatment were lower than expected, and many factors contributed to the underuse of clinical services.

McBride P, Schrott HG, Plane MB, Underbakke G, Brown RL. Primary care practice adherence to National Cholesterol Education Program guidelines for patients with coronary heart disease. *Arch Intern Med* 1998;158:1238–44.

This study examined the patterns of cholesterol screening and management by primary care physicians after publication of the NCEP ATP II guidelines. The authors reported the dietary counseling and drug therapy provided for patients with cardiovascular disease in primary care practice, their patients' level of success in meeting ATP-II treatment goals, and factors that influenced cholesterol screening and management. Data were collected from medical records and patient and physician questionnaires from practices near four regional centers in Wisconsin, Minnesota, and Iowa from 1993–1995. The medical record review yielded lipid panel results for 579 patients; only 84 (14.5%) had an LDL level below 100 mg/dl. Logistic regression analysis showed that physician time in practice, patient education level, and cholesterol level predicted the dietary counseling and drug therapy provided. The study data suggested that physicians are more likely to treat hyperlipidemia aggressively when they perceive that patients are at higher risk, and they do not consider cardiovascular disease a requirement for targeting LDL goal levels of less than 100 mg/dl. These factors may be related to the lack of adherence to NCEP ATP II guidelines and may contribute to the number of patients who do not have a lipid panel obtained and are not treated to reach the recommended LDL goals.

Straka RJ, Taheri R, Cooper SL, Tan AWH, Smith JC. Assessment of hypercholesterolemia

control in a managed care organization. *Pharmacotherapy* 2001;21:818–27.

This retrospective study assessed 124,971 members of a managed care organization for their degree of lipid control according to the NCEP ATP II guidelines. Of 6538 patients with a history of coronary disease, 2170 (33%) did not have a fasting lipid profile recorded. Of 4368 with a recorded lipid measurement, 2632 (60%) did not meet their goal LDL level of less than 100 mg/dl. Only 35% of patients with a history of CHD attained their LDL goal. The group without CHD but with two or more risk factors had 17,267 patients. Of these, 10,131 (59%) had no fasting lipid profile recorded. Of the 7136 patients with a recorded lipid measurement, 3276 (46%) did not achieve their LDL goal of less than 130 mg/dl. Therefore, only 46% of all patients who had a recorded lipid measurement, had no history of CHD, and had two or more risk factors achieved their LDL goals.

This study also assessed the ability to treat patients with diabetes to their LDL goal. Of 4995 patients with diabetes but no history of CHD, 2152 (43%) did not have a recorded fasting lipid profile. Of the 2843 remaining patients, only 588 (21%) achieved their LDL goal of less than 100 mg/dl. Possible reasons for failure to achieve LDL goal in all groups were inadequate use of pharmacologic agents (39%–80% of patients in each group were not receiving drug therapy) and lack of appropriate follow-up (as evidenced by large populations without a fasting lipid profile). Possible limitations of the study were inadequate capturing of patients' smoking history and family history of heart disease. Also, the large percentage of patients without a fasting lipid profile may have contributed to overestimation of the percentages of patients achieving goal.

Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* 2002;288:462–7.

This Canadian population-based cohort study assessed 2-year adherence to statin therapy in three groups: 22,379 patients with recent ACS, 36,106 with chronic CAD, and 85,020 receiving primary prevention. Within 6 months, approximately 25% of patients in all three groups had discontinued their statin therapy. At 2 years, adherence rates were 61.7% in the ACS group, 58.5% in the CAD group, and 46.8% in the primary prevention group. Factors associated

with increased adherence were comorbidities, such as hypertension and diabetes, and increased physician visits. Factors associated with decreased adherence were lower disease severity, male sex, increased number of prescriptions, and increased number of different physicians. Many patients in the lower risk groups may have discontinued their statin therapy because they could not perceive its benefit. Patients should be reminded to adhere to their statin therapy in order to receive the benefits seen in controlled trials.

Schectman G, Hiatt J. Drug therapy for hypercholesterolemia in patients with cardiovascular disease: factors limiting achievement of lipid goals. *Am J Med* 1996;100:197–204.

This retrospective cohort study assessed whether NCEP goals were being achieved in clinical settings. The study involved 244 patients with either CAD or peripheral vascular disease who were receiving treatment for hypercholesterolemia at a large Veterans Affairs medical center. Results showed that the lipid-lowering drug therapy reduced LDL levels 25%–42% from baseline in patients with mild-to-severe hypercholesterolemia. Also, approximately 72% of those with baseline LDL levels of 160 mg/dl or less achieved their LDL target goal of 130 mg/dl or less with the drug therapy. On the other hand, less than 50% of patients whose baseline LDL level was 160 mg/dl or greater achieved target goal. Multivariate analysis indicated that factors associated with achieving study target goals were baseline LDL and triglyceride levels, adherence, and combination therapy versus monotherapy. The benefit of this study is that it affirmed the use of NCEP guidelines for providing adequate treatment to patients with hypercholesterolemia who also have cardiovascular disease.

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 cholesterol goals. *Arch Intern Med* 2000;160:459–67.

Whether patients with dyslipidemia receiving lipid-lowering therapy achieve LDL goals has been a concern. Using NCEP guidelines as a gauge for therapeutic outcomes, the multicenter L-TAP assessed 4888 adults with dyslipidemia who had been receiving consistent lipid-lowering

therapy for at least 3 months. Of the 4888 patients, 23% were at low risk (fewer than two risk factors and no evidence of CHD), 47% were at high risk (two or more risk factors and no evidence of CHD), and 30% had CHD. Patients were assessed at study enrollment and end point. The overall success rate for achieving NCEP-specified LDL target levels was 38%; low-risk patients had the highest success rate (68%), and those with established CHD had the lowest rate (18%). Although drug therapy was significantly more effective than nondrug therapy in all risk groups, large proportions of patients treated with lipid-lowering drugs did not achieve their LDL target level. This suggests the need for a more aggressive approach to therapy in these patients.

Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a cardiac hospitalization atherosclerosis management program (CHAMP). *Am J Cardiol* 2001;87:819–22.

In patients with CAD, a secondary prevention medical therapy such as a cardiac hospitalization atherosclerosis management program (CHAMP) has been hypothesized to reduce mortality by starting treatment with several agents— aspirin, cholesterol-lowering agents, β -blockers, and ACE inhibitors—along with diet and exercise counseling, before hospital discharge. This study followed patients discharged after myocardial infarction 2 years before and 2 years after the CHAMP. Across the board, patients after the CHAMP had much better treatment rates and clinical outcomes, which persisted throughout successive follow-up visits. Outcomes after the CHAMP were a 24% increase in therapy with aspirin, 50% increase in β -blocker use, 52% increase in ACE inhibitor use, and 80% increase in statin use. In addition, achievement of an LDL level of 100 mg/dl or less increased by 52%. The significant improvements in clinical outcomes after the CHAMP further substantiate the need for secondary prevention medical therapy in patients after hospitalization for acute myocardial infarction.

Studies Assessing Combination Pharmacotherapy

Statin and Fibrate

Garg A, Grundy SM. Gemfibrozil alone and in combination with lovastatin for treatment of

hypertriglyceridemia in NIDDM. *Diabetes* 1989;38:364–72.

This randomized, double-blind, placebo-controlled study assessed the effectiveness of lipid-lowering drugs in patients with non-insulin-dependent diabetes mellitus and hypertriglyceridemia despite good glycemic control. The study included six patients with moderate hypertriglyceridemia (plasma triglyceride level 250–500 mg/dl) and 10 with marked hypertriglyceridemia (triglyceride level above 500 mg/dl). In phase I of the study, patients were given gemfibrozil 600 mg twice/day or placebo for 28 days; these two treatments were then crossed over for the next 28-day period. In phase II, patients were given either gemfibrozil 600 mg twice/day plus lovastatin 20 mg/day or matched placebo for 28 days; these treatments were crossed over for the last 28-day period. In patients with marked hypertriglyceridemia, gemfibrozil alone compared with placebo significantly reduced triglyceride and VLDL levels and increased LDL and HDL levels. In phase II, the combination of gemfibrozil and lovastatin further reduced total cholesterol, LDL, triglyceride, and VLDL levels compared with gemfibrozil alone, but did not change HDL levels. Patients with marked versus moderate hypertriglyceridemia also experienced significant reductions in triglyceride and VLDL levels with gemfibrozil monotherapy, but to a lesser degree. Increases in LDL were not statistically significant, and HDL levels did not change. In phase 2, combination therapy produced significant reductions in total cholesterol, LDL, triglyceride, and VLDL levels compared with gemfibrozil monotherapy, but the extent of these reductions were similar to those seen in patients with marked hypertriglyceridemia. Again, HDL levels remained unchanged.

Overall, this study showed that gemfibrozil alone did not produce benefits in overall lipoprotein profiles but effectively decreased triglyceride and VLDL levels. Addition of lovastatin to gemfibrozil further reduced atherogenic apolipoprotein B-containing lipoproteins, especially in the marked hypertriglyceridemia group, but did not result in additional increases in HDL. Therefore, the authors concluded that combination therapy can be a reasonable therapeutic choice for patients with marked triglyceride levels.

Kayikcioglu M, Ozerkan F, Soydan I. Effectiveness and safety of alternate-day

simvastatin and fenofibrate on mixed hyperlipidemia. *Am J Cardiol* 1999;83:1135–7.

To minimize the adverse effects often associated with combination therapy with a statin and fibric acid, the authors evaluated the safety and efficacy of simvastatin and fenofibrate administered on alternate days. The study enrolled 74 patients with mixed hyperlipidemia who were receiving monotherapy but were not meeting their lipid goals according to NCEP guidelines. Patients were randomized to receive either simvastatin 10 mg and fenofibrate 250 mg every other day or simvastatin 10 mg and fenofibrate 250 mg every day with dinner. After 6 weeks of follow-up, plasma total cholesterol, LDL, triglyceride, and apolipoprotein B levels decreased from baseline by 31%, 34%, 55%, and 20%, respectively, in the alternate-day group; HDL and apolipoprotein A-I levels increased by 18% and 12%, respectively. In the every-day group, decreases in total cholesterol, LDL, triglyceride, and apolipoprotein B levels were 31%, 36%, 54%, and 18%, respectively; HDL and apolipoprotein A-I levels increased by 18% and 12%, respectively. In addition, fewer adverse events occurred in the alternate-day group. No patients had increased liver enzyme or creatine kinase levels, whereas four patients in the every-day group had increased creatine kinase levels and five had increased alanine aminotransferase levels. This study—the first to investigate the effects of alternate-day administration of lipid-lowering agents—found equal efficacy and improved safety of this administration schedule compared with every-day administration.

