Update in General Internal Medicine

John V.L. Sheffield, MD, and Eric B. Larson, MD, MPH

Our goal for this Update in General Internal Medicine is to update practicing internists on the past year's clinically important research papers. We compiled these articles with the help of general internists and subspecialists from the University of Washington, along with the editors of *ACP Journal Club*.

Cardiovascular Disease and Statin Use

This year's trial results indicate a real change in our understanding of indications for the use of statins. In type 2 diabetic patients with at least 1 additional risk factor for coronary heart disease, lipid-lowering treatment with statins is effective for primary prevention of cardiovascular disease (CVD). In patients with acute coronary syndromes, early initiation of intensive lipid-lowering treatment to achieve serum low-density lipoprotein (LDL) cholesterol levels below 1.80 mmol/L (<70 mg/dL) prevents major cardiovascular events more effectively than moderate lipid lowering. Intensive lipid lowering is also beneficial for patients with stable coronary disease. These results indicate that statin treatment could benefit a greater number of patients and that target LDL cholesterol levels for treatment of patients at highest risk should be lower than previously recommended. Because these findings indicate that patients are now more likely to be using statins for many years, we are reassured to learn that treatment for as long as 10 years appears to be safe.

Statins Prevented Cardiovascular Events in High-Risk Patients with Type 2 Diabetes

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. [PMID: 15325833]

This randomized, double-blind, placebo-controlled trial from the United Kingdom and Ireland assessed the effectiveness of atorvastatin for primary prevention of major cardiovascular events in patients with type 2 diabetes and normal serum LDL cholesterol levels. The trial involved 2838 adults (32% women; 94% white) 40 to 75 years of age (mean age, 62 years) with type 2 diabetes mellitus and at least 1 additional CVD risk factor: hypertension (84%), current cigarette use (22%), albuminuria (17%), or retinopathy (30%). The investigators assigned patients to receive either 10 mg of atorvastatin per day ($n = 1428$) or placebo ($n = 1410$). Mean baseline measurements were hemoglobin A_{1c} level, 7.8%; LDL cholesterol level, 3.03 mmol/L (117 mg/dL); and triglyceride level, 1.67 mmol/L (148 mg/dL). Patients with a history of CVD, serum LDL cholesterol levels greater than 4.14 mmol/L (>160 mg/dL), triglyceride levels greater than 6.78 mmol/L (>600 mg/dL), or creatinine levels greater than 150.28 μmol/L (>1.7 mg/dL) were excluded.

The investigators terminated the study early, after a mean follow-up of 3.9 years, because atorvastatin significantly reduced the risk for a first cardiovascular event, for any acute coronary event, and for stroke (**Table 1**). The mean LDL cholesterol level in the atorvastatin group, 2.12 mmol/L (82 mg/dL), was much lower than that in the placebo group, which remained essentially at baseline (3.03 mmol/L [117 mg/dL]). A 27% reduction in overall mortality with atorvastatin was not statistically significant. Adverse events occurred infrequently (1.1%) in both groups.

In conclusion, 10 mg of atorvastatin per day was safe and effective in reducing the risk for first CVD events, including stroke, in patients with type 2 diabetes who did not have high levels of LDL cholesterol. The results confirm the Heart Protection Study finding that, irrespective of pretreatment LDL cholesterol level, statins prevent cardiovascular events in people with type 2 diabetes and at least 1 additional CVD risk factor.

Intensive Lipid Lowering Was More Effective Than Moderate Lipid-Lowering after Acute Coronary Syndromes

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. [PMID: 15007110]

The optimal serum level of LDL cholesterol for patients with coronary artery disease is unclear. This randomized, controlled trial was designed to determine whether high-dose atorvastatin prevented recurrent cardiovascular events more effectively than a standard dose of pravastatin in pa-

See also:

Web-Only
Conversion of tables into slides

Ann Intern Med. 2005;143:212-221.
For author affiliations, see end of text.

tients with acute coronary syndromes. The investigators enrolled 4162 patients (mean age, 58 years; 22% women; 91% white) who had been hospitalized at 1 of 349 sites in 8 countries for an acute coronary syndrome within the past 10 days. Patients received either standard therapy (pravastatin, 40 mg/d) or intensive therapy (atorvastatin, 80 mg/d). Patients were also randomly assigned to receive a monthly 10-day course of gatifloxacin or placebo in a 2×2 factorial design. Trial criteria excluded patients who had used an 80-mg dose of any statin previously and those who had used a fibrate, niacin, or medication that inhibited cytochrome P-450 3A4 within the month before randomization. Also excluded were patients who had undergone a revascularization procedure within 6 months of randomization, were scheduled to undergo coronary artery bypass grafting, or had a serum creatinine level greater than 176.8 μmol/L (>2.0 mg/dL).

The primary end point was a composite of all-cause mortality, myocardial infarction (MI), unstable angina requiring hospitalization, revascularization procedure at least 30 days after randomization, and stroke. The prevalence of coronary risk factors was as follows: diabetes mellitus, 18%; hypertension, 50%; current cigarette use, 37%; and previous MI, 18%. The treatment groups had equivalent baseline characteristics except for peripheral arterial disease, which was more common among the pravastatin group (6.6% vs. 5.0%; $P = 0.03$). Patients received appropriate medical treatment. Concomitant medications during the treatment period were aspirin, 93%; clopidogrel or ticlopidine, 72% initially and 20% at 1 year; β-blockers, 85%; and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 83%.

Mean follow-up was 24 months. The median LDL cholesterol level was 2.46 mmol/L (95 mg/dL) in the standard-dose pravastatin group and 1.60 mmol/L (62 mg/dL) in the high-dose atorvastatin group ($P < 0.001$). Median HDL cholesterol increased by 8.1% in the pravastatin group and by 6.5% in the atorvastatin group ($P < 0.001$).

