

Update in General Internal Medicine

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This Update in General Internal Medicine incorporates a diverse range of topics that includes hormone replacement therapy, statins, exercise, hypertension, prostate cancer, diabetes care, and antioxidant vitamins. We compiled these articles with the help of our colleagues in the Department of Medicine at the University of Washington, Seattle, Washington, and the editors of *ACP Journal Club*.

Hormone Replacement Therapy

The big news in women's health in 2002 came from the Women's Health Initiative (WHI) report, which found that combined hormone replacement therapy (HRT) (estrogen plus progestin) exposes postmenopausal women to more risk than benefit. Before this report, most observational studies showed that HRT decreased risk for heart disease by as much as 35%. In retrospect, however, many of these studies did not control adequately for possible confounders, especially those related to major coronary risk factors and socioeconomic factors (1).

Combined Estrogen plus Progestin Replacement Therapy Increased Risk for Heart Disease and Breast Cancer among Postmenopausal Women with Intact Uteruses

Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-33. [PMID: 12117397]

The WHI recruited 16 608 healthy women who had intact uteruses and were 50 to 79 years of age (mean age, 63.3 years) from 40 U.S. clinical centers. Eighty-four percent of the women were white. The researchers conducted a randomized trial to determine the effects of HRT with combined estrogen plus progestin. Participants were randomly assigned to receive 0.625 mg of conjugated equine estrogens per day plus 2.5 mg of medroxyprogesterone per day in a single pill or placebo. Incident coronary disease and invasive breast cancer were primary outcomes. A global index summarizing risks and benefits for stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, and total mortality was a secondary outcome measure.

On the recommendation of the data and safety monitoring board, the trial was stopped after an average follow-up of 5.2 years because the risk for invasive breast cancer in the combined HRT group exceeded the predetermined termination threshold. (The threshold for stopping the study was low to avoid harming healthy women with a preventive treatment.) The combined HRT

group had higher rates of invasive breast cancer (38 events per 10 000 women compared with 30 events per 10 000 women in the placebo group) and coronary heart disease (CHD) (37 events per 10 000 women compared with 30 events per 10 000 women in the placebo group). The global index was also higher in the combined HRT group (hazard ratio, 1.15 [95% CI, 1.03 to 1.28]), and incidence of stroke and pulmonary embolism, in particular, was higher. The combined HRT group did, however, have lower rates of colorectal cancer and hip fracture. Total mortality was the same in the two groups. Overall, the findings were consistent across subgroups defined on the basis of age, ethnicity, risk status, and previous disease. Of interest, 42% of the women taking combined HRT stopped using it before the study was stopped, and 11% of women assigned to placebo crossed over to the HRT group. These protocol violations should tend to even out differences in the outcomes experienced by the HRT and placebo groups, which may mean that the observed outcomes are smaller than if the violations had not occurred.

In a related study (2), the WHI reported quality-of-life measures collected at baseline and at 1 year in all women and at 3 years in a subgroup of 1511 women. Combined HRT had no meaningful effect on health-related quality of life. Among women 50 to 54 years of age with moderate to severe vasomotor symptoms, combined HRT improved vasomotor symptoms and resulted in a small improvement in sleep disturbance but had no effect on other measures such as vitality, mental health, depression, and sexual satisfaction. Recently, the WHI reported a slight but statistically significant increase in dementia among users of combined HRT (3).

In summary, the landmark conclusion of the WHI's findings is that combined HRT should not be used to prevent disease in postmenopausal women with intact uteruses. Hormone replacement therapy may still be indicated, however, to control menopausal symptoms. For women considering combined HRT for this purpose, the WHI provides the best measure of risks and benefits, and the current recommended practice is to prescribe the lowest effective hormone dose for the shortest possible duration (4). An estrogen-only arm of this trial is ongoing.

Statins

Reports support expanded indications for statins among the population at high risk for a coronary event. Several noteworthy papers published in 2002 highlighted the safety of long-term statin use as well. One caveat to statin

use: Phillips and colleagues (5) reported that four patients taking statins experienced weakness due to statin-induced myopathy, a rare complication that did not occur in clinical trials despite large sample sizes. In practice, many patients report muscle symptoms while receiving statin therapy. This particular study was special because patients had normal creatine kinase levels, improved while not taking statin therapy, and had specific microscopic findings on muscle biopsy. When patients report severe myalgia, a trial period off therapy is indicated.