Farnier M, Dejager S. Effect of combined fluvastatin-fenofibrate therapy compared with fenofibrate monotherapy in severe primary hypercholesterolemia: French fluvastatin study group. *Am J Cardiol* 2000;85:53–7.

This 16-week, double-blind study assessed the safety and efficacy of combination therapy with fluvastatin and fenofibrate compared with fenofibrate monotherapy in 102 patients with severe primary hypercholesterolemia. Patients were randomized to receive micronized fenofibrate 200 mg plus placebo once/day, micronized fenofibrate 200 mg plus fluvastatin 20 mg once/day, or micronized fenofibrate 200 mg plus fluvastatin 40 mg once/day. Of the 102 patients, 96 finished the study. At week 16, the mean decrease in LDL level was 21% with fenofibrate alone, 32% with fenofibrate plus

fluvastatin 20 mg, and 41% with fenofibrate plus fluvastatin 40 mg ($p < 0.001$). Triglyceride levels decreased by 29% with fenofibrate alone, by 39% with fenofibrate plus fluvastatin 20 mg, and by 40% with fenofibrate plus fluvastatin 40 mg ($p < 0.05$). The HDL levels were moderately increased in all treatment groups, but increases were largest in patients receiving fenofibrate plus fluvastatin 20 mg due to hyperresponders in that group. In all lipid parameters except apolipoprotein A-I, the combination therapy groups had significantly better responses than those receiving fenofibrate alone.

In terms of safety, the frequency of adverse events was similar among the three treatment groups. One patient receiving fenofibrate plus fluvastatin 40 mg was withdrawn from the study due to elevated liver enzyme levels, but this patient had similar reactions to other statins and fenofibrate alone. No patients were withdrawn from the study due to elevated creatine kinase levels. This study addressed the fear that combination therapy poses excessive risk of adverse events. Results demonstrated that addition of fluvastatin to fenofibrate produced marked improvement in LDL, total cholesterol, apolipoprotein B, and triglyceride levels in a dose-dependent manner without increasing myopathy rates.

Glueck CJ, Oakes N, Speirs J, Tracy T, Lang J. Gemfibrozil-lovastatin therapy for primary hyperlipoproteinemias. *Am J Cardiol* 1992;70:1-9.

This retrospective, observational study assessed the safety and efficacy of long-term combination therapy with gemfibrozil 1.2 g/day and lovastatin 20-40 mg/day in 80 patients with primary mixed hyperlipidemia who did not reach their lipid goals while receiving monotherapy. Patients included in the study had been receiving combination therapy for at least 6 months. With the combination therapy, no significant changes occurred in glucose, blood urea nitrogen, creatinine, liver function, or creatine kinase levels between baseline and the final visit ($p < 0.01$). The frequency of liver function test levels that were 3 times the upper normal limit or greater was 0.02%; the frequency of creatine kinase levels that were 3 times the upper normal limit or greater was 0.1%. After a mean of 21 months of combination therapy, decreases were noted in total cholesterol (22%), LDL (26%), triglycerides (35%), and total cholesterol:HDL

ratio (24%). Combination therapy was discontinued in 3% of study patients due to muscle symptoms or high creatine kinase concentration, or both. No rhabdomyolysis, myoglobinuria, or renal failure was reported. Overall, this study supports other similar trials demonstrating that gemfibrozil in combination with lovastatin effectively modified lipid profiles with infrequent adverse events and no cases of rhabdomyolysis.

Eliav O, Schurr D, Pfister P, Friedlander Y, Leitersdorf E. High-dose fluvastatin and bezafibrate combination treatment for heterozygous familial hypercholesterolemia. *Am J Cardiol* 1995;76(2):76A-9.

This 88-week, open-label study evaluated the combination of bezafibrate and high-dose fluvastatin in patients with severe heterozygous familial hypercholesterolemia who did not reach their target LDL level with combination therapy in a previous study. Patients received fluvastatin 40 mg twice/day for 6 weeks; bezafibrate 200 mg/day, was then added for 6 weeks in patients who did not reach their LDL goal. Dosages were then titrated to fluvastatin 80 mg/day and slow-release bezafibrate 400 mg/day for 66 weeks. Interim results up to week 36 are presented in this article. Mean LDL levels were reduced from 300 to 205 mg/dl (32%) with fluvastatin monotherapy; the addition of bezafibrate 200 mg further reduced LDL levels to 193 mg/dl. Increasing bezafibrate to 400 mg for 24 weeks reduced the mean LDL level to 184 mg/dl. From week 0 to week 36, mean total cholesterol level was reduced from 365 to 245 mg/dl, triglyceride level from 136 to 94 mg/dl. In addition, mean HDL level increased from 38 to 42 mg/dl. To this point, no significant elevations were seen in liver function enzyme or creatine kinase levels. Overall, the interim results of this study demonstrate that fluvastatin can be safely and effectively added to bezafibrate to produce favorable results in LDL, total cholesterol, triglyceride, and HDL levels.

Spence JD, Munoz CE, Hendricks L, Latchinian L, Khouri HE. Pharmacokinetics of the combination of fluvastatin and gemfibrozil. *Am J Cardiol* 1995;76:80A-3.

This open-label, crossover, single-center study involving 6 weeks of active treatment after a 4-week washout period was conducted to determine whether any pharmacokinetic

interaction occurred between fluvastatin and gemfibrozil. Seventeen patients were randomized to receive fluvastatin 20 mg/day or gemfibrozil 600 mg twice/day for 2 weeks, followed by both drugs in combination for 2 weeks. Then, for another 2 weeks, patients received monotherapy with the agent they did not receive in the first 2-week phase. Of the 17 study patients, 16 completed the study. No significant changes were noted in any of the safety laboratory test results for any treatment. No significant differences occurred in area under the curve, maximum plasma concentration, or time to maximum concentration when the two drugs were taken together versus alone. Therefore, the study results suggest that no clinically significant pharmacokinetic interaction would be expected when patients take these two drugs together.

Leitersdorf E, Muratti EN, Eliav O, Peters TK. Efficacy and safety of triple therapy (fluvastatin-bezafibrate-cholestyramine) for severe familial hypercholesterolemia. *Am J Cardiol* 1995;76:84A-8.

This 60-week, open-label, extension study evaluated the safety and efficacy of combination therapy with three lipid-lowering drugs administered to patients with severe heterozygous familial hypercholesterolemia who completed three previous studies. The patients initially received fluvastatin monotherapy, then double therapy with fluvastatin and bezafibrate, and finally triple therapy with fluvastatin, bezafibrate, and cholestyramine. At the end of the study, 13 patients were still receiving the triple therapy. Adding bezafibrate to fluvastatin reduced total cholesterol levels by 8.2% ($p < 0.002$), LDL levels by 9% ($p < 0.001$), and triglyceride levels by 26.4% ($p < 0.001$), and increased HDL levels by 13.3% ($p < 0.01$). Adding cholestyramine reduced LDL by another 5.2%, for a total reduction of 35.4% with triple therapy from drug-free baseline level. No notable abnormalities were seen in liver function enzyme or creatine kinase levels. This study showed that triple therapy with fluvastatin, bezafibrate, and cholestyramine reduced lipid levels to a greater extent than single or double therapy (which patients with severe familial hypercholesterolemia require) without increasing the risk of adverse events.

Smit JW, Jansen GH, de Bruin TW, Erkelens DW. Treatment of combined hyperlipidemia with fluvastatin and gemfibrozil, alone or in

combination, does not induce muscle damage. *Am J Cardiol* 1995;76:126A-8.

This prospective, double-blind, placebo-controlled study assessed the effects of fluvastatin and gemfibrozil on muscle in patients with combined hyperlipidemia. Of 21 study patients, seven each were randomized to receive fluvastatin 40 mg/day, gemfibrozil 600 mg twice/day, or both for 6 weeks. Before and after the 6-week treatment period, patients underwent an exercise muscle-provocation test. Serum creatine kinase and myoglobin levels were determined before exercise testing and 1 and 8 hours after testing. In all groups, preexercise creatine kinase and myoglobin levels were not affected by any of the three treatments. At 48 hours after exercise testing, a muscle needle biopsy obtained from the quadriceps muscle was classified as normal, abnormal, or indeterminate. Abnormal muscle histology was seen in two patients before therapy, whereas one patient in each monotherapy group had abnormal histology after treatment. Study results suggested that fluvastatin and gemfibrozil as monotherapy or combination therapy did not induce muscle damage in these patients. This study was unique in that it evaluated the possibility of muscle damage and myopathy based on muscle biopsies and histologic data.

Ellen RL, McPherson R. Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. *Am J Cardiol* 1998;81:60B-5.

This study evaluated the long-term safety and efficacy of fenofibrate in combination with low-dose simvastatin or pravastatin in 80 patients with combined hyperlipidemia and high risk for CAD. Patients had normal hepatic and renal function and no other significant disease or laboratory abnormality that would compromise their safety. Baseline laboratory tests were conducted while patients were receiving monotherapy—39 with a statin and 41 with fenofibrate. After the second agent was added, 63 patients received pravastatin 20 mg/day plus regular fenofibrate 300 mg/day or micronized fenofibrate 200 mg/day; 17 received simvastatin 10 mg/day plus fenofibrate 200 mg/day. After a mean of 2 years of combination therapy, triglyceride levels decreased by 41% from baseline ($p < 0.001$), LDL levels decreased by 28% ($p < 0.001$), and HDL levels increased by 22% ($p < 0.001$). None of the patients experienced

clinically significant increases in liver function enzyme or creatine kinase levels during this study, and none reported muscle symptoms or malaise. Overall, the study showed that combination therapy with low-dose statin and fibrate resulted in greater improvements in lipid profiles than monotherapy with either agent. Also, the combination therapy was safe in patients with good general health and normal renal function. Despite the fears of myopathy with combination therapy, this study adds support that statins and fibrates can be administered together with favorable results and should remain a consideration for certain high-risk patients.