High-dose atorvastatin was substantially more effective in reducing Kaplan–Meier estimates of 2-year event rates for the composite cardiovascular end point (22.4% vs. 26.3%; hazard ratio, 0.84 [95% CI, 0.74 to 0.95]; number needed to treat for benefit [NNT_B], 26). The benefit occurred as early as 30 days after randomization and was consistent over time. The intensive treatment group had substantial reductions in risk for unstable angina (3.8% vs. 5.1%; hazard ratio, 0.71; $P = 0.02$; NNT_B, 77) and revascularization procedures (16.3% vs. 18.8%; hazard ratio, 0.86; $P = 0.04$; NNT_B, 40). A 28% reduction in the risk for death from any cause was not statistically significant ($P = 0.07$).

The group that benefited the most from the intensive therapy had an LDL cholesterol level greater than 3.24 mmol/L (>125 mg/dL) (27% of all study patients), and their 2-year event rate for the composite cardiovascular end point was 20.1% versus 28.2% with pravastatin (hazard ratio, 0.65 [CI, 0.5 to 0.85]). The group with LDL cholesterol levels less than 3.24 mmol/L (<125 mg/dL) did not benefit as much (2-year event rates, 23.5% vs. 25.6%; hazard ratio, 0.95; [CI, 0.80 to 1.10]).

Adverse drug effects were slightly higher in the intensive treatment group. A 3-fold increase in serum alanine aminotransferase level was about 3 times more common than in the standard therapy group (3.3% vs. 1.1%). Discontinuation of the study drug was slightly higher in the standard therapy group (33.0% vs. 30.4%); discontinuation due to myalgia or elevation in serum creatine kinase level occurred in 2.7% of the standard therapy group and 3.3% of the intensive therapy group ($P > 0.2$).

In summary, an intensive lipid-lowering statin regimen provided greater protection against major cardiovascular events than a standard regimen for patients who had recently had an acute coronary syndrome. These patients benefited from early and continued LDL cholesterol lowering to levels substantially below current target levels. On the basis of these and other recent trial results, the Adult Treatment Panel III of the National Cholesterol Education Program has introduced new guidelines for the management of high cholesterol (1), including an updated risk definition. The panel now advocates a serum LDL treatment threshold of 2.59 mmol/L (100 mg/dL) for persons with diabetes and higher cardiovascular risk. Because high-dose statin regimens are associated with more adverse effects, clinicians should regularly monitor their patients' serum alanine aminotransferase levels and question them about symptoms.

Table 1. **Effects of Atorvastatin (10 mg/d) vs. Placebo on Primary and Secondary Outcomes**

Event Type	Placebo, %	Atorvastatin, %	Hazard Ratio (95% CI)	Number Needed To Treat to Benefit
Primary end points (cardiovascular events)	9.0	5.8	0.63 (0.48–0.83)	31
Acute coronary events	5.5	3.6	0.64 (0.45–0.91)	53
Coronary revascularization	2.4	1.7	0.69 (0.41–1.16)	
Stroke	2.8	1.5	0.52 (0.31–0.89)	77
Secondary end points				
Death from any cause	5.8	4.3	0.73 (0.52–1.01)	
Any acute cardiovascular event	13.4	9.4	0.68 (0.55–0.85)	25

Management Issues in Coronary Artery Disease

Exercise Reduced the Risk for Ischemic Coronary Events More Than Percutaneous Coronary Angioplasty in Patients with Single-Vessel Coronary Artery Disease

Hambrecht R, Walther C, Mobius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. Circulation. 2004;109:1371-8. [PMID: 15007010]

This randomized, controlled trial from Germany compared the effects of exercise training with outcomes from percutaneous coronary intervention (PCI) with stenting in 101 men 70 years of age or younger (mean age, 61 years) who had stable single-vessel coronary artery disease. The investigators measured the effects of either intervention on clinical symptoms, angina-free exercise capacity, myocardial perfusion, cost-effectiveness, and frequency of a combined clinical end point. The combined end point included cardiac death, stroke, coronary artery bypass grafting, angioplasty, acute MI, and worsening angina resulting in hospitalization. Cost-effectiveness was the average expense needed to improve the patient's Canadian Cardiovascular Society angina class by 1 class.

The investigators randomly assigned patients either to begin 12 months of exercise training (20 minutes of bicycle ergometry per day) or to undergo PCI. The exercise program involved using a bicycle ergometer at 70% of the symptom-limited maximal heart rate under close supervision for 10 minutes, 6 times daily for 2 weeks. After that, patients exercised at home on a bicycle ergometer for 20 minutes daily and participated in one 60-minute group aerobic session per week.

During the 12-month study period, more patients in the exercise group remained free of ischemic events (88% vs. 70%; odds ratio [OR], 0.33 [CI, 0.12 to 0.90]; $P = 0.023$). Patients in both groups experienced similar improvements in symptoms, but only patients in the exercise group improved their exercise capacity and maximal oxygen uptake ($P < 0.01$). They showed improvement over the PCI group within 3 to 4 months of starting the exercise program. Patients in the PCI group were more likely to require hospital admission for repeated procedures related to worsening angina. Exercise training was more cost-effective than PCI ($3429 vs. $6956 to gain 1 Canadian Cardiovascular Society class; $P < 0.001$). Follow-up imaging studies showed improved scintigraphic myocardial perfusion distal to the original target coronary stenosis in both groups. Angiography in the patients in the exercise group showed substantially less overall progression of coronary artery disease ($P = 0.035$).

In summary, this remarkable paper demonstrated that, in carefully selected persons with stable single-vessel coronary artery disease, an aerobic exercise program was more effective than PCI with stenting for reducing the risk for ischemic coronary events. Exercise training was also more cost-effective. As the authors stated, PCI without exercise is suboptimal treatment.