Simvastatin Reduced Mortality and Vascular Events in Patients at High Risk for Cardiovascular Disease

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. [PMID: 12114036]

This large, randomized trial from the United Kingdom's Heart Protection Study Collaborative Group aimed to determine whether adding simvastatin to current therapy in patients with an elevated 5-year risk for coronary death would reduce all-cause mortality and improve outcomes. The authors enrolled 20 536 adults, age 40 to 80 years, with coronary disease, noncoronary atherosclerosis, or diabetes mellitus. The mean baseline cholesterol level was 5.91 mmol/L (228 mg/dL), and the mean low-density lipoprotein cholesterol level was 3.39 mmol/L (131 mg/dL). Participants were randomly assigned to receive 40 mg of simvastatin daily or placebo.

The benefits of therapy became apparent after about 2 years. After 5 years, overall mortality was significantly reduced among the simvastatin group compared with the placebo group (12.9% vs. 14.7%; number needed to treat for benefit [NNT_B], 56) because of a highly significant reduction in the coronary disease death rate and a marginally significant reduction in other vascular deaths. Of note, the incidence of the first major vascular event (myocardial infarction, stroke, or revascularization) was 19.8% in the simvastatin group and 25.2% in the placebo group (NNT_B, 18 to 22), a proportionate reduction that was consistent across subgroups defined on the basis of age, sex, history of coronary disease, and baseline cholesterol level. Of importance, this reduction in risk occurred both in the 3421 high-risk patients with a baseline low-density lipoprotein cholesterol level lower than 2.59 mmol/L (100 mg/dL) and the 3982 diabetic persons without coronary disease. Furthermore, statin therapy had no apparent adverse effects, including no excess myalgias, myopathy, hepatitis, or cancer. Statins had no effect on cognitive decline or osteoporosis.

In summary, patients with a high 5-year risk for CHD, including all patients with coronary disease regardless of baseline cholesterol level, patients with noncoronary atherosclerosis, and patients with diabetes without coronary disease, could benefit from adding a statin to existing treatment.

Pravastatin Therapy Reduced Mortality and Cardiovascular Events without Adverse Effects

Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. *Lancet*. 2002;359:1379-87. [PMID: 11978335]

This follow-up from the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study showed that pravastatin therapy reduced mortality and cardiovascular events and had no adverse effects in patients with a history of acute coronary syndromes. As in the Heart Protection Study, the benefits of statin therapy began to appear at about 2 years. In addition, this study, which has the longest documented follow-up of a statin-therapy cohort to date, indicates that statins are safe for up to at least 8 years.

Statins Were Effective and Safe for Elderly, High-Risk Patients

Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623-30. [PMID: 12457784]

This study, which enrolled 5804 patients 70 to 82 years of age with a history of or risk factors for vascular disease, aimed to investigate the safety and efficacy of statins in high-risk patients older than age 70 years. After 3.2 years, pravastatin reduced the incidence of coronary death or nonfatal myocardial infarction (10.1% vs. 12.2%; NNT_B, 48) in patients with previous coronary disease and elevated cholesterol levels. Of note, pravastatin did not reduce event rates for patients without previous coronary disease or patients with average cholesterol levels. Side effects appeared insignificant. Overall, the results support a secondary prevention strategy that includes giving statins to older, high-risk patients if indicated under current National Cholesterol Education Program guidelines (6) and if reasonable according to prognosis and patient preference.

Exercise

For years, research has suggested advantages from regular exercise. In 2002, several papers convincingly showed that exercise can play an important role in both the prevention and management of diabetes mellitus and slow the rate of functional decline in elderly persons. The aging of the U.S. population and the growing rates of obesity and type 2 diabetes mellitus make these findings especially important.

Exercise Reduced Disease Incidence and Improved Disease Management

Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403. [PMID: 11832527]

The Diabetes Prevention Project-2 (DPP-2) used a very strategic and highly selective enrollment process. Researchers began with more than 158 000 potential participants, of whom they tested almost 31 000 and enrolled 3234. Participants were nondiabetic persons (mean age, 51 years), 68% were women, and 45% were members of minority groups. All had risk factors for type 2 diabetes mellitus, including elevated fasting and postload plasma glucose concentrations. The enrollees had a body mass index of at least 24 kg/m² (mean, 34 kg/m²) and a generally sedentary lifestyle. Participants were randomly assigned to three groups: a lifestyle modification program, metformin (850 mg twice daily), or placebo.