Leitersdorf E, Muratti EN, Eliav O, Peters TK. Efficacy and safety of a combination fluvastatin-bezafibrate treatment for familial hypercholesterolemia: comparative analysis with a fluvastatin-cholestyramine combination. *Am J Med* 1994;96:401-7.

This short-term, double-blind, randomized, parallel-group study compared the efficacy and safety of the combination of fluvastatin 20 or 40 mg/day plus bezafibrate 400 mg/day with the combination of fluvastatin 40 mg/day plus cholestyramine 8 g/day in 38 patients with familial hypercholesterolemia. After 12 weeks of monotherapy with fluvastatin 40 mg/day, bezafibrate was added to fluvastatin 20 mg/day and cholestyramine was added to fluvastatin 40 mg/day for 6 weeks. Cholestyramine decreased LDL level by 12.9%, whereas bezafibrate decreased LDL by 7.5% ($p=NS$). Triglyceride levels increased by 24.1% with cholestyramine but decreased by 14.5% with bezafibrate ($p<0.01$). The HDL level increased in both groups, but to a larger extent with bezafibrate (20.2% vs 7.5% with cholestyramine, $p<0.01$). After another period of fluvastatin monotherapy, bezafibrate and cholestyramine were again added to fluvastatin, but the dosage of fluvastatin was 40 mg/day in both groups. This time, bezafibrate and cholestyramine reduced LDL levels by 12.6% and 13.8%, respectively ($p=NS$). Again, triglyceride levels increased by 26% with cholestyramine and decreased by 26.4% with bezafibrate ($p<0.001$); HDL increases were similar in the two groups. No notable abnormalities in liver enzyme or creatine kinase levels were seen in the two groups. Overall, combination therapy was safe, effective, and well tolerated. The bezafibrate-fluvastatin combination

produced a larger reduction in LDL levels with fluvastatin 40 mg/day compared with fluvastatin 20 mg/day. The study showed that the combination of bezafibrate and fluvastatin is superior to the combination of cholestyramine and fluvastatin in reducing triglyceride and increasing HDL levels.

Wiklund O, Angelin B, Bergman M, et al. Pravastatin and gemfibrozil alone and in combination for the treatment of hypercholesterolemia. *Am J Med* 1993;94:13-20.

This study was the first to evaluate the safety and efficacy of a combination of pravastatin and gemfibrozil in patients with primary hypercholesterolemia. The study enrolled 290 patients who were randomized to receive 12 weeks of pravastatin 40 mg/day, gemfibrozil 600 mg twice/day, a combination of both drugs, or placebo. Combination therapy reduced total cholesterol levels by 29%, LDL by 37%, VLDL by 50%, triglycerides by 42%, and apolipoprotein B by 31%, and increased HDL by 17% and apolipoprotein A-I by 6% (all $p\leq 0.01$). The combination was more effective in altering these lipid parameters than either drug alone. The frequency of musculoskeletal pain and creatine kinase level elevation was slightly higher in the combination therapy group. Two patients from this group were removed from the study due to asymptomatic creatine kinase level elevation. However, no severe myopathy or rhabdomyolysis was reported in any of the study groups. Overall, the study showed that combination therapy could be safe and helpful in normalizing the lipid pattern in patients with mixed hyperlipidemia without risk of serious adverse events.

Illingsworth DR, Bacon S. Influence of lovastatin plus gemfibrozil on plasma lipids and lipoproteins in patients with heterozygous familial hypercholesterolemia. *Circulation* 1989;79:590-6.

This study examined the effects of lovastatin alone and in combination with gemfibrozil in 12 patients with heterozygous familial hypercholesterolemia. Patients first received lovastatin 40 mg twice/day for 10 weeks, then gemfibrozil 600 mg twice/day was added for another 12 weeks. Mean total cholesterol level decreased from 395 mg/dl at baseline to 274 mg/dl with lovastatin monotherapy ($p<0.001$) and then to 259 mg/dl with combination therapy ($p=NS$). The LDL response was similar, with mean levels decreasing from 321 mg/dl at baseline to 207 mg/dl with

lovastatin ($p < 0.01$) and then to 194 mg/dl with combination therapy ($p = \text{NS}$). However, LDL levels increased in three patients when gemfibrozil was added. The HDL levels increased with each addition, but differences were not statistically significant. Triglyceride levels decreased from 145 to 105 mg/dl with lovastatin and then to 80 mg/dl ($p < 0.05$) with combination therapy. One patient experienced muscle pain and increased creatine kinase concentration during combination therapy, necessitating discontinuation of both drugs. This patient was later treated with lovastatin and colestipol without recurrence of symptoms. None of the other patients experienced significant increases in creatine kinase or transaminase levels. Similar to other studies, this trial demonstrated that the addition of gemfibrozil to a statin resulted in small and variable effects on total cholesterol, and especially on LDL level. In patients with heterozygous familial hypercholesterolemia with very high levels of total cholesterol and LDL, this small benefit may not outweigh the increased risk of myopathy with combination therapy. Therefore, the authors did not support treatment with the combination in this patient population.

Murdock DK, Murdock AK, Murdock RW, et al. Long-term safety and efficacy of combination gemfibrozil and HMG-CoA reductase inhibitors for the treatment of mixed lipid disorders. *Am Heart J* 1999;138:151–5.

This study evaluated the safety and efficacy of long-term combination therapy with gemfibrozil and any statin in patients with CAD, peripheral vascular disease, or carotid arterial disease and mixed dyslipidemia not controlled with a single agent. A total of 252 patients from a lipid clinic were prospectively tracked for a mean of 2.4 years. Treatment with gemfibrozil was started in 148 patients who had markedly elevated triglyceride levels (> 400 mg/dl) or depressed HDL levels (< 30 mg/dl). In these patients, gemfibrozil alone had little effect on total cholesterol, but combination therapy decreased baseline total cholesterol from 222 to 181 mg/dl ($p < 0.001$), increased HDL from 30 to 36 mg/dl ($p < 0.01$), and decreased triglyceride levels from 361 to 212 mg/dl ($p < 0.03$). Statin therapy was started first in 104 patients due to markedly elevated baseline total cholesterol levels (> 300 mg/dl). In these patients, the changes in HDL and triglyceride levels from statin alone were not significant. However, combination therapy reduced baseline total cholesterol from 246 to

192 mg/dl ($p < 0.01$), increased HDL from 33 to 38 mg/dl ($p < 0.03$), and decreased triglycerides from 314 to 183 mg/dl ($p < 0.001$). Of 68 patients whose combination therapy was terminated, six experienced myalgia, one had an asymptomatic 5-fold rise in alanine aminotransferase, and one had myalgia and a creatine kinase level 12 times the upper limit of normal. Overall, the combination of a statin and gemfibrozil improved lipid profiles to a greater extent than either agent alone in patients with mixed lipid disorders. In this study, the benefit of combination therapy in the high-risk population outweighed the low risk of toxicity. Unfortunately, the study was not powered to distinguish differences in adverse-event rates between different statins, which would have been useful information.

East C, Bilheimer DW, Grundy SM. Combination drug therapy for familial combined hyperlipidemia. *Ann Intern Med* 1988;109:25–32.

This prospective trial compared the efficacy of gemfibrozil and colestipol with gemfibrozil and lovastatin in patients with familial combined hyperlipidemia with types 2b and 4 hyperlipoproteinemia. Patients with type 2b hyperlipoproteinemia are characterized by elevated VLDL, LDL, triglyceride, and cholesterol levels, whereas those with type 4 have elevated VLDL and triglyceride levels. In the first of two study phases, patients received 8 weeks of dietary therapy and then 8 weeks of gemfibrozil 600 mg twice/day. In the second phase, gemfibrozil was continued, but patients also were randomized to receive either colestipol 10 g twice/day or lovastatin 20 mg twice/day for 8 weeks and then crossed over to receive the other drug for another 8 weeks. The first 4 weeks of each period were considered washout, and samples were taken during the second 4 weeks.

Nine patients with type 2b were analyzed separately from eight with type 4 hyperlipoproteinemia. Although gemfibrozil reduced triglyceride and VLDL levels in type 4 patients, it failed to lower total cholesterol or apolipoprotein B levels and even increased LDL. However, the combination of lovastatin and gemfibrozil in both groups produced greater reductions in LDL and apolipoprotein B levels and significantly increased HDL compared with gemfibrozil and colestipol, as well as gemfibrozil alone. The addition of colestipol to gemfibrozil appeared to partially reverse the action of gemfibrozil alone in lowering triglycerides and VLDL and in raising HDL levels. Clinical side effects during drug

therapy were relatively minor, and no abnormalities in blood chemistry profiles were reported. Overall, the study suggested that gemfibrozil alone may not be adequate therapy for lowering LDL and apolipoprotein B levels in patients with type 2b and 4 hyperlipoproteinemia. In this short-term study, the addition of lovastatin to gemfibrozil generally provided more favorable outcomes than the addition of colestipol, without incidence of myalgia, myopathy, or rhabdomyolysis.

Statin and Niacin

Arntz HR, Agrawal R, Wunderlich W, et al. Beneficial effects of pravastatin (\pm cholestyramine/niacin) initiated immediately after a coronary event (the randomized lipid-coronary artery disease [L-CAD] study). *Am J Cardiol* 2000;86:1293–8.

This study compared cholesterol-lowering therapy begun immediately after myocardial infarction or balloon angioplasty with usual outpatient treatment on the course of coronary atherosclerosis and clinical outcomes. Patients aged 75 years or younger who had experienced either acute myocardial infarction or emergency balloon angioplasty and whose baseline LDL level was 130–300 mg/dl were randomized to receive intensive hypolipidemic therapy (group A) or usual care (group B). Intensive therapy included pravastatin alone or in combination with either niacin or cholestyramine to achieve an LDL goal level of less than 130 mg/dl. Pravastatin was started a mean \pm SD of 6 ± 5 days after the qualifying event. Analysis was performed by quantitative angiography at baseline, 6 months, and 24 months. However, a complete series of evaluable angiographs was available for fewer than half of the randomized patients in each group. Mean baseline LDL level was 176 mg/dl in group A (70 patients) and 172 mg/dl in group B (56 patients).