Coronary Artery Revascularization before Vascular Surgery Did Not Substantially Alter the Long-Term Outcome

McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med. 2004;351:2795-804. [PMID: 15625331]

This randomized, controlled trial aimed to determine the benefit of coronary artery revascularization for stable coronary artery disease before elective major vascular surgery. Cardiologists from 18 Veterans Affairs medical centers screened 5859 patients who had been referred for vascular surgery. Patients were excluded if they had low cardiac risk, urgent need for surgery, severe coexisting illness, successful previous revascularization, nonobstructive coronary stenosis not amenable to revascularization, left main coronary stenosis of 50% or greater, left ventricular ejection fraction of less than 0.2, or severe aortic stenosis. After screening, 510 patients (mean age, 66 years) were eligible for the study. These patients were at increased risk for perioperative cardiac complications and clinically significant coronary artery disease. Their indications for vascular surgery included repair of an expanding abdominal aortic aneurysm (33%) or lower-extremity arterial occlusion (67%).

The investigators randomly assigned the patients to undergo either coronary artery revascularization or no revascularization before elective major vascular surgery. The frequency of treatment with β-blockers (85%), statins (54%), and aspirin (73%) was similar in the 2 groups.

Among the group assigned to revascularization, 59% received PCI and 41% received bypass surgery. This group underwent vascular surgery a median of 54 days after randomization. The group that did not receive revascularization underwent vascular surgery a median of 18 days after randomization ($P < 0.001$). Within 30 days of the planned vascular operation, an MI occurred in 12% of the coronary revascularization group and in 14% of the group ($P > 0.2$) that did not undergo revascularization. At 2.7 years, mortality was 22% in the patients who received revascularization compared with 23% of those who did not (relative risk, 0.98 [CI, 0.70 to 1.37]; $P > 0.2$).

We conclude from this study that, in carefully screened patients with stable coronary artery disease who receive effective medical therapy, coronary revascularization before elective vascular surgery does not improve long-term outcome. The finding answers a major question in the preoperative management of these patients. Now, with this issue settled, experts recommend further research to determine the best screening strategy to identify very high-risk patients and the value of medical therapies beyond β-blockers, such as statins, angiotensin-converting enzyme inhibitors, and antiplatelet agents.

Hypertension

In the past, we have talked extensively about medical therapy for hypertension, but this year we are focusing on one of the many interesting studies about home measurement.

Home Blood Pressure Measurements Were More Accurate Than Office Measurements among Elderly Hypertensive Patients

Bobrie G, Chatellier G, Genes N, et al. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA. 2004; 291:1342-9. [PMID: 15026401]

The added prognostic value of home blood pressure measurement has been unknown. This French study aimed to assess its value compared with clinical measurement. The study included 4939 hypertensive patients over the age of 60 years (mean age, 70; 48.9% men). Hypertension was defined as blood pressure higher than 140/90 mm Hg for office measurements and higher than 135/85 mm Hg for home measurements. The patients' usual general practitioners recruited and followed them, and their participation was not constrained by the type of treatment they were receiving. At baseline, 55% of patients took more than 2 classes of antihypertensive drugs.

The study took place in 2 phases. The first was an evaluation to determine baseline blood pressure. The physicians determined baseline blood pressure from 6 readings at 2 office visits, separated by 2 weeks, using a mercury monometer blood pressure device. The patients determined baseline home blood pressure by taking about 6 readings per day over a 4-day period, particularly at the beginning and the end of each day, using a semiautomatic oscillometric Omron-705CP (Omron Corp, Tokyo, Japan) blood pressure cuff. The mean of these readings determined the baseline measurements: 152/85 mm Hg in the office and 146/82 mm Hg at home.

The second phase was a 3-year prospective observational period during which the general practitioners managed the patients' hypertension. The primary end point was cardiovascular mortality, and the secondary end points were total mortality and the combination of cardiovascular mortality, nonfatal MI, nonfatal stroke, transient ischemic attack, hospitalization for angina or heart failure, PCI, and coronary artery bypass grafting.

At baseline, only 13.9% of the patients had their hypertension controlled both in the office and at home; 13.3% had elevated blood pressure in the office but not at home ("white-coat hypertension"); 9.4% had elevated blood pressure at home but not in the office (also known as "masked hypertension"); and 63.4% had uncontrolled hypertension by both measurements. During the 3-year follow-up period, there were 205 deaths (85 attributed to CVD) and 324 patients had more than 1 cardiovascular event. Neither the office nor the home blood pressure predicted cardiovascular mortality or total mortality. However, after adjustment for known cardiovascular risk factors, home blood pressure was significantly predictive of combined cardiovascular events (adjusted OR for home systolic blood pressure, 1.02 [CI, 1.01 to 1.02]; $P < 0.001$) while office measurement was not. For every increase of 10 mm Hg in home systolic blood pressure, the risk for a cardiovascular event increased by 17.2%; for each increase in diastolic blood pressure of 5 mm Hg, the risk increased by 11.7%.

In a multivariable model that used patients with controlled hypertension at home and office as the referent, the hazard ratio of cardiovascular events was double for patients with elevated blood pressure in both settings (hazard ratio, 1.96 [CI, 1.27 to 3.02]) and for patients with elevated blood pressure at home but not in the office (hazard ratio, 2.06 [CI, 1.22 to 3.47]). The rate of cardiovascular events in patients with white-coat hypertension did not differ from that in patients with controlled hypertension (hazard ratio, 1.18 [CI, 0.67 to 2.10]).