The goals of the lifestyle intervention were a 7% reduction in body weight and 150 minutes of physical activity, such as brisk walking, per week. Participants received one-on-one instruction on how to change diet, exercise, and behavior through a 16-week curriculum. If participants did not meet goals after the first round, they repeated the instructional program. At 24 weeks, half of the participants in the lifestyle intervention group had reached the weight loss goal and 74% were meeting the exercise goal. These numbers declined somewhat over time, but they remained higher than baseline throughout follow-up.

After 2.8 years of follow-up, the incidence of diabetes per 100 person-years was 4.8 in the lifestyle group, 7.8 in the metformin group, and 11.0 in the placebo group. The lifestyle program and metformin reduced diabetes incidence by 58% (NNT_B, 7) and 31% (NNT_B, 14), respectively, compared with placebo. The lifestyle program was effective across all subgroups, including age, sex, and ethnicity. In summary, lifestyle intervention and metformin reduced the incidence of diabetes during a 2.5-year period. These results confirm those of a previous study (7).

Exercise Prevented Functional Decline in Frail, Elderly Patients

Gill TM, Baker DI, Gottschalk M, et al. A program to prevent functional decline in physically frail, elderly persons who live at home. *N Engl J Med*. 2002;347:1068-74. [PMID: 12362007]

The authors hoped to determine whether functional decline, which is associated with substantial morbidity in elderly persons, could be prevented with exercise. They randomly assigned 188 physically frail, home-dwelling patients (≥ 75 years of age) to a 6-month program of active physical rehabilitation focusing on physical impairments in balance, strength, ability to transfer, and mobility or to an educational program (as a control). In the exercise group, patients performed resistive exercises designed to strengthen major muscles in the lower and upper extremities.

At 7 and 12 months, patients in the exercise group had significantly reduced rates of functional decline, according to disability scores, compared with controls. The exercise benefited participants with moderate frailty but not those with severe frailty or cognitive impairments. The frequency

of admission to a nursing home did not differ significantly between the two groups. This study suggests, however, that many elderly patients living at home can benefit from vigorous physical rehabilitation.

In summary, the studies published in 2002 add to mounting evidence that exercise can reduce the incidence of diabetes among persons at risk; ameliorate functional decline; and have beneficial effects in persons with and at risk for cardiovascular disease, osteoporosis, hypertension, and obesity. Practitioners are left to consider how best to promote behavioral change for their patients. To date, the U.S. Preventive Services Task Force has concluded that there is insufficient evidence to determine whether counseling patients to promote physical activity helps prevent disease (8).

Hypertension

Hypertension is a perennial Update topic. This year, the results of a major portion of the Antihypertensive and Lipid Lowering Treatment To Prevent Heart Attack Trial (ALLHAT) increased our certainty that thiazide diuretics are the generally preferred first-line agent for treatment of hypertension. Thiazides reduce blood pressure effectively, result in fewer major cardiovascular events, and are inexpensive. Overall mortality and major CHD outcomes are similar with diuretics, calcium-channel blockers, and angiotensin-converting enzyme (ACE) inhibitors.

Thiazide Diuretics Are the Most Effective Class for Reducing Hypertension-Related Morbidity

Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-97. [PMID: 12479763]

In ALLHAT, a thiazide diuretic was compared with an ACE inhibitor or calcium-channel blocker for reduction of incidence of CHD or other cardiovascular disease events. The 6-year multicenter trial enrolled 33 357 participants 55 years of age or older with hypertension (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or taking antihypertensive medication) and at least one other risk factor for CHD. The participants were randomly assigned to receive a diuretic (chlorthalidone), a calcium-channel blocker (amlodipine), or an ACE inhibitor (lisinopril). After a mean follow-up of 4.9 years, the rates of primary outcomes, total mortality, and combined fatal CHD and nonfatal myocardial infarction were the same in all three groups. The rate of congestive heart failure (CHF) was higher with amlodipine than with chlorthalidone. Rates of cardiovascular disease and CHF were

higher with lisinopril than with chlorthalidone, particularly among black persons. Metabolic side effects, including hypokalemia, elevated cholesterol levels, and new-onset type 2 diabetes mellitus, were more frequent with chlorthalidone.