An LDL level less than 130 mg/dl was achieved in 40 patients with pravastatin alone and in eight with combination therapy; the remaining group A patients did not reach goal and could not tolerate niacin or cholestyramine. No group B patients maintained LDL at goal level, and only 13 received any lipid treatment. Mean LDL reduction in group A was 28%, and the mean LDL level at 6 months was 122 mg/dl. A clinically significant increase in lumen diameter was measured in 23 of 77 stenoses in group A compared with 7 of 72 stenoses in group B.

Group B also had a statistically significantly higher rate of diameter decreases over the 24-month study period. No significant effect on angioplasty restenoses was noted. Clinical event rates were also significantly lower in group A. Although this study was designed to evaluate combination therapy, most patients who required the addition of niacin or cholestyramine were unable to tolerate it and thus were receiving pravastatin monotherapy and did not achieve LDL goal. Additional limitations of the study were its small sample size and high dropout rate. However, despite less than optimal LDL reduction, progression of coronary atherosclerosis appeared to be slowed and clinical outcomes improved.

O'Keefe JH Jr, Harris WS, Nelson J, et al. Effects of pravastatin with niacin or magnesium on lipid levels and postprandial lipemia. *Am J Cardiol* 1995;76:480–4.

This 18-week, parallel-design study compared the effects of pravastatin 20 mg/day plus either niacin 1 g 3 times/day, magnesium 800 mg 3 times/day, or placebo once/day on lipid lowering in patients with low HDL levels and hypertriglyceridemia. Magnesium supplementation had previously been reported to improve HDL, triglycerides, insulin resistance, and blood pressure. The study enrolled 65 patients, and although placebo control was attempted, the niacin-treated patients usually developed adverse effects (e.g., flushing and pruritis) and thus disclosed. Major study end points were LDL3 (the more atherogenic, small, dense LDL), HDL, and triglyceride levels; exaggerated postprandial lipemia; and total cholesterol:HDL ratios. Randomization allowed for the 22% dropout rate seen in the pravastatin-niacin group; therefore, 21 patients in the pravastatin-niacin group and 18 in each of the other two treatment groups completed the study.

The LDL level decreased 25% in the pravastatin-niacin group compared with 13% in the pravastatin-magnesium group and 14% in the pravastatin-placebo group; these percentages are less than would usually be expected with pravastatin 20 mg alone. The LDL3 level decreased by 43% in the pravastatin-niacin group, which was significantly greater than the change seen in the other groups. The HDL level was significantly increased (29%) and triglyceride levels were decreased (42%) in the pravastatin-niacin group. The only significant change in the other groups was a 15% reduction in triglyceride

levels in the pravastatin-placebo group. The only significant change in characteristics of postprandial lipemia was a decrease in triglyceride content of remnant lipoprotein particles in the pravastatin-niacin group. In this small study, niacin in combination with pravastatin was superior to magnesium or placebo in improving non-LDL lipid risk factors.

Jacobson TA, Chin MM, Fromell GJ, Jokubaitis LA, Amorosa LF. Fluvastatin with and without niacin for hypercholesterolemia. *Am J Cardiol* 1994;74:149–54.

This double-blind study investigated the addition of immediate-release niacin titrated to a maximum of 3 g/day with fluvastatin 20 mg or placebo. Seventy-four patients with LDL levels of 160 mg/dl or greater were randomized to receive fluvastatin 20 mg/day or placebo for 6 weeks. Immediate-release niacin was then added to both treatment regimens for an additional 9 weeks. The LDL levels decreased by 21% with fluvastatin monotherapy ($p < 0.001$ vs placebo), and by 40% after the addition of niacin, compared with 25% for the niacin control group ($p < 0.001$). Lipoprotein(a) decreased by 37% in patients receiving fluvastatin-niacin but was unaltered in those receiving fluvastatin alone. No clinically significant adverse events were seen with monotherapy or combination therapy. This study was limited by its small sample size and short duration, but it demonstrated the effectiveness of this combination on the lipoprotein profile.

Davignon J, Roederer G, Montigny M, et al. Comparative efficacy and safety of pravastatin, nicotinic acid and the two combined in patients with hypercholesterolemia. *Am J Cardiol* 1994;73:339–45.

This placebo-controlled, randomized trial compared pravastatin 40 mg twice/day, extended-release niacin 1000 mg twice/day, and the combination of both agents in patients with type IIa or IIb hyperlipidemia. The study consisted of a short-term phase of 8 weeks (158 patients) and a long-term phase (143 patients) of up to 88 weeks. The primary efficacy criterion was absolute reduction in LDL compared with baseline level. Mean baseline LDL level ranged from 227.1–234.8 mg/dl in all groups. Reduction in LDL level at 8 weeks was greatest with the combination therapy (41.5%) versus pravastatin alone (32.72%) and niacin alone (16.11%). Increases in HDL were statistically significantly

different from baseline and placebo in all groups. Triglyceride level reduction was best in the combination group (34.85%). Of interest, reductions in the niacin-alone group (11.43%) were less than expected given the known characteristics of the drug. Similar results were seen during the long-term phase. Clinical adverse events were more common in the niacin and combination groups, where flushing and gastrointestinal complaints predominated. Statistically but not clinically significant increases in hepatic enzyme and creatine kinase levels were more frequent in the niacin-containing regimens; combination therapy was discontinued in one patient during the long-term phase due to chemical hepatitis. Although of interest in characterizing the effects on lipoproteins of this drug combination in comparison with monotherapy with each component, this study was limited by its small sample size and the inclusion of a niacin preparation that is in limited use today.

Heudebert GR, Van Ruiswyk J, Hiatt J, Schectman G. Combination drug therapy for hypercholesterolemia: the trade-off between cost and simplicity. *Arch Intern Med* 1993;153:1828–37.

This article was published before the results of clinical outcome trials with the statins and was guided by NCEP ATP II recommendations for administration of niacin and/or sequestrants as first-line therapy to achieve the target LDL level of less than 130 mg/dl. The authors compared this recommendation with administration of lovastatin as initial therapy if multidrug regimens were required to achieve goal LDL level. Prospective data regarding tolerance and effectiveness of niacin, sequestrants, and lovastatin were collected, and a decision tree was used to compare the complexity and cost of three sequential drug algorithms used for initial LDL levels of 160, 190, 220, and 250 mg/dl. Actual drug and laboratory costs were used. Sensitivity analyses were performed on the tolerance and effectiveness of each drug as well as drug and laboratory cost estimates. The authors were not surprised to find that the algorithm using lovastatin first achieved goal more often and with fewer concurrent drugs; in addition, it was relatively less expensive as the initial LDL level increased. Although the direct clinical applicability of this information is now limited by the acceptance of statins as the standard for

initial therapy in most patients, this article may be useful for practitioners attempting to develop algorithms for combination drug therapies.

Bays HE, Dujovne CA, McGovern ME, et al. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADVICOR Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol* 2003;91:667–72.

This 16-week, randomized, open-label, dose-comparison study compared the lipid-altering effects of extended-release niacin 1000–2000 mg once/day plus lovastatin 40 mg/day with standard doses of simvastatin 10–40 mg/day and atorvastatin 10–40 mg/day. Special emphasis was placed on comparison of starting doses of all agents. Inclusion criteria were an LDL level 160 mg/dl or greater in patients with CAD, triglyceride levels less than 300 mg/dl, and HDL levels less than 45 mg/dl in men and less than 50 mg/dl in women. Patients with a fasting blood glucose level above 115 mg/dl and those with diabetes were excluded. Mean age of the 315 study patients was 53 years, and most were overweight Caucasian men. Mean baseline LDL level was 191 mg/dl, triglycerides 170 mg/dl, HDL 38 mg/dl, and lipoprotein(a) 21 mg/dl. Patients were randomized to one of four treatment groups, and treatment was titrated over 12 weeks to the maximum dose tolerated. Patients who did not tolerate titration were withdrawn from the study; no dosage reductions were allowed.

Extended-release niacin 1000 mg–lovastatin 40 mg lowered LDL level as effectively (38%) as atorvastatin 10 mg (38%) and simvastatin 20 mg (35%), and increased HDL level and lowered triglycerides and lipoprotein(a) levels significantly more. Extended-release niacin 2000 mg–lovastatin 40 mg lowered LDL 42%, increased HDL 32%, and lowered lipoprotein(a) 21% compared with 49%, 6%, and 0% with atorvastatin 40 mg and 39%, 7% and 2% with simvastatin 40 mg, respectively. Dizziness and flushing occurred more frequently in the extended-release niacin–lovastatin groups and accounted for more dropouts from the study. Otherwise, the frequency of adverse effects was low and was similar among treatment groups. This study demonstrated that a combination extended-release niacin–lovastatin product can produce LDL reductions similar to those achieved with low doses of atorvastatin and low-

to-moderate doses of simvastatin, with superior improvement in other lipid risk factors.

Kashyap ML, McGovern ME, Berra K, et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. *Am J Cardiol* 2002;89:672–8.

This study evaluated the long-term safety of once-daily extended-release niacin–lovastatin by meeting regulatory guidelines for minimum exposure to lipid-modifying agents (at least 600 patients had been exposed for 6 months, 200 for 12 months). Eligible patients were aged 21 years or older and had type IIa or IIb hyperlipidemia; the NCEP ATP II target LDL guidelines were used for the enrollment criteria. Mean age of the study patients was 59 years (range 25–84 yrs), and most were Caucasian men; 37% had CAD and 11% reported a history of diabetes. Extended-release niacin 500 mg–lovastatin 10 mg was started for 1 month and was then increased monthly by niacin 500–lovastatin 10 mg up to niacin 2000–lovastatin 40 mg, which was maintained through week 52 if tolerated. Of the 814 patients who received study drug, 604 were evaluable at 28 weeks and 226 at 52 weeks, meeting the study goals for minimum drug exposure.