In summary, in elderly patients with hypertension, blood pressure measured at home predicted cardiovascular events more accurately than blood pressure measured in the office. Self-measurement identified patients who had white-coat hypertension and those with masked hypertension, potentially improving prognostic assessment in up to 25% of patients. Patients with elevated blood pressure at home but not in the office had the same prognosis as patients with uncontrolled hypertension. These findings suggest that more blood pressure measurements over time will more accurately reflect a patient's true blood pressure. Also, self-monitoring probably results in better blood pressure control because the patient is more actively engaged in his own care, thereby encouraging adherence and assuring treatment more appropriate to actual blood pressure levels. Of course, blood pressure is an intermediate end point. Whether incorporating home blood pressure measurement into standard treatments would improve cardiovascular outcomes remains an unanswered question.

Weight Loss Programs

A Low-Carbohydrate Diet Improved Short-Term Weight Loss and Serum Levels of Triglycerides and High-Density Lipoprotein Cholesterol Compared with a Low-Fat Diet

Yancy WS Jr, Olsen MK, Guyton JR, et al. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. Ann Intern Med. 2004;140:769-77. [PMID: 15148063]

Although low-carbohydrate diets are popular, research on their effects is at an early stage. This randomized, con-

trolled trial compared a low-carbohydrate ketogenic diet program with a low-fat, low-cholesterol, reduced-calorie diet program. The investigators enrolled 120 overweight (mean body mass index, 34 kg/m^2) hyperlipidemic volunteers from the community. Mean total cholesterol level was 6.21 mmol/L (240 mg/dL) and mean age was 45 years; 76% of the volunteers were women. The investigators assigned them to a low-carbohydrate diet (initially, < 20 g of carbohydrate daily) plus nutritional supplementation, or a low-fat diet (< 30% of calories from fat, < 300 mg of cholesterol daily, and reduced intake of 500 to 1000 kcal/d). Individuals in both groups also received a recommendation for exercise and participated in group meetings. Outcome measures were body weight, body composition, fasting serum lipid levels, and tolerability.

Dropout rates were high in both groups; 24% of patients in the low-carbohydrate group and 43% of patients in the low-fat group withdrew. Patients in the low-fat group who withdrew primarily cited "schedule conflicts" ($n = 15$) and dissatisfaction with weight loss ($n = 6$); patients who withdrew from the low-carbohydrate group primarily cited "side effects" ($n = 3$).

At 24 weeks, patients in the low-carbohydrate group lost more weight than those in the low-fat diet group (mean change, −12.9% vs. -6.7%; $P < 0.001$). Patients in both groups lost substantially more fat mass than fat-free mass. The low-carbohydrate diet resulted in greater decreases in serum triglyceride levels (change, −0.83 mmol/L [−74.2 mg/dL] vs. −0.31 mmol/L [−27.9 mg/dL]; $P = 0.004$) and greater increases in high-density lipoprotein cholesterol (change, 0.142 mmol/L [5.5 mg/dL] vs. −0.04 [−1.6 mg/dL]; $P < 0.001$). Changes in LDL cholesterol levels were minor in both groups.

Adverse effects were more common in the low-carbohydrate group than in the low-fat group ($P < 0.05$ for each comparison), including constipation (68% vs. 35%), headache (60% vs. 40%), halitosis (38% vs. 8%), muscle cramps (35% vs. 7%), diarrhea (23% vs. 7%), weakness (25% vs. 8%), and rash (13% vs. 0%). Another study that compared the effects of the Atkins diet, the Zone diet, the standard Weight Watchers diet, and the Dean Ornish diet, found that adherence to any regulated diet, not the diet program itself, was the most important predictor of the weight loss achieved and of improvements in lipid, C-reactive protein, and insulin levels (2). Individual responses to weight loss programs vary. We can encourage overweight patients to experiment with a variety of programs that emphasize healthy food sources, to engage in regular exercise, and to aim for long-term change in eating habits rather than short-term rapid weight loss. We can now consider low-carbohydrate diets a reasonable option among many. Research should now address self-management and behavioral change at every stage from initiation of diet change to long-term diet adherence and maintenance.

Cyclooxygenase Inhibitors

At the close of 2004, results from unpublished trials of selective cyclooxygenase-2 (COX-2) inhibitors reported increased cardiovascular risk; rofecoxib and valdecoxib were later withdrawn from the market. Subsequent discussion has focused on whether the pharmaceutical companies should have withdrawn the drugs earlier, the role of the U.S. Food and Drug Administration (FDA), and shortcomings of the current postmarketing surveillance process.

Cyclooxygenase Inhibitors Were Associated with Increased Cardiovascular Risk

Juni P, Nartey L, Reichenbach S, et al. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet. 2004;364:2021-9. [PMID: 15582059]

On 30 September 2004, Merck announced the voluntary withdrawal of rofecoxib due to an associated increase in cardiovascular risk that was reported in the unpublished results of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study. The researchers who performed this meta-analysis sought to determine whether evidence of harm associated with use of rofecoxib was available before September 2004. They searched resources, including the Cochrane Controlled Trials Register, MEDLINE, scientific conference proceedings, journal citations, and the proceedings of relevant FDA advisory panels. They also contacted experts in the field. Eighteen randomized, controlled trials involving 25 273 patients met criteria for inclusion in the meta-analysis.

The combined relative risk for MI associated with rofecoxib use was 2.24 (CI, 1.24 to 4.02), with little evidence of heterogeneity between trials. Cumulative meta-analysis indicated that an increased risk for MI became evident in 2000. At the end of 2000, 52 MIs had occurred in 20 742 patients, and the relative risk for MI was 2.3 (CI, 1.22 to 4.33). Inclusion of the results of subsequent trials narrowed the confidence interval, but the relative risk remained constant. The investigators concluded that rofecoxib increases the risk for MI and that better monitoring of cumulative trial results would have led to this conclusion in 2000.