In summary, thiazide-type diuretics such as chlorthalidone are superior to ACE inhibitors or calcium-channel blockers in preventing major CVD events. They are also less expensive. Therefore, thiazide diuretics should be the preferred first-line treatment for hypertension. If blood pressure control is inadequate after first-line treatment with another agent, a thiazide should be the preferred second step.

An ACE Inhibitor Was Slightly More Effective Than a Thiazide Diuretic for Initial Treatment of Hypertension in White Men

Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting—enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med.* 2003;348:583-92. [PMID: 12584366]

This study presents a contrast to ALLHAT. The Australian National Blood Pressure Study-2 (ANBP-2), an open-label trial conducted in more than 1500 family practices, enrolled more than 6000 patients 65 to 84 years of age, 50% of whom were women, who had untreated hypertension. Patients were randomly assigned to initial treatment with either a thiazide diuretic or an ACE inhibitor. After random assignment to one of these drug categories, the general physician selected a specific thiazide or ACE inhibitor. Hydrochlorothiazide was the most commonly used diuretic, and enalapril was the most commonly used ACE inhibitor. Overall, participants in ANBP-2 were more active and had fewer major risk factors for CHD than the ALLHAT population (Table 1). Only 5% of patients enrolled in ANBP-2 were black, in contrast to 32% in ALLHAT.

Table 1. Comparison of Key Characteristics of the Antihypertensive and Lipid Lowering Treatment To Prevent Heart Attack Trial and the Australian National Blood Pressure Study-2*

Characteristic	ALLHAT	ANBP-2
Trial design	Randomized, double-blind	Randomized, open-label
Enrollment, <i>n</i>	33 357	6083
Black ethnicity, %	32	5
Disease end points, <i>n</i>		
Cardiovascular disease	6455	823
Coronary disease	3956	368
Congestive heart failure	1482	147
Group for which the main trial results were significant	All subgroups	Men only

* ALLHAT = Antihypertensive and Lipid Lowering Treatment To Prevent Heart Attack Trial; ANBP-2 = Australian National Blood Pressure Study-2.

Both treatments reduced blood pressure effectively, and the two groups had the same rates of all-cause mortality. Treatment with the ACE inhibitor resulted in a lower rate of combined cardiovascular events because of a highly significant reduction in cardiovascular events in men. Overall rates of CHD events, congestive heart failure, and stroke were the same in the two groups. An ACE inhibitor appeared to be somewhat more effective than a thiazide diuretic for initial treatment in this active, elderly population, but further study is required to determine whether this benefit is confined to men.

Ethnic differences in response to antihypertensive drugs are likely to explain the slightly discrepant results of ALLHAT and ANBP-2 (Table 1). African-American persons respond particularly well to treatment with thiazide diuretics and experience less reduction in blood pressure and less preservation of left ventricular function with ACE inhibitors than white patients (9). The recently published Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension favors thiazide diuretics for initial treatment in the absence of compelling indications to use other agents (10), but physicians clearly have many effective options for treating individual patients.

Losartan Proved More Effective for the Treatment of Hypertension in High-Risk Patients with Left Ventricular Hypertrophy

Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet.* 2002;359:995-1003. [PMID: 11937178]

Lindholm LH, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet.* 2002;359:1004-10. [PMID: 11937179]

Kjeldsen SE, Dahlof B, Devereux RB, et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. *JAMA.* 2002;288:1491-8. [PMID: 12243636]

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) studies compared the effects of angiotensin-receptor blockers and β -blockers in patients with hypertension and left ventricular hypertrophy by using electrocardiographic criteria. In the main study, 9193 participants age 55 to 80 years (mean age, 67 years), 92% of whom were white, were randomly assigned to receive losartan-based or atenolol-based antihypertensive treatment for at least 4 years. The other two reports described results in subgroups: patients with diabetes and patients with isolated systolic hypertension.