Over 52 weeks, changes in lipoprotein profiles were dose related, with LDL level reduction ranging from 25–45%, HDL level increase 11–41%, triglyceride level reduction 16–42%, and lipoprotein(a) level reduction 2–25%. The predominant adverse effect was flushing, which caused 105 patients to withdraw. Dyspepsia was reported in 6–8% of patients; headache (7%), dizziness (5%), and hyperglycemia (5%) also occurred. One 58-year-old, obese man with hypertension and CAD developed diabetes. Three patients were withdrawn from the study after experiencing serious gastrointestinal disorders that were considered at least possibly drug related. Creatine kinase level elevations of more than 10 times the upper limit of normal occurred in two patients, both of whom experienced exercise-related injuries; one withdrew from the study. Overall, extended-release niacin–lovastatin was well tolerated over 52 weeks in this controlled study of relatively healthy patients.

Statin and Resin

Denke MA, Grundy SM. Efficacy of low-dose cholesterol-lowering drug therapy in men with

moderate hypercholesterolemia. *Arch Intern Med* 1995;155:393–9.

This study investigated the efficacy of a low-dose combination of a resin (cholestyramine) with a statin (lovastatin) in reducing LDL concentration. Three drug regimens were tested in 26 men with moderate hypercholesterolemia: cholestyramine 8 g/day, cholestyramine 8 g/day plus lovastatin 5 mg/day, and lovastatin 20 mg/day. Cholestyramine 8 mg/day reduced LDL level from 173 to 151 mg/dl ($p < 0.005$); the cholestyramine-lovastatin combination further reduced LDL level to 131 mg/dl ($p < 0.005$), similar to results with lovastatin 20 mg. This study is significant because it demonstrated that a low-dose resin-statin combination resulted in a significant reduction in LDL level, similar to results with a higher statin dose. Thus, a low-dose resin-statin combination is a viable option for management of elevated LDL concentrations.

Ito MK, Shabetai R. Pravastatin alone and in combination with low-dose cholestyramine in patients with primary hypercholesterolemia and coronary artery disease. *Am J Cardiol* 1997;80:799–802.

Another important study demonstrated the efficacy of low-dose combination therapy with a resin and a statin in addition to demonstrating the cost-effectiveness of combination therapy. This randomized, open-label, parallel-design study evaluated 59 patients who received pravastatin 10 mg/day in combination with cholestyramine 5 g/day or pravastatin 20 mg/day. If LDL concentration remained greater than 100 mg/dl after 6 weeks of this therapy, pravastatin was increased to 20 mg/day in the combination group and to 40 mg/day in the monotherapy group. The results demonstrated that the lower-dose combination treatment had similar effects on lipoproteins as low- and high-dose monotherapy. In addition, the higher-dose combination therapy had superior effects in reducing LDL level compared with pravastatin 20 mg ($p = 0.0006$) or 40 mg ($p = 0.033$). Cost-effectiveness of the combination therapy was similar to that of monotherapy with pravastatin 20 mg/day and superior to that of pravastatin 40 mg/day. Overall, this study is important because it demonstrated that not only is low-dose resin-statin combination therapy effective in treating hypercholesterolemia but it also may be a cost-effective alternative to higher-dose statin therapy.

Statin and Ezetimibe

Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;40:2125–34.

This randomized, single-blind study determined the efficacy and safety of treatment with both ezetimibe and simvastatin in patients with primary hypercholesterolemia. A total of 591 patients received one of 10 treatments: ezetimibe 10 mg/day; simvastatin 10, 20, 40, or 80 mg/day; ezetimibe 10 mg/day plus simvastatin 10, 20, 40, or 80 mg/day; or placebo. The combination of ezetimibe and simvastatin resulted in significantly greater reductions in LDL level and significantly greater increases in HDL levels compared with simvastatin alone. When pooled doses were evaluated, ezetimibe and simvastatin provided 13.8% and 7.5% greater reductions in LDL and triglyceride levels, respectively, and a 2.4% increase in HDL level compared with pooled doses of simvastatin alone. The authors also noted that ezetimibe 10 mg in combination with simvastatin 10 mg resulted in a 44% reduction in LDL level, similar to that seen with simvastatin 80 mg alone. An incremental increase also was noted in LDL level reduction when ezetimibe was added to simvastatin 80 mg compared with simvastatin 80 mg alone. All treatments had a similar safety profile. Addition of ezetimibe 10 mg to simvastatin provided an incremental benefit in LDL and triglyceride level reduction and in HDL level increase. Also, the combination was well tolerated compared with statin therapy alone.

This study demonstrated that with all doses of simvastatin, an incremental benefit on lipid profile may occur when ezetimibe 10 mg/day is added for treatment of primary hypercholesterolemia. In addition, low-dose simvastatin in combination with ezetimibe had effects similar to those of high-dose simvastatin therapy. This finding may have important clinical application, especially for patients who cannot tolerate high-dose statin therapy. One important issue not addressed by this study is the effect of the ezetimibe-simvastatin combination on the pleiotropic effects associated with statin therapy compared with statin therapy alone, especially across dose ranges.

Ballantyne CM, Hourii J, Notarbartolo A, et al. Effect of ezetimibe coadministered with

atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation* 2003;107:2409–15.

This study determined the efficacy and safety of treatment with both ezetimibe and atorvastatin in patients with primary hypercholesterolemia. A total of 628 patients were randomized to receive one of 10 treatments: ezetimibe 10 mg; atorvastatin 10, 20, 40, or 80 mg; ezetimibe 10 mg plus atorvastatin 10, 20, 40, or 80 mg; or placebo. The combination of ezetimibe and atorvastatin resulted in significantly greater reductions in LDL, triglyceride, and CRP levels, and significantly greater increases in HDL levels compared with atorvastatin alone. When pooled doses were evaluated, ezetimibe and atorvastatin provided 12%, 8%, and 10% greater reductions in LDL, triglyceride, and CRP levels, respectively, and a 3% increase in HDL level compared with pooled doses of atorvastatin alone. Ezetimibe alone had no effect on CRP level. The authors also noted that ezetimibe 10 mg in combination with atorvastatin 10 mg resulted in a 50% reduction in LDL level, similar to the 51% reduction seen with atorvastatin 80 mg alone. However, a greater reduction (43%) in CRP level was noted with atorvastatin 80 mg than with the combination of ezetimibe 10 mg and atorvastatin 10 mg/day (25%). An incremental increase also was noted in LDL and CRP level reduction when ezetimibe was added to atorvastatin 80 mg compared with atorvastatin 80 mg alone. All treatments had a similar safety profile. Addition of ezetimibe 10 mg to atorvastatin provided an incremental benefit in LDL and triglyceride level reduction and in HDL level increase. Similar results in lowering CRP level were also observed with atorvastatin doses greater than 10 mg. Also, the combination was well tolerated compared with statin therapy alone.

This study and its results were nearly identical to the preceding simvastatin study, except that CRP level was also measured. The nearly identical results from these studies suggest that with regard to effects on lipid levels, a class effect seems to occur with the statins when ezetimibe is added to the regimen. Also of note, the addition of ezetimibe further reduced CRP levels. The mechanisms for this effect on CRP level still need to be elucidated. This effect may be clinically important in targeting CRP level reduction. Also of note, however, is that using a low-dose statin-ezetimibe combination does not have the same effect on CRP level (and perhaps other

pleiotropic effects) as high-dose monotherapy with a statin. This finding may be a factor when selecting therapy for individual patients.

Gagne C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002;105:2469–75.

This randomized, double-blind study determined the efficacy and safety of treatment with both ezetimibe and either atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Fifty patients receiving open-label simvastatin 40 mg/day or atorvastatin 40 mg/day with or without concomitant LDL apheresis were randomized to receive one of the following treatments for 12 weeks: atorvastatin 80 mg/day or simvastatin 80 mg/day (17 patients), ezetimibe 10 mg/day plus atorvastatin 40 mg/day or simvastatin 40 mg/day (16 patients), or ezetimibe 10 mg/day plus atorvastatin 80 mg/day or simvastatin 80 mg/day (17 patients). Patients receiving ezetimibe and either 40 mg or 80 mg of a statin had significantly greater LDL level reductions than those receiving 80 mg of a statin without ezetimibe (20.7% vs 6.7%, $p=0.007$). This study demonstrated that in patients with homozygous familial hypercholesterolemia, addition of ezetimibe to statin therapy resulted in greater LDL level reductions than with statin therapy alone.

Ziajka PE, Reis M, Kreul S, King H. Initial low-density lipoprotein response to statin therapy predicts subsequent low-density lipoprotein response to the addition of ezetimibe. *Am J Cardiol* 2004;93:779–80.

The authors of this small (37 patients), retrospective study explored the notion that hyporesponders to statin therapy are hyperabsorbers. They speculated that ezetimibe added to statin therapy would result in an inverse correlation between the initial LDL response to statin therapy and the response with combination therapy. In other words, hyporesponders to statin therapy would be hyperresponders when ezetimibe was added. Linear regression analysis showed a significant correlation with a negative slope ($r=0.77$, $p<0.001$). In eight of the 37 patients, LDL level reduction was greater than 40% when ezetimibe was added. Overall, this interesting study has a number of major

limitations. However, the authors have presented enticing data to potentially explain exaggerated responses that may occur when ezetimibe is added to statin therapy.

Other Important Pharmacotherapy Studies

Niacin

McKenney JM, Proctor JD, Harris S, Chinchili VM. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; 271:672–7.

This randomized, double-blind, parallel-group trial compared immediate-release and sustained-release niacin in 46 patients with hypercholesterolemia across a dose range that started at 500 mg/day and was titrated every 6 weeks to a maximum of 3000 mg/day. The two treatment groups (immediate- and sustained-release niacin) were similar at baseline except for their HDL levels. Sustained-release niacin reduced LDL level significantly more than immediate-release niacin with daily doses above 1000 mg. This reduction, up to 50%, is greater than that seen in other studies using sustained-release niacin; the lack of success in other studies may be due to hepatotoxicity that developed in the study patients. Immediate-release niacin resulted in significantly higher HDL levels than sustained-release niacin at all doses except 1500 mg. No significant differences between dosage forms were noted with regard to triglyceride level reductions.