A posting on the FDA Web site in November 2004 reported similar results about rofecoxib (3). Investigators conducted a nested case–control study within a base cohort consisting of all patients between the ages of 18 and 84 years enrolled in the Kaiser Permanente system who filled at least 1 prescription for a COX-2 inhibitor or for a nonselective, nonsteroidal anti-inflammatory drug (NSAID). By design, the patients were without a previous diagnosis of cancer, severe organ failure, organ transplantation, or HIV/AIDS. The authors defined case-patients as those who had acute MI or out-of-hospital

sudden cardiac death. They matched controls to case-patients for age, sex, region, and index date.

The most common exposures were to ibuprofen and naproxen. A total of 350 071 person-years of NSAID exposure and 1772 incident cases were available for the study. The adjusted risk for serious coronary events with rofecoxib (all doses) was increased 1.40-fold (CI, 1.03-fold to 1.90-fold) compared with past NSAID use and 1.63-fold (CI, 1.12-fold to 2.36-fold) compared with celecoxib use. The adjusted risk associated with high-dose rofecoxib was 3.15 (CI, 1.14 to 8.75) compared with the risk associated with past use of an NSAID. The adjusted risk for serious coronary events with celecoxib (all doses) was not significantly different from that seen with past NSAID use (adjusted OR, 0.86 [CI, 0.69 to 1.07]). Adjusted risk for serious coronary events was also increased with naproxen (adjusted OR, 1.18 [CI, 1.04 to 1.35]) and other NSAIDs (adjusted OR, 1.16 [CI, 1.04 to 1.30]). The risk associated with ibuprofen use did not reach statistical significance (adjusted OR, 1.09 [CI, 0.99 to 1.21]).

In December 2004, the National Cancer Institute suspended a placebo-controlled trial of colon adenoma prevention because of increased cardiovascular risk with celecoxib, and the National Institutes of Health halted a placebo-controlled trial of dementia prevention because of increased risk with naproxen. Valdecoxib has been associated with severe cutaneous reactions and a 3-fold increase in adverse cardiovascular events following cardiac bypass surgery (4). Valdecoxib was removed from the market in April 2005.

The demonstration of increased cardiovascular risk with multiple selective COX-2 inhibitors suggests a class effect that may extend to nonselective NSAIDs. Physicians should prescribe cyclooxygenase inhibitors—especially COX-2 inhibitors—with caution, particularly to patients at moderate to high cardiovascular risk. Giving low-dose aspirin with a COX-2 inhibitor reduces the thrombotic risk but also eliminates the gastrointestinal protective benefit. If an alternative to a cyclooxygenase inhibitor is not acceptable, clinicians should prescribe the lowest effective dose of the drug for the shortest time possible. At present, it is not possible to define groups of patients who can take these drugs safely for a prolonged period.

Hormone Replacement Therapy

Conjugated Equine Estrogen Increased Risk for Stroke among Women without a Uterus

Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004; 291:1701-12. [PMID: 15082697]

Previous studies based on data from the Women's Health Initiative have demonstrated that combination hormone replacement therapy (HRT) increases the risk for heart disease and invasive breast cancer in postmenopausal women with a uterus. This study examined the effects of estrogen-only HRT on rates of chronic disease incidence among women who have had a hysterectomy. This component of the Women's Health Initiative was a randomized, double-blind, placebo-controlled trial conducted in 40 U.S. clinical centers. The study included 10 739 postmenopausal women between the ages of 50 and 79 years with previous hysterectomy (mean age, 63.6 years; 77% white); 4.1% of patients reported a history of coronary heart disease.

The investigators randomly assigned patients to conjugated equine estrogen, 0.625 mg/d, or to placebo. Primary outcomes were coronary heart disease (nonfatal MI or cardiac death) and invasive breast cancer. A global index of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism, colorectal cancer, hip fracture, and death from other causes. Blinded physician adjudicators confirmed clinical events.

The study was stopped early after an average follow-up of 6.8 years. An analysis of the data compared the effects of conjugated equine estrogen versus placebo (**Table 2**). Conjugated equine estrogen had no effect on incidence of coronary heart disease or invasive breast cancer; it did, however, increase stroke risk and decrease hip fracture risk. The differences in hazards emerged early in the study and persisted throughout follow-up. Findings were consistent across all race and age groups and were not influenced by risk status or previous disease. Of the women in the treatment group, 54% stopped therapy during the study; 9.1% of those assigned to placebo started HRT during the study. Consequently, these results may be biased toward the null and may therefore underestimate both harms and benefits. In summary, these findings suggested that postmenopausal women with previous hysterectomy should not take HRT for the general prevention of chronic disease.

Another analysis last year of Women's Health Initiative data also debunked the commonly held belief that HRT might prevent dementia (5). The investigators found that postmenopausal women receiving hormone therapy, either combination HRT or estrogen alone, experienced a significantly increased risk for probable dementia (hazard ratio, 1.76). In a related study, investigators found that women assigned to conjugated equine estrogen scored lower on cognitive tests than those assigned to placebo (6).

These studies have provided further evidence that postmenopausal women should not take HRT for general prevention of chronic disease. Hormone replacement therapy is indicated for the treatment of menopausal symptoms but should be prescribed at the lowest effective dose for the shortest time possible. What remains unknown is whether the results of Anderson and colleagues' study, which primarily examined conjugated equine estrogen, apply to other HRT formulations, doses, and routes of administra-

Table 2. **Effects of Conjugated Equine Estrogen (0.625 mg/d) vs. Placebo on Rates of Chronic Disease after Hysterectomy***

Variable	Annual Event Rate per 10 000 Women		Hazard Ratio (Nominal 95% CI)
	CEE	Placebo	
Primary outcomes			
Coronary heart disease	49	54	0.91 (0.75–1.12)
Invasive breast cancer	26	33	0.77 (0.59–1.01)
Total mortality	81	78	1.04 (0.88–1.22)
Global index	192	190	1.01 (0.91–1.12)
Stroke	44	32	1.39 (1.10–1.77), $P = 0.007$
Pulmonary embolism	13	10	1.34 (0.87–2.06)
Colorectal cancer	17	16	1.08 (0.75–1.55)
Hip fracture	11	17	0.61 (0.41–0.91), $P = 0.01$
Death, other causes	53	50	1.08 (0.88–1.32)

* CEE = conjugated equine estrogen.

tion, and whether they apply to younger menopausal women.