After a mean follow-up of 4.7 years, blood pressure reduction was similar with both treatments, but the losar-

tan group had a lower incidence of the composite outcome of cardiovascular death, myocardial infarction, or stroke (508 events with losartan vs. 588 with atenolol; hazard ratio, 0.87 [CI, 0.77 to 0.98]) because of a significant reduction in the incidence of stroke with losartan in all subgroups. In the diabetes subgroup, all-cause mortality was significantly lower with losartan (11% vs. 17%; hazard ratio, 0.61 [CI, 0.45 to 0.84]). More regression of left ventricular hypertrophy, fewer new cases of diabetes, and fewer adverse effects leading to drug withdrawal occurred with losartan than with atenolol. In summary, these studies demonstrate that angiotensin-receptor blockade is more effective and better tolerated than β -adrenergic receptor blockade for the treatment of hypertension in the high-risk group of patients with left ventricular hypertrophy.

Cardiology

We focused on two cardiology articles that have had an important impact on medical practice. One study examined B-type natriuretic peptide (BNP) levels as a test for left ventricular dysfunction. The other compared the effectiveness of rate-control and rhythm-control management strategies for atrial fibrillation in older persons.

BNP Levels Are Useful for Diagnosis of CHF in Patients with Acute Dyspnea

Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med.* 2002;347:161-7. [PMID: 12124404]

In this prospective, international study of 1586 emergency department patients with acute dyspnea (average age, 64 years; 44% women), the investigators measured BNP levels at presentation. Two independent cardiologists who were blinded to BNP test results but had access to all other clinical information assigned final diagnoses. Patients were excluded from the study if their dyspnea was clearly not the result of heart failure or if they had acute myocardial infarction or renal failure.

Final diagnoses were acute CHF in 47% of patients, noncardiac dyspnea with baseline left ventricular dysfunction in 5%, and no CHF in 49% (percentages have been rounded). Mean BNP levels differed significantly by group (acute CHF, 675 pg/mL; noncardiac dyspnea with baseline left ventricular dysfunction, 346 pg/mL; no CHF, 110 pg/mL) and correlated with disease severity. In addition, BNP proved to be the most accurate predictor of acute CHF; a BNP level greater than 100 pg/mL had 90% sensitivity and 76% specificity. Cardiomegaly on chest radiography was the next best predictor, followed by history of CHF and rales on examination.

In summary, BNP was the most accurate clinical pre-

dictor of left ventricular dysfunction in patients presenting with acute dyspnea, and levels correlated with disease severity. Levels of BNP also increase in response to increases in right ventricular end-diastolic pressure, which may occur in pulmonary parenchymal disease or pulmonary vascular diseases. Further experience will inform us about shortcomings of this new test. Meanwhile, BNP testing can help us improve diagnostic judgments when the cause of dyspnea cannot be clearly determined by other clinical factors.

Rate-Control Therapy Was as Effective as Rhythm Control in Patients with Recurrent Atrial Fibrillation, with Fewer Adverse Events

Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347:1825-33. [PMID: 12466506]

In this randomized, controlled trial, the authors compared the effectiveness of rhythm control and rate control in 4060 patients with atrial fibrillation who were at least 65 years of age (mean age, 70 years). Thirty-nine percent of patients were women, and 89% were white. Inclusion criteria included the judgment that atrial fibrillation was likely to recur or require long-term treatment and a history indicating a high risk for stroke or death. At baseline, 65% of patients had recurrent fibrillation that had been present for more than 2 days and less than 6 weeks, and 70% had hypertension. In 3311 patients with echocardiograms available at baseline, 65% had left atrial enlargement and 26% had left ventricular dysfunction.

All patients were in atrial fibrillation at the outset of the study. In the rate-control group, β -blockers, calcium-channel blockers, and digoxin were used individually or in combination to achieve a resting heart rate of less than 80 beats/min and an ambulatory heart rate of less than 110 beats/min. Cardioversion was not used. All patients received warfarin to achieve an international normalized ratio of 2 to 3. In the rhythm-control group, antiarrhythmic drugs were prescribed and cardioversion was used as necessary to achieve sinus rhythm. Anticoagulation was recommended but could be discontinued if sinus rhythm was maintained for 4 to 12 weeks. Intention-to-treat analysis based on original assignment was used.

At 3.5 years, a trend toward increased mortality with rhythm control (28% vs. 21%; hazard ratio, 1.15 [CI, 0.99 to 1.34]) persisted after adjustment for major risk factors. Certain subgroups had a notably higher risk for death with rhythm control, including patients without CHF or known CHD. When the study ended after 5 years, 63% of the rhythm-control patients were in sinus rhythm compared with 35% in the rate-control group. Over the course of the study, more rhythm-control patients were hospitalized, and rhythm-control patients also experienced more adverse drug effects (41% vs. 17%; $P < 0.01$).