The most common adverse effect in the immediate-release niacin group was vasodilatory, such as flushing, prompting 39% of the patients in that group to withdraw from the study. The most common adverse effect with sustained-release niacin was hepatotoxicity, prompting 78% of the patients in that group to withdraw before achieving the target daily dose of 3000 mg. Most cases of hepatotoxicity occurred with daily doses of 2000 mg or greater. A significant increase was noted in liver enzyme levels with sustained-release niacin at doses above 1500 mg ($p < 0.05$). Also, sustained-release niacin was associated with significant increases in fasting glucose levels at daily doses above 1500 mg ($p = 0.009$). The increased toxicity of sustained-release niacin precludes its widespread use in the treatment of hypercholesterolemia.

Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-

release forms of niacin on lipoproteins in hyperlipidemic patients: clues to mechanism of action of niacin. *Metabolism* 1985;34:642–50.

This study compared immediate- and time-release niacin in 65 patients over a 6-month period to assess the differences in changes in lipid indexes, lipoprotein subclasses, and adverse events. Thirty-four patients in the immediate-release niacin group and 31 in the time-release niacin group received 500 mg 3 times/day (1500 mg/day) during the first month and then 1000 mg 3 times/day (3000 mg/day) during months 2–6. Dropout rates were similar among patients in both groups—25% for those receiving immediate-release and 18% for time-release niacin. Patients receiving immediate- versus time-release niacin had significantly decreased triglyceride levels (45.2 vs 15.2 mg/dl) and significantly increased HDL levels (12.9 vs 4.1 mg/dl) when results were averaged over months 2–6 ($p < 0.05$). Both compounds significantly increased HDL3, but only immediate-release niacin significantly increased HDL2 ($p < 0.05$). The time-release group had less flushing than the immediate-release group, but the difference was not significant. The time-release group had significantly increased gastrointestinal adverse reactions ($p < 0.05$), which limited achievement of the 3000-mg daily dose to a mean of 2000 mg. Thus, immediate-release niacin was effective in treating lipoprotein abnormalities and resulted in similar rates of flushing compared with time-release niacin in this study. Generally, sustained- and extended-release forms of niacin minimize the flushing adverse reactions.

Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial: arterial disease multiple intervention trial. *JAMA* 2000;284:1263–70.

The effects of immediate-release niacin on lipoproteins and glycemic control in 468 patients (125 with diabetes) were assessed over 48 weeks in the Arterial Disease Multiple Intervention Trial (ADMIT). Patients with hemoglobin A_{1c} (A1C) values above 9.0% were excluded from the trial. One group of patients (237 patients—64 with diabetes, 173 without) received immediate-release niacin in doses up to 3000 mg/day or a maximally tolerated dose. The other group (231 patients—61 with diabetes, 170 without) received placebo. No significant differences

between groups were noted at baseline, except that the placebo-treated patients with diabetes were older than the niacin-treated patients with diabetes ($p=0.04$). Niacin reduced total cholesterol, triglyceride, and LDL levels, and increased HDL levels in patients with and without diabetes compared with placebo ($p<0.001$ for all comparisons). The reductions were not significantly different between patients with and without diabetes. Niacin caused an increase in plasma glucose level in patients with diabetes (8.1 mg/dl, $p=0.04$) and without diabetes (6.3 mg/dl, $p\leq 0.001$). No change in A1C was observed in niacin patients with diabetes; however, A1C was decreased 0.3% in placebo patients with diabetes, resulting in a significant difference ($p=0.05$). No significant changes in A1C were noted in niacin- or placebo-treated patients without diabetes ($p=0.38$). The changes in glucose level were mild, which may be accounted for by the allowed titration in antidiabetic drugs (increased insulin [$p=0.09$] and oral hypoglycemics [$p=0.94$]). However, none of the changes reached statistical significance. Niacin also caused significant increases in uric acid levels in patients with and without diabetes ($p<0.001$), but did not significantly increase alanine aminotransferase levels ($p=0.09$). Thus, niacin at dosages of 3000 mg/day or lower in patients with controlled type 2 diabetes is effective and can be used safely with proper monitoring.

Grundy SM, Vega GL, McGovern ME, et al, for the Diabetes Multicenter Research Group. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of Niaspan trial. *Arch Intern Med* 2002;162:1568–76.

The efficacy and safety of extended-release niacin in 148 patients with diabetes over a 16-week period was assessed in this double-blind, placebo-controlled trial. All patients had a fasting blood glucose level of 200 mg/dl or less and an A1C value of 9% or less. Patients were divided into three treatment groups: placebo, extended-release niacin 1000 mg/day, and extended-release niacin 1500 mg/day. The significant differences in baseline characteristics of the group receiving extended-release niacin 1000 mg/day versus the other groups were higher weight, higher body mass index, and lower HDL levels. Compared with placebo, both niacin

groups had significantly increased HDL levels ($p<0.05$). Only extended-release niacin 1500 mg/day significantly reduced triglyceride and LDL levels compared with placebo ($p<0.05$). This may be explained by the higher weight and body mass index in patients receiving extended-release niacin 1000 mg/day. A trend was noted in favor of the 1500-mg niacin dose in reducing lipoprotein(a) and CRP levels and in increasing LDL particle size, but this did not reach significance. No significant changes were noted in fasting blood glucose level between the three groups, but the group receiving extended-release niacin 1500 mg/day had significantly increased A1C values compared with placebo ($p=0.048$). All groups were similar with regard to uric acid and liver enzyme levels, and episodes of flushing. Thus, extended-release niacin can be used safely and effectively in patients with diabetes.

Meyers CD, Carr MC, Park S, Brunzell JD. Varying cost and free nicotinic acid content in over-the-counter niacin preparations for dyslipidemia. *Ann Intern Med* 2003;139:996–1002.

This study assessed the differences between various over-the-counter preparations of niacin (immediate-release, sustained-release, and no-flush) in terms of cost and free nicotinic acid concentrations. Ten brands of immediate-release niacin, nine brands of sustained-release niacin, and 10 brands of no-flush niacin, all at 500 mg/tablet or capsule, were assessed. Assessment was based on high rates of sales deduced from national sales figures and high rates of recommendations from clinical lipidologists quantified through an e-mail survey. Cost analysis was determined by the following equation: monthly cost = ($\$/\text{mg}$) \times (2000 mg/day) \times (30 days/month). Immediate-release niacin was the least expensive preparation at a mean \pm SD cost of $\$7.10 \pm \$1.13/\text{month}$, and sustained-release niacin was second at $\$9.76 \pm \$1.74/\text{month}$; no-flush niacin was the most expensive at $\$21.70 \pm \$1.95/\text{month}$ ($p<0.001$, no-flush niacin compared with both immediate-release and sustained-release niacin).

Measurement of free nicotinic acid concentrations showed that immediate-release niacin and sustained-release niacin had similar mean \pm SD levels (520.4 ± 12.6 mg and 502.6 ± 19.3 mg, respectively) whereas no-flush niacin had no detectable levels of free nicotinic acid. No-flush niacin is composed of inositol hexaniacinate, which is an inositol molecule

esterified to six molecules of nicotinic acid. Hydrolysis of the ester bonds to release free nicotinic acid takes time and does not result in therapeutic concentrations of nicotinic acid, therefore resulting in no benefit of niacin therapy to treat hyperlipidemia. Over-the-counter compounds that should be recommended are Slo-Niacin (Upsher Smith, Minneapolis, MN) and Enduracin (Endurance Products Co., Tigard, OR) for sustained-release niacin, and Squibb (Princeton, NJ) and Rugby (Westbury, NY) for immediate-release niacin.

Fibrates

Chapman MJ. Fibrates in 2003: therapeutic action in atherogenic dyslipidaemia and future perspectives. *Atherosclerosis* 2003;171:1–13.

This comprehensive review article explores the role of fibrates in correcting the atherogenic dyslipidemias (low HDL and elevated triglyceride levels) associated with type 2 diabetes, metabolic syndrome, and type IIb (mixed) lipid phenotype. Figures enhance understanding of the text. The lipid-lowering and pleiotropic effects of fibrates are discussed. The author concludes that the lipid-modulating and antiinflammatory effects of fibrate therapy alone or in combination may decrease premature atherosclerosis and cardiovascular disease; however, more information is needed regarding how fibrates change the atherogenicity of LDL.

Prueksaritanont T, Zhao JJ, Ma B, et al. Mechanistic studies on metabolic interactions between gemfibrozil and statins. *J Pharmacol Exp Ther* 2002;301:1042–51.

Dog and human liver microsomes were used to explore the mechanism of the clinical pharmacokinetic interactions between statins and gemfibrozil. Dogs were used as an animal model for humans to study the interaction between simvastatin and gemfibrozil because gemfibrozil increases only the simvastatin hydroxyl acid concentration (not the simvastatin concentration). In addition, the interpatient variability of area under the curve for simvastatin hydroxyl acid exists in dogs as in humans. The results suggest that gemfibrozil modulates the pharmacokinetics of simvastatin hydroxyl acid by inhibiting its glucuronidation. Tests conducted in human liver microsomes suggest that gemfibrozil inhibited glucuronidation of atorvastatin and simvastatin hydroxyl acids to a greater extent than the CYP3A4-mediated oxidation. Gemfibrozil

inhibited the glucuronidation and the CYP2C8- and CYP3A4-mediated oxidation pathways for cerivastatin, which may explain the increased susceptibility of gemfibrozil to interact with cerivastatin.

Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos* 2002;30:1280–7.