Dementia

Donepezil Produced Minimal Improvements in Cognition and Function in Persons with Alzheimer Disease

Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004;363:2105-15. [PMID: 15220031]

Much effort has been focused on finding a treatment for Alzheimer disease, and anticholinesterase inhibitors have been the most promising. These drugs produce small improvements in cognitive and global assessments in Alzheimer disease. In this study, the investigators wanted to measure the effects of the anticholinesterase inhibitor donepezil on functional outcomes: disability, dependence, behavioral and psychological symptoms, caregivers' psychological well-being, and delay in institutionalization. They also wanted to determine which patients were most likely to benefit and the most effective dose and duration of treatment.

The researchers enrolled 565 community-dwelling patients (mean age, 75 years) who had mild to moderate Alzheimer disease. During a 12-week run-in period, they randomly assigned these patients to receive either donepezil (5 mg/d) or placebo. The 486 patients who completed this period were then randomly assigned again to receive either donepezil (5 or 10 mg/d) or placebo. The double-blind treatment continued as long as judged appropriate. The 2 primary end points were entry into institutional care and the progression of disability as defined by loss of activities on the Bristol Activities of Daily Living Scale.

Over a 2-year follow-up, the investigators found that the treatment group scored slightly higher than the placebo group. With donepezil, cognitive scores on the Mini-Mental State Examination (Psychological Assessment Resources, Lutz, Florida) were, on average, 0.8 point higher ($P < 0.001$); functionality scores on the Bristol scale averaged 1.0 point higher ($P < 0.001$) with donepezil. Donepezil, however, had no effect on institutionalization, progression of disability, behavioral or psychological symptoms, caregiver stress, costs, adverse events, or death.

In summary, this helpful study demonstrated that anticholinesterase inhibitors may produce modest symptomatic improvements, but they probably do not alter the disease course. Donepezil is not cost-effective, and the benefits were below minimally relevant thresholds. Physicians should individualize the decision to treat and pay careful attention to clinical response and adverse effects. More effective treatments are needed.

Pulmonary Medicine

Tiotropium Improved Health Outcomes but Increased Cost in Patients with Chronic Obstructive Pulmonary Disease

Oostenbrink JB, Rutten van Molken MP, Al MJ, et al. One-year cost-effectiveness of tiotropium versus ipratropium to treat chronic obstructive pulmonary disease. Eur Respir J. 2004;23:241-9. [PMID: 14979498]

Chronic obstructive pulmonary disease is a disease generally characterized by irreversible airway obstruction. The effectiveness of the newer, once-daily bronchodilator tiotropium, however, has prompted some authors to consider a revised definition of chronic obstructive pulmonary disease. According to this more optimistic line of thought, the disease is characterized by "partially reversible" airway obstruction predominantly governed by cholinergic mechanisms. The authors of this paper wanted to learn the economic consequences of substituting the tiotropium for the older drug ipratropium in patients with the disease. They performed two 1-year randomized, double-blind clinical trials in the Netherlands and Belgium. The trials involved

535 current or former smokers with mild to moderate chronic obstructive pulmonary disease (ratio of FEV_1 to FVC, < 70%; FEV_1, ≤ 65% of predicted). The investigators assigned the patients in a 2:1 ratio to receive either a single daily dose of tiotropium (18 μg/d) or 2 puffs of ipratropium (20 μg administered 4 times daily).

At the end of 1 year, the investigators found that the mean frequency of exacerbations was slightly lower in the tiotropium group: 0.74 per patient ($n = 344$) versus 1.01 in the ipratropium group ($n = 175$). The tiotropium group also saw a greater improvement in quality of life; 52% had a clinically meaningful improvement on the St. George's Respiratory Questionnaire compared with 35% of the ipratropium group ($P = 0.001$). Also, hospital admissions and unscheduled office visits were significantly less among the tiotropium group.

The mean annual health care costs, including the cost of the study drugs, were €1721 in the tiotropium group and €1541 in the ipratropium group (difference, €180). Incremental cost-effectiveness ratios were €667 per exacerbation avoided and €1084 per patient with a relevant improvement on the St. George's Respiratory Questionnaire. The authors concluded that substituting tiotropium for ipratropium in patients with chronic obstructive pulmonary disease offered improved health outcomes at an increased cost of €180 per patient per year. The additional cost to use tiotropium was justified in terms of cost-effectiveness because it reduced exacerbation and improved lung function, dyspnea, and quality-of-life scores.

Prostate Cancer

Prostate Cancer Common among Men with "Normal" Prostate-Specific Antigen Levels

Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng per milliliter. N Engl J Med. 2004;350:2239-46. [PMID: 15163773]

The investigators wanted to determine the prevalence of prostate cancer among asymptomatic men with a prostate-specific antigen (PSA) level of 4.0 ng/mL or less. The study sample comprised enrollees in the randomized, controlled Prostate Cancer Prevention Trial. Of 18 882 men enrolled in the prevention trial, the investigators assigned 9459 to receive placebo and have an annual PSA measurement and a digital rectal examination. Among the cohort assigned to placebo, 2950 men (age range, 62 to 91 years; 94% white) who had never had a PSA level greater than 4.0 ng/mL or abnormal results on a digital rectal examination received a final PSA determination and underwent a prostate biopsy after being in the study for 7 years.