Stroke rates were identical—8.2%—in both groups, and stroke was not restricted to people in atrial fibrillation. In fact, 69% of patients in the rhythm-control group and 45% of patients in the rate-control group were in sinus rhythm at the time of their stroke. Most strokes in the rhythm-control group occurred after anticoagulation had been discontinued; anticoagulation was often subtherapeutic at the time of a stroke in the rate-control group. A European trial involving 522 patients with persistent atrial fibrillation (11) reported similar results in 2002, as did the earlier Pharmacological Intervention in Atrial Fibrillation (PIAF) trial (12).

In summary, older patients with recurrent atrial fibrillation and risk factors for stroke fare at least as well when managed with a rate-control strategy as with rhythm control. The rate-control strategy has advantages, such as a lower risk for adverse drug effects and, probably, ease of implementation. In addition, anticoagulation should be continued for longer than 12 weeks (and perhaps indefinitely) after return of sinus rhythm. These results are probably not generalizable to younger patients without structural heart disease and may not apply to patients with a first episode of atrial fibrillation, but they are likely to affect the vast majority of patients with atrial fibrillation seen in general internal medicine practice.

Prostate Cancer

We were particularly interested in a study of the treatment of localized prostate cancer, since radical prostatectomy is widely performed but its impact on survival is unclear.

Radical Prostatectomy for Localized Cancer Reduced Disease-Specific Mortality but Doubled Risk for Erectile Dysfunction and Incontinence

Holmberg L, Bill-Axelsson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med.* 2002;347:781-9. [PMID: 12226148]

The Scandinavian Prostatic Cancer Group conducted a randomized trial to measure the efficacy of radical prostatectomy as treatment for localized prostate cancer. The investigators enrolled 695 men younger than 75 years of age (mean age, 64.7 years) with newly diagnosed prostate cancer (stage T1b, T1c, or T2) from October 1989 through February 1999 and followed them through 2000. Of these men, 75% were described as having palpable tumors; only 5% received a diagnosis through prostate-specific antigen screening. Exclusion criteria included extreme elevation of prostate-specific antigen levels, poorly differentiated cancer, or urinary obstruction. Participants were randomly assigned to watchful waiting or radical prostatectomy.

After 6 years, the rate of prostate cancer death (4.6%

vs. 8.9%; hazard ratio, 0.5 [CI, 0.77 to 0.91]; NNT_B, 23) and risk for distant metastases (10.1% vs. 15.5%) were significantly lower in the surgery group compared with the watchful waiting group, but there was no effect on overall survival. In an accompanying report (13), the group surveyed 87% of the participants about quality-of-life measures. The prevalences of erectile dysfunction (80% vs. 45%) and incontinence (49% vs. 21%) were significantly higher in the surgery group (the surgeons did not use a nerve-sparing technique), and the prevalence of obstructive symptoms was significantly lower after surgery (28% vs. 44%). Overall, quality-of-life ratings were similar in the two groups, as were ratings of depression and anxiety.

In summary, radical prostatectomy for localized disease reduced disease-specific mortality and risk for metastasis but resulted in very high rates of erectile dysfunction and incontinence. Quality-of-life ratings were similar, as was overall mortality. Management decisions regarding localized prostate cancer remain complicated, but this paper provides useful information for patients and physicians. The implications for prostate cancer screening are also unclear, and the U.S. Preventive Services Task Force concludes that there is still insufficient evidence to recommend for or against routine screening for prostate cancer using prostate-specific antigen (14).

Diabetes Care

Two papers with implications for the management of diabetes mellitus caught our attention. The first studied the effect of varying the timing of long-acting insulin administration, and the second studied a multifactorial intervention to prevent vascular disease in patients with type 2 diabetes mellitus and microalbuminuria.