This study used human hepatocytes to investigate the effects of fibrates on the major metabolic pathways of statin hydroxyl acids (β -oxidation, glucuronidation, and CYP-mediated oxidation). The results suggest that the pharmacokinetic interaction between gemfibrozil and simvastatin is not due to the inhibitory effect of gemfibrozil on β -oxidation of simvastatin hydroxyl acid. These findings substantiate the results from a previous trial showing that gemfibrozil interacts with simvastatin by glucuronidation of simvastatin hydroxyl acid, not the CYP3A-mediated oxidation. Gemfibrozil inhibited the oxidation of rosuvastatin and cerivastatin, but not of atorvastatin. Gemfibrozil inhibited lactonization of the statin hydroxyl acids in a concentration-dependent manner for atorvastatin, cerivastatin, rosuvastatin, and simvastatin. Rosuvastatin hydroxyl acid underwent glucuronidation. Fenofibrate had minimal effect on the metabolic pathways of simvastatin hydroxyl acid. The authors concluded that these results provide a possible explanation for the difference between interactions observed among statin-fibrate combinations.

Statins

Coons JC. Hydroxymethylglutaryl-coenzyme A reductase inhibitors in osteoporosis management. *Ann Pharmacother* 2002;36:326–30.

This literature review outlines the postulated mechanism for statins as bone anabolic agents and analyzes the data available through May 2001. In vitro, statins act to promote osteoblast proliferation and differentiation through their stimulation of the expression of the bone morphogenetic protein-2 (*BMP-2*) gene. The currently available evidence supporting a positive relationship between statins and bone mineral density and reduction of fractures is from observational studies. Three large case-control studies indicated a reduction in fracture risk in patients taking statins, whereas one found no

evidence for that hypothesis. Prospective studies to evaluate this question have yet to be published.

Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998;81:582-7.

The CURVES study evaluated the comparative dose efficacy of atorvastatin 10, 20, 40, and 80 mg; simvastatin 10, 20, and 40 mg; pravastatin 10, 20, and 40 mg; lovastatin 20, 40, and 80 mg; and fluvastatin 20 and 40 mg in patients with hypercholesterolemia after 8 weeks of treatment. Mean age of the 534 patients randomized was 55 years (range 20-80 yrs); 59% were men, and most were Caucasian. Mean baseline LDL level ranged from 192-244 mg/dl in each treatment group. Mean LDL level reductions were as follows: atorvastatin 10, 20, 40, and 80 mg—38%, 46%, 51%, and 54%, respectively; simvastatin 10, 20, and 40 mg—28%, 35%, and 41%, respectively; pravastatin 10, 20, and 40 mg—19%, 24%, and 34%, respectively; lovastatin 20, 40, and 80 mg—29%, 31%, and 48%, respectively; and fluvastatin 20 and 40 mg—17% and 23%, respectively. Atorvastatin 10 mg was statistically significantly more effective in reducing LDL levels than the other drugs at all doses except for simvastatin 20 and 40 mg, pravastatin 40 mg, and lovastatin 80 mg. Atorvastatin 20 mg was statistically significantly more effective in reducing LDL levels than the other drugs at all doses except for lovastatin 80 mg.

Jones PH, Davidson MH, Stein EA, et al, for the STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol* 2003;92:152-60.

This 6-week, parallel-group, open-label, randomized trial compared rosuvastatin 10, 20, 40, and 80 mg with atorvastatin 10, 20, 40, and 80 mg; pravastatin 10, 20, and 40 mg; and simvastatin 10, 20, 40, and 80 mg across dose ranges for LDL level reduction. The study, which included 2431 patients, administered the doses of drugs that were, except for rosuvastatin, approved by the FDA at that time. Eligible patients had baseline LDL levels that were stable

at 160-250 mg/dl (mean baseline level ~190 mg/dl) and triglyceride levels less than 400 mg/dl. The LDL level reductions were as follows: rosuvastatin 10, 20, 40, and 80 mg—45.8%, 52.4%, 55%, and percentage not provided, respectively; atorvastatin 10, 20, 40, and 80 mg—36.8%, 42.6%, 47.8%, and 51.1%, respectively; pravastatin 10, 20, and 40 mg—20.1%, 24.4%, and 29.7%, respectively; and simvastatin 10, 20, 40, and 80 mg—28.3%, 35%, 38.8%, and 45.8%, respectively. Of patients meeting NCEP goals, 89% were receiving rosuvastatin 20 or 40 mg; 29% of patients had an LDL goal of less than 100 mg/dl. Two patients receiving rosuvastatin 80 mg developed acute renal failure of uncertain etiology; this dose was never approved by the FDA. Otherwise, no differences were noted among groups regarding reported adverse effects or withdrawn treatment. This study was well powered and designed to characterize LDL level reductions with a new agent, rosuvastatin, compared with other available and widely administered statin agents.

McGowan MP, for the Treating to New Target (TNT) Study Group. There is no evidence for an increase in acute coronary syndromes after short-term abrupt discontinuation of statins in stable cardiac patients. *Circulation* 2004;110:2333-5.

This article was a response to two previous publications that found that risk of death and myocardial infarction increased significantly when statins were abruptly withdrawn after hospital admission for ACS. The data reported in this article were derived from the washout and open-label randomization phases of the TNT study, which enrolled patients with stable CAD. A total of 16,619 patients entered the dietary lead-in drug-washout period; of these, 9395 were receiving previous statin therapy. On entry into the washout period, mean \pm SD LDL level was 106 ± 30.4 mg/dl; during this period, 24 primary cardiac events occurred. On entry into the open-label run-in period, mean \pm SD LDL level was 153 ± 37.8 mg/dl; 31 primary events were recorded during this period. Based on this report, patients with stable CAD who discontinue their statin therapy abruptly for up to 6 weeks do not appear to have an increased risk of precipitating ACS. The report was not designed to answer the question of whether patients with ACS have an increased risk of death or myocardial infarction when these drugs are similarly withdrawn.

Resins

Konzem SL, Gray DR, Kashyap ML. Effect of pharmaceutical care on optimum colestipol treatment in elderly hypercholesterolemic veterans. *Pharmacotherapy* 1997;17:576–83.

This small, prospective, randomized study investigated whether pharmacist-physician comanagement (pharmaceutical care group) could improve patient adherence with colestipol therapy and outcomes. Forty men with hypercholesterolemia were equally divided and assigned to receive either pharmaceutical care or usual care by a physician. All patients were followed for 52 weeks. In the pharmaceutical care group, a pharmacist provided education about hypercholesterolemia, colestipol dosage titration, adverse-effect management, and instructions for follow-up. Patients were given an 8-week supply of colestipol, docusate sodium, and psyllium. The pharmacist phoned the patients during weeks 2, 4, 6, 26, and 52, and met with patients after 8 weeks to evaluate fasting lipid panel results, assess acceptance of therapy, and provide prescription refills. After 52 weeks, the pharmaceutical care group achieved greater LDL level reductions than the usual care group (16.0% vs 9.4%), and more patients in the pharmaceutical versus usual care group (29.4% vs 5.0%, $p < 0.5$) achieved their NCEP ATP II goal LDL level.

Spence JD, Huff MW, Heidenheim P, et al. Combination therapy with colestipol and psyllium mucilloid in patients with hyperlipidemia. *Ann Intern Med* 1995;123:493–9.

This randomized, parallel-group, double-blind, controlled trial evaluated the efficacy, safety, and compliance of colestipol 5 g, colestipol 2.5 g plus psyllium 2.5 g, psyllium 5 g, and cellulose placebo 5 g in 121 patients who had primary hypercholesterolemia and had followed a NCEP step 2 diet for 1 year. Fasting lipid levels, apolipoprotein concentrations, and quality of life were assessed at baseline, 4 weeks, and 10 weeks. Packet counts were used to assess compliance. No statistically significant differences were noted between the colestipol group and the combination group with respect to individual lipid parameters. The psyllium-colestipol combination was more effective in lowering the total cholesterol:HDL ratio than either drug or placebo alone ($p < 0.05$). The authors concluded that quality of life was best with the combination therapy and worst with placebo and with

psyllium alone, but no other information was provided. No statistically significant difference was noted in compliance between treatment groups.

Novel Targets

Bays H, Stein EA. Pharmacotherapy for dyslipidaemia: current therapies and future agents: review. *Expert Opin Pharmacother* 2003;4:1901–38.

This article reviews potential targets for intervention of lipid metabolism that are in development. These include newer statins, bile acid transport inhibitors, sterol regulatory element binding protein cleavage-activating protein-activating ligand, microsomal transport protein inhibitors, cholesteryl ester transfer protein (CETP) inhibitors and vaccines, acylcoenzyme A cholesterol acyltransferase inhibitors, mixed peroxisome proliferator activated receptor agonists, and revival of squalene inhibitors. The authors comment that many of these agents are being investigated with available agents as fixed-dose combinations.

de Grooth GJ, Klerkx AH, Stroes ES, Stalenhoef AF, Kastelein JJ, Kuivenhoven JA. A review of CETP and its relation to atherosclerosis. *J Lipid Res* 2004;45:1967–74.

Cholesteryl ester transfer protein promotes the transfer of cholesteryl esters from HDL to apolipoprotein B-containing lipoprotein particles. Thus, CETP action in most cases directly relates to decreased HDL levels. This article reviews the role of CETP in lipoprotein metabolism and cardiovascular risk. In addition, drug development studies of two CETP inhibitors in animals and humans are reviewed. In humans, phase I and II studies have shown significant increases in HDL with CETP inhibition. Whether this has an antiatherogenic effect is not known. The authors acknowledge the complexity of the relationship between CETP, HDL, and atherogenesis, and thus conclude that it is too early to predict whether these compounds will be useful.

Kong W, Wei J, Abidi P, et al. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nat Med* 2004;10:1344–51.

This study identifies berberine (a compound isolated from a Chinese herb) as a potential

cholesterol-lowering compound that increases hepatic LDL receptor protein 2.6-fold in hypercholesterolemic hamsters by a mechanism different from that of statins. Berberine does not inhibit cellular cholesterol biosynthesis through the sterol regulatory element binding protein pathway that is the primary mechanism of statins. In this study, 91 humans with hypercholesterolemia were randomized to receive berberine 0.5 g or placebo for 3 months. Berberine significantly reduced total cholesterol, LDL, and triglyceride levels by 29%, 25%, and 35%, respectively. No change in HDL level was observed in the berberine-treated patients, and no significant change was observed in any lipid parameters in the placebo-treated patients. Improved liver function was also observed in a subgroup of patients randomized to receive berberine compared with those who received placebo. The investigators speculate that this may have been due to reduced fat storage in the liver. This hypothesis is supported by animal data demonstrating reduced hepatic fat staining in berberine-treated animals compared with control animals. This study identifies a potential hypolipidemic substance with a mechanism of action different from that of the statins.