Prostate cancer was diagnosed in 449 (15.2%) men with serum PSA levels less than 4.0 ng/mL at baseline, 67 of whom had a Gleason score of 7 or higher (14.9% of the tumors, 2.9% of all men). All tumors were confined to the prostate (stage T1). The prevalence of prostate cancer and high-grade tumors increased proportionately with PSA level (**Table 3**). A family history of prostate cancer (OR, 1.39; $P = 0.01$) and an increase in PSA level (OR, 1.65 per 1.0-unit increase; $P < 0.001$) were positively associated with cancer risk. Black race (OR, 4.14; $P = 0.001$) and higher PSA levels (OR, 2.10 per 1.0-unit increase; $P < 0.001$) were associated with high-grade cancer.

In summary, false-negative results can occur regardless of the patient's PSA level, and biopsy-detected prostate cancer is not rare among men with PSA levels of 4.0 ng/mL or less. The implications for screening are unclear, but these results underlined the importance of discussing with patients—before testing—the known drawbacks of screening, including the potential for false-negative results. Results from the ongoing Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial funded by the National Cancer Institute will not be available for several years.

A PSA Increase of More than 2.0 ng/mL in the Year before Diagnosis of Prostate Cancer Translated to an Increased Risk for Cancer-Related Death

D'Amico AV, Chen MH, Roehl KA, et al. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med. 2004;351:125-35. [PMID: 15247353]

The investigators tried to use information available at diagnosis and surgery to identify men at especially high risk for death from prostate cancer after radical prostatectomy. The study involved 1095 men (median age, 65.4 years) with localized prostate cancer treated with radical prostatectomy. Each participant had been enrolled in a prospective cancer screening trial at Barnes-Jewish Hospital in St. Louis, Missouri. The investigators measured the rate of increase in the serum PSA level (the PSA velocity) during the year before diagnosis, the PSA level at diagnosis, the Gleason score, and the clinical tumor stage. They then assessed whether this information predicted the time to death from prostate cancer and death from any cause after

Table 3. **Prevalence of Prostate Cancer and the Proportion of High-Grade Tumors in Relation to Prostate-Specific Antigen Levels**

Prostate-Specific Antigen Level, *ng/mL*	Cancer Prevalence, %	Prevalence of Tumors with Gleason Score of ≥7, %
0–0.5	6.6	12.5
0.6–1.0	10.1	10.0
1.1–2.0	17.0	11.8
2.1–3.0	23.9	19.1
3.1–4.0	26.9	25.0

radical prostatectomy. According to the study protocol, the authors performed prostate biopsy if the PSA exceeded 2.5 ng/mL. Cancer was organ-confined for all men (stage T1c, 74%; stage T2, 29%), and the median PSA level was 4.3 ng/mL (43% had a PSA level of ≤4.0 ng/mL).

After a median of 5.1 years, 366 cancer recurrences and 84 deaths (27 attributed to prostate cancer) had occurred. A PSA velocity greater than 2.0 ng/mL in the year before radical prostatectomy was associated with a substantially shorter time to death from prostate cancer ($P < 0.001$) and death from any cause ($P = 0.01$). Within 7 years of diagnosis, up to 28% of men with a PSA velocity greater than 2.0 ng/mL per year had died of prostate cancer; in comparison, 3 of 833 men with a PSA velocity less than 2.0 ng/mL had died (median followup, 4.8 years). A PSA velocity greater than 2.0 ng/mL per year was also associated with the presence of lymph node metastases ($P < 0.001$), higher pathologic stage ($P < 0.001$), and high-grade cancer ($P = 0.03$). A PSA level greater than 10 ng/mL ($P < 0.001$), Gleason score of 8 to 10 ($P = 0.02$), and clinical tumor stage T2 ($P < 0.001$) were also associated with an increased rate of death from prostate cancer and death from any cause.

In summary, men whose PSA level increases more than 2.0 ng/mL in the year before diagnosis of prostate cancer may have a higher risk for dying of prostate cancer despite undergoing radical prostatectomy. If the predictive value of a high PSA velocity is confirmed in prospective cohort studies, this biomarker could help identify men who might benefit from other treatments in addition to radical prostatectomy.

Preventive Medicine

Vaccination against Human Papillomavirus Prevented Cervical Infection and Cytologic Abnormalities

Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet. 2004;364:1757-65. [PMID: 15541448]

Chronic infection with human papillomavirus (HPV) types 16 and 18 (HPV-16 and HPV-18) is responsible for up to 70% of cases of cervical cancer. The investigators designed this phase II randomized, controlled clinical trial to determine the efficacy and safety of a virus-like particle vaccine against HPV-16 and HPV-18. They randomly assigned 1113 women age 15 to 25 years (mean age, 20 years) to receive 3 doses of either the vaccine or placebo on a 0-month, 1-month, and 6-month schedule. At entry, the patients were free of HPV infection as determined by serologic tests and tests for cervical HPV DNA. Risk factors for HPV acquisition (smoking, number of sexual partners, and age of onset of sexual activity) were similar in both groups. Exclusion criteria included a history of more than 6 sexual partners, abnormal results on Papanicolaou tests or excisional treatment of the cervix, and ongoing treatment for external condylomata. The women were monitored for up to 27 months for HPV infection by using self-obtained cervicovaginal samples and cervical cytologic tests. Vaccine safety and immunogenicity were also evaluated during this time.

Vaccine efficacy was 91.6% against incidental cervical infection with HPV-16 or HPV-18 ($P < 0.001$) and 100% against persistent infection ($P = 0.007$). Vaccine efficacy was 93.5% ($P < 0.001$) against cytologic abnormalities associated with HPV-16 or HPV-18 infection.