Administering Long-Acting Insulin at Bedtime Reduced Risk for Hypoglycemia

Fanelli CG, Pampanelli S, Porcellati F, et al. Administration of neutral protamine Hagedorn insulin at bedtime versus with dinner in type 1 diabetes mellitus to avoid nocturnal hypoglycemia and improve control. A randomized, controlled trial. *Ann Intern Med.* 2002;136:504-14. [PMID: 11926785]

This open-label crossover trial randomly assigned 22 patients with type 1 diabetes mellitus (mean age, 29 years) but no apparent microvascular complications to one of two insulin regimens for 4 months, then switched them to the other regimen for another 4 months. One regimen was a mixed treatment in which human regular and neutral protamine Hagedorn (NPH) insulin were administered before dinner, and the other was a split treatment in which human regular insulin was administered before dinner and NPH insulin was administered at bedtime. At the end of

each 4-month period, the participants were admitted to a metabolic ward for overnight glucose monitoring and assessment of counterregulatory and cognitive responses to stepwise insulin infusion.

Nocturnal hypoglycemia was considerably less frequent when NPH insulin was administered at bedtime compared with before dinner (mean [\pm SE], 0.10 ± 0.02 episode per patient-day vs. 0.28 ± 0.04 episode per patient-day). Bedtime administration also resulted in lower fasting blood glucose levels (mean [\pm SE], 7.6 ± 0.2 mmol/L vs. 8.3 ± 0.5 mmol/L [137 ± 4 mg/dL vs. 160 ± 8 mg/dL]; $P = 0.030$), less variable fasting blood glucose levels (SD range, 2.0 ± 0.4 vs. 3.5 ± 0.6 ; $P = 0.001$), and lower hemoglobin A_{1c} values (mean [\pm SE], $7.0\% \pm 0.11\%$ vs. $7.5\% \pm 0.15\%$; $P = 0.004$) than predinner administration. Furthermore, patients had better awareness of hypoglycemia and their sympathetic and autonomic responses to hypoglycemia increased earlier after the 4-month period of bedtime NPH insulin administration than after the period of predinner administration. Cognitive function declined during hypoglycemia to the same degree after both treatment periods.

In summary, administering long-acting insulin at bedtime reduces the frequency of nocturnal hypoglycemia and results in better overall glycemic control and autonomic responses to hypoglycemia than predinner administration. These results confirm long-standing conventional wisdom that administering long-acting insulin at bedtime is a safer and more effective way to control fasting blood glucose levels. The use of glargine instead of NPH insulin at bedtime and insulin lispro instead of regular insulin at dinner could further reduce risk for nocturnal hypoglycemia.

Lifestyle Interventions Reduced Morbidity in Type 2 Diabetes Mellitus

Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med.* 2003;348:383-93. [PMID: 12556541]

Investigators randomly assigned 160 Danish patients (mean age, 55 years) with type 2 diabetes and microalbuminuria to conventional treatment according to their general practitioners or to a multifactorial intervention with aggressive goals for lifestyle, blood pressure, glycemic con-

Table 2. Treatment Goals for Intensive Therapy in the Steno-2 Study

Goal Category	Description
Lifestyle	Fat intake <30% of total calories Exercise 30 min, 3–5 times/wk Smoking cessation
Blood pressure	<130/80 mm Hg
Glycosylated hemoglobin level	<6.5%
Fasting total cholesterol level	<175 mg/dL (<4.53 mmol/L)
Fasting triglyceride levels	<150 mg/dL (<1.7 mmol/L)

trol, and lipids (Table 2). All patients in the intensive therapy group received an ACE inhibitor (captopril, 50 mg twice daily, or dose equivalent) and aspirin, 150 mg/d. The primary end point was a composite of cardiovascular death, myocardial infarction, stroke, revascularization, or amputation.

At a mean follow-up of 7.8 years, 44% of the participants in the conventional treatment group experienced a macrovascular disease end point compared with 24% in the intensive therapy group (hazard ratio, 0.47; NNT_B, 5). Microvascular complications (with the exception of peripheral neuropathy) also developed at significantly higher rates in the conventional group (NNT_B for 7.8 years to prevent one case of nephropathy, retinopathy, and autonomic neuropathy was 3 to 4). The largest differences in clinical variables achieved between the two treatment groups were lower systolic blood pressure and total cholesterol concentration in the intensive therapy group. The intensive therapy group also achieved slight but significantly greater decreases in glycosylated hemoglobin values, diastolic blood pressure, and triglyceride levels than the conventional therapy group. Body mass index, total energy intake, and total weekly exercise did not differ between groups.

In summary, a multifactorial intervention designed to achieve aggressive goals for lifestyle, blood pressure, glycemic control, and lipids is a potent way to reduce risk for vascular complications in patients with type 2 diabetes mellitus and microalbuminuria.