Role of Lipid-Lowering Therapy in Patients with Metabolic Syndrome

Hulthe J, Bokemark L, Wikstrand J, Fagerberg B. The metabolic syndrome: LDL particle size, and atherosclerosis: the atherosclerosis and insulin resistance (AIR) study. *Arterioscler Thromb Vasc Biol* 2000;20:2140–7.

This study assessed whether small, dense LDL particles (pattern B) were related to metabolic syndrome and subclinical atherosclerosis as measured by intimal medial thickness in the carotid and femoral arteries after ultrasound testing in 391 clinically healthy men. Patients were divided into three groups: 62 with metabolic syndrome, 252 with more than one metabolic syndrome risk factor, and 77 with no metabolic syndrome risk factors. Patients with metabolic syndrome had elevated body mass index, blood pressure, heart rate, total cholesterol, and apolipoprotein B compared with the other two groups. Significantly higher mean values for intimal medial thickness were found in the metabolic syndrome group than in the other groups in the carotid artery ($p < 0.001$) and femoral artery ($p = 0.022$). However, no significant differences were noted in plaque

occurrence and size between the groups. Pattern B patients had significantly elevated body mass index, blood pressure, heart rate, total cholesterol, triglyceride levels, and plasma insulin levels compared with the larger LDL subtype. Patients with pattern B had a higher prevalence of moderate-to-large plaques, and decreasing LDL peak particle size was associated with increasing intimal medial thickness of the arteries. Thus, patients with metabolic syndrome are more likely to have small, dense LDL particles and increased thickening of the carotid and femoral arterial walls.

Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third national health and nutrition examination survey. *JAMA* 2002;287:356–9.

Data from the third National Health and Nutrition Examination Survey were examined to assess the prevalence of metabolic syndrome in adults from the United States. Metabolic syndrome is defined as meeting three or more of the following criteria: abdominal obesity (waist circumference > 102 cm in men, > 88 cm in women), hypertriglyceridemia (triglyceride level ≥ 150 mg/dl), low HDL level (< 40 mg/dl in men, < 50 mg/dl in women), hypertension (blood pressure $\geq 130/85$ mm Hg or receiving anti-hypertensive drug therapy), and high fasting glucose level (≥ 110 mg/dl or receiving anti-diabetic drug therapy). Roughly 24% of adults (47 million patients) have metabolic syndrome, and the prevalence increases with age to more than 40% in patients older than 60 years. In men, Caucasians and Mexican-Americans have higher rates of abdominal obesity, low HDL levels, and hypertriglyceridemia; African-Americans have higher rates of hypertension; and Mexican-Americans have higher rates of hyperglycemia. In women, Mexican-Americans and African-Americans have higher rates of abdominal obesity; African-Americans have higher rates of hypertension; and Mexican-Americans have higher rates of low HDL levels, hypertriglyceridemia, and hyperglycemia. Prevalence was similar between men and women, except that rates were higher in Mexican-American women (26% higher) and African-American women (57% higher) than their male counterparts. Thus, metabolic syndrome is prevalent in American society and needs to be reduced through intensive diet and exercise programs as well as proper medical management.

Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002;288:2709–16.

This study assessed whether the presence of metabolic syndrome increased the risk of death due to CHD, cardiovascular disease, or any cause in 1209 men with and without metabolic syndrome who were followed for a median of 11.6 years. During follow-up, 109 deaths occurred, with 27 due to CHD and 46 due to cardiovascular disease. According to the NCEP ATP III guidelines, metabolic syndrome was associated with an age-adjusted increased risk of death due to CHD (RR 3.40, 95% CI 1.37–8.43). No significant association was found between the NCEP ATP III criteria regarding cardiovascular disease and all-cause mortality unless the model was adjusted for other factors. The WHO criteria for metabolic syndrome were significantly associated with death due to CHD, cardiovascular disease, and mortality across various models. When assessing unadjusted Kaplan-Meier hazard curves, metabolic syndrome was associated with an increased mortality in CHD (RR 3.77, 95% CI 1.74–8.17), cardiovascular disease (RR 3.55, 95% CI 1.96–6.43), and all-cause mortality (RR 2.43, 95% CI 1.64–3.61). Thus, metabolic syndrome is associated with increased mortality in middle-aged men who are initially free of cardiovascular disease and diabetes.

Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* 2001;285:1585–91.

The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) showed a 22% reduction in the combined rate of nonfatal myocardial infarction and CHD death in 1264 men receiving gemfibrozil 1200 mg/day versus 1267 men receiving placebo over a 5.1-year period. This study assessed how well the changes in each lipid variable correlated with reduced outcomes. Only HDL concentrations significantly predicted nonfatal myocardial infarction and CHD death at baseline and during treatment ($p=0.048$ and 0.01 , respectively). Also, after controlling for diabetes, hypertension, smoking, age, and body mass index, HDL level was the only lipid parameter to significantly predict a reduction in CHD events. For every 5-mg/dl increase in HDL, there was an 11% relative risk reduction in nonfatal myocardial infarction

or CHD death (95% CI 0.81–0.98). No other lipid parameter was predictive. This benefit of HDL level accounted for only 23% of the treatment benefit. The other major lipid parameters did not contribute to treatment effect, and perhaps other favorable effects of gemfibrozil contribute to this reduction. Thus, raising HDL concentration can reduce the occurrence of new coronary events independent of changes in LDL concentration.

Laaksonen DE, Lakka H-M, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol* 2002;156:1070–7.

This prospective cohort study assessed the ability of different metabolic syndrome criteria (from the NCEP ATP III and WHO) in predicting the occurrence of diabetes in 1005 middle-aged men followed for 4 years. Patients who met the WHO criteria for metabolic syndrome were almost 9 times more likely to develop diabetes over 4 years than those without the syndrome. The WHO criteria had high sensitivity (0.83 for prevalent, 0.67 for incident) and specificity (0.78–0.80). The NCEP ATP III criteria had lower sensitivity for prevalent (0.61) and incident (0.41) than the WHO criteria, but NCEP ATP III had more specificity (0.89–0.90). The main difference between the criteria is the definition of abdominal obesity. The WHO criteria uses waist:hip measurement ratios above 0.90 as indicative of abdominal obesity, whereas the NCEP ATP III uses waist circumference above 102 cm. All men who developed diabetes had a waist:hip ratio above 0.90, whereas less than a third of those who developed diabetes had a waist circumference above 102 cm. However, most men who did not develop diabetes also had a waist:hip ratio above 0.90, reducing specificity of the measurement. When the waist circumference cutoff point was reduced to 94 cm or greater, it captured 59% of the men who developed diabetes. Both sets of criteria were valid in predicting the prevalence and occurrence of diabetes, but perhaps the waist circumference criteria in the NCEP ATP III guidelines should be lowered to capture more individuals who are likely to develop the disease.

Ford ES, Giles WH. A comparison of the prevalence of the metabolic syndrome using two

proposed definitions. *Diabetes Care* 2003;26:575–81.

This study applied two different sets of criteria for metabolic syndrome—those from the NCEP ATP III and the WHO—to data from NHANES III to assess whether differences existed between the two for identifying patients with the syndrome. For 8608 patients aged 20 years or older, NCEP ATP III and WHO identified 23.9% and 25.1%, respectively, as having metabolic syndrome. The two sets of criteria were similar for assessing the population, but the WHO criteria identified more African-American men (24.9%) than the NCEP ATP III criteria (16.5%). This may be due to the different measurements of central adiposity between the two sets of criteria; the WHO criteria identified 3 times as many African-American men. Also, more African-American men were captured due to the inclusion of microalbuminuria in the WHO criteria. Both sets of criteria associated increased serum insulin concentrations with increased homeostasis model assessment scores in patients with metabolic syndrome versus those without the syndrome. Both sets of criteria predicted clinical end points of cardiovascular disease, such as heart attack, stroke, and chronic heart failure; the ORs derived from the WHO criteria had higher numbers but significant overlapping of the CIs with the ORs derived from the NCEP ATP III criteria. Thus, both sets of criteria are adequate for assessing most patients with metabolic syndrome, but perhaps a more inclusive set of criteria can be developed.

Grundy SM. Hypertriglyceridemia, atherogenic dyslipidemia, and the metabolic syndrome. *Am J Cardiol* 1998;81(4A suppl B):18B–25.

Hypertriglyceridemia plays a large role in the development of atherogenic dyslipidemia and may be atherogenic on its own. Triglyceride-rich lipoproteins are derived intestinally (chylomicrons) and hepatically (VLDL). As these particles are metabolized, they decrease in size and may become atherogenic. Particles richer in cholesteryl esters tend to be more atherogenic

and may be seen in the setting of hypertriglyceridemia. Thus, patients with high triglyceride levels have atherogenic particles outside their LDL, and they should have their non-HDL as well as LDL assessed. Their non-HDL cholesterol goals are 30 mg/dl above their LDL goals. Hypertriglyceridemia also leads to the lipid triad, or atherogenic dyslipidemia. The lipid triad consists of an elevated triglyceride level, low HDL level, and small, dense LDL particles. When triglyceride-rich lipoproteins are present (due to hypertriglyceridemia), they exchange triglycerides for cholesteryl esters with LDL and HDL particles. This lowers the cholesterol content in HDL particles, resulting in low HDL levels. Also, the triglycerides are hydrolyzed from the LDL particles, decreasing their size and producing small, dense LDL particles. Each component of the lipid triad increases atherogenicity.

Metabolic syndrome is a metabolic disorder consisting of the lipid triad, insulin resistance (with or without glucose intolerance), hypertension, and a prothrombotic state. Treatment should focus on weight loss and increased physical activity initially. Second, medical management should begin with insulin-sensitizing agents such as metformin or a thiazolidinedione (glitazone). Finally, individual risk factors should be treated with statins primarily to lower non-HDL cholesterol, niacin or fibrates to modify the lipid triad, various agents for treatment of hypertension, and aspirin to modify the prothrombotic state.

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