Two women in the vaccine group and 27 in the placebo group had cytologic abnormalities associated with HPV-16 or HPV-18 infection. Three abnormalities were reported for the vaccine group: 1 instance of atypical squamous cells of undetermined significance and 2 cases of low-grade squamous intraepithelial lesions. The placebo group, in comparison, reported the following: 15 patients with atypical squamous cells of undetermined significance, 14 cases of low-grade squamous intraepithelial lesions, and 1 instance of high-grade squamous intraepithelial lesion. Cervical intraepithelial neoplasia developed in 6 women in the placebo group and 1 in the vaccine group. In the vaccinated woman with the neoplasm, the biopsy specimen contained HPV-51; in the unvaccinated women, the biopsy contained HPV-16.

No serious adverse vaccination-related events occurred, and the vaccine was highly immunogenic. At 7 months, 100% of vaccine recipients were HPV-16 seropositive and 99.7% were HPV-18 seropositive. At 18 months, 100% of recipients were seropositive against both HPV types. The level of antibody generated by vaccination was much higher than that induced by natural infection.

The study demonstrated that, at least over this defined time span, a virus-like particle vaccine was safe, immunogenic, and efficacious against persistent infection and cytologic abnormalities. The vaccine may be licensed soon and offers real promise for reducing cervical cancer incidence.

A Meta-Analysis of Trial Data Suggested that Vitamin D May Prevent Falls

Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA. 2004;291:1999-2006. [PMID: 15113819]

About 30% of people older than 65 years of age and 40% to 60% of people older than 80 years of age fall every year, frequently sustaining injuries as a result. In this meta-analysis, the investigators examined the role of vitamin D in preventing older people (mean age, 60 years) from falling. They analyzed relevant randomized, double-blind, controlled trials that involved the method of fall ascertainment

and definition of falls. They included 5 of 38 identified studies in the primary analysis and 5 other studies in a sensitivity analysis. Studies that enrolled patients who were in unstable health were excluded.

The primary analysis involved 5 randomized, controlled trials and 1237 participants. The trials lasted from 2 months to 3 years. Vitamin D was associated with reduced odds of falling (corrected OR, 0.78 [CI, 0.64 to 0.92]) compared with calcium or placebo. Fifteen patients would need to be treated with vitamin D to prevent 1 person from falling. There were insufficient data to formally test which dose of vitamin D would be most beneficial; however, individual trial results suggested that 800 IU was effective and 400 IU was not. In the sensitivity analysis, the authors included 5 additional studies involving 10 001 participants. The effect size was smaller but still significant (corrected relative risk, 0.87 [CI, 0.80 to 0.96]). The benefit from vitamin D occurred independently of formulation, calcium supplementation, duration of therapy, and patient sex. Because of the small sample sizes, the results for calcium supplementation and cholecalciferol were inconclusive.

In conclusion, vitamin D supplementation among ambulatory or institutionalized older individuals in stable health was associated with a 20% reduction in the risk for falls. The mechanism may relate to improved muscle function rather than stronger bones. The most effective dose of vitamin D is unknown, and further studies should examine the effect of alternative types of vitamin D and the role of calcium supplementation.

Early and Intensive Cigarette Use Linked to Highest Mortality among Smokers

Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004;328:1519. [PMID: 15213107]

In 1951, the investigators began gathering information on the smoking habits of 34 439 male British physicians. Their landmark publication in 1954 established the association of cigarette smoking with premature death. This follow-up study reported cohort outcomes at 50 years. Lifelong smokers died, on average, 10 years before lifelong nonsmokers. The earlier the age of smoking cessation, the more years of life expectancy gained: Cessation at age 60, 50, 40, or 30 years gained about 3, 6, 9, or 10 years of life expectancy, respectively. Thus, a person who stopped smoking at age 30 years regained all of the life expectancy that he would have lost had he continued smoking; the longer a person waited, the fewer years of life expectancy were regained by cessation. The findings are not surprising, but the length of time that the researchers followed these individuals and the landmark nature of their original report make the study findings noteworthy.

Conclusions

Our experience preparing this year's Update in General Internal Medicine leads us to several conclusions. First, the evidence base about the management of common, important general health problems continues to improve. Second, *medical management*—a term that has heretofore implied underlying ill health and a consignment to bad outcomes—had a potent effect on preventing CVD and reducing perioperative complications. Third, postmarketing surveillance to monitor long-term drug safety and effectiveness is a growing issue for internists and the general public. Finally, we were gratified to see victories for such common-sense approaches as exercise, self-monitoring, and smoking cessation.

From Harborview Medical Center and Group Health Cooperative, Seattle, Washington.

Potential Financial Conflicts of Interests: None disclosed.

Requests for Single Reprints: Eric B. Larson, MD, MPH, Group Health Cooperative, Center for Health Studies, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101-1448.

Current author addresses are available at www.annals.org.

References

1. **Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al.** Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227-39. [PMID: 15249516]

2. **Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ.** Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA. 2005;293:43-53. [PMID: 15632335]

3. **Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, et al.** Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet. 2005;365:475-81. [PMID: 15705456]

4. **Furberg CD, Psaty BM, FitzGerald GA.** Parecoxib, valdecoxib, and cardiovascular risk [Editorial]. Circulation. 2005;111:249. [PMID: 15655125]

5. **Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al.** Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004;291:2947-58. [PMID: 15213206]

6. **Espeland MA, Rapp SR, Shumaker SA, Brunner R, Manson JE, Sherwin BB, et al.** Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004;291:2959-68. [PMID: 15213207]

Current Author Addresses: Dr. Sheffield: Harborview Medical Center, Box 359782, 325 Ninth Avenue, Seattle, WA 98104.

Dr. Larson: Center for Health Studies, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101-1448.