Antioxidant Vitamins

In 2002, many negative trials of commonly used herbal treatments and vitamin supplements were published. In the space available, we summarize results indicating that antioxidant vitamins do not prevent vascular or other diseases. In addition, we note that St. John's wort had no effect on major depression (15), echinacea was ineffective for treatment of the common cold (16), and ginkgo did not enhance memory (17).

Antioxidants Failed To Have Any Effect on Morbidity or Mortality

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. [PMID: 12114037]

A second aim of the Heart Protection Study was to assess the effect of antioxidant vitamins on the incidence of vascular disease, cancer, and other adverse outcomes. As described in the Statins section, this large study involved 20 536 adults age 40 to 80 years with CHD, other arterial disease, or diabetes. The participants were randomly assigned daily antioxidant vitamin supplementation (vitamin

E, 600 mg; vitamin C, 250 mg; and β -carotene, 20 mg) or placebo. After 5 years, participants assigned to take supplements had higher plasma concentrations of vitamin E, vitamin C, and β -carotene, but the groups had the same all-cause mortality, vascular events, incident cancers, hospitalization rates, tests of pulmonary function, and cognitive function. There were also no adverse effects.

A related study, the Women's Angiographic Vitamin and Estrogen (WAVE) trial (18), also assessed the effects of antioxidant vitamin supplementation. In this trial, 423 postmenopausal women with at least one coronary stenosis were randomly assigned in a 2×2 factorial design to receive combined HRT, antioxidant vitamin supplementation (vitamin E, 400 IU twice daily, and vitamin C, 500 mg twice daily), both, or placebo. After 2.8 years, neither HRT nor antioxidant vitamins affected angiographic progression, and there was a suggestion of harm with each treatment. Death, nonfatal myocardial infarction, or stroke occurred in 26 patients in the vitamin group and 18 patients in the control group (hazard ratio, 1.5 [CI, 0.8 to 2.9]).

According to the findings of these two studies, antioxidant vitamin supplementation does not prevent vascular disease in high-risk adults and should not be used.

Vitamin E Increased Severity of Respiratory Infections in Elderly Patients

Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA*. 2002;288:715-21. [PMID: 12169075]

This trial randomly assigned 652 noninstitutionalized adults age 60 years and older (mean age, 73 years) to receive vitamin E, 200 mg; multivitamin-mineral supplements; both; or placebo in a double-blind, 2×2 factorial trial. Neither treatment reduced the frequency of infections, but illness severity was worse with vitamin E, including more symptoms, more fever, and greater restriction of activity.

Conclusions

Our experience preparing this year's Update in General Internal Medicine leads us to several conclusions. First, the evidence base has improved for the management of major, common problems. For combined HRT, we have experienced a sea change. Second, for studies involving drugs, widespread public awareness of results occurs rapidly and provides a major impetus to physicians to become informed about potential implications for practice. Third, the most potent interventions, based on NNT_B , affect patients at especially high risk, are complex, and involve be-

havioral change (for example, lifestyle programs to prevent diabetes) and intensive risk factor modification (for example, multifactorial intervention to prevent vascular disease in patients with type 2 diabetes and microalbuminuria). Successful implementation of these potent therapies will often require a team approach and, especially, the active involvement of informed patients to achieve shared goals. Realizing the potential impact of these complex interventions in everyday practice is a major challenge for office practitioners. Finally, areas of great uncertainty, such as screening for prostate cancer, remain, and we look forward to the results of ongoing trials for the guidance they might provide.

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The possibilities and probabilities are all we have to work with in medicine, though. What we are drawn to in this imperfect science, what we in fact covet in our way, is the alterable moment—the fragile but crystalline opportunity for one's know-how, ability, or just gut instinct to change the course of another's life for the better. In the actual situations that present themselves, however—a despondent woman arrives to see you about a newly diagnosed cancer, a victim bleeding from a terrible injury is brought pale and short of breath from the scene, a fellow physician asks for your opinion about a twenty-three-year-old with a red leg—we can never be sure whether we have such a moment or not. Even less clear is whether the actions we choose will prove either wise or helpful. That our efforts succeed at all is still sometimes a shock to me. But they do. Not always, but often enough.

Atul Gawande
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