PRACTICAL POINTERS
FOR
PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

MARCH 2004

JAMA, NEJM, BMJ, LANCET

ARCHIVES INTERNAL MEDICINE

ANNALS INTERNAL MEDICINE

PUBLISHED BY PRACTICAL POINTERS, INC.

EDITED BY RICHARD T. JAMES JR. MD

400 AVINGER LANE, SUITE 203

DAVIDSON NC 28036 USA

Rjames6556@aol.com

www.practicalpointers.org

HIGHLIGHTS AND *EDITORIAL COMMENTS* MARCH 2004

3-1 ACTUAL CAUSES OF DEATH IN THE UNITED STATES, 2000

This article defines the "actual" causes of death as underlying-modifiable-behavioral risk factors which predispose to the "disease" which is labeled as the cause of death

About half of all deaths could be attributed to a limited number of largely preventable behaviors: tobacco, poor diet and physical inactivity, alcohol, firearms, sexual behavior, and illicit drug use.

Interventions to prevent and increase cessation of smoking, improve diet, and increase physical activity must become a much higher priority in the public health and health care systems.

The most striking finding is the substantial increase (to about 400 000) in the number of estimated deaths attributable to poor diet and physical inactivity. The gap between deaths due to poor diet and inactivity and those due to smoking has narrowed substantially. "It is clear that if the increasing trend of overweight is not reversed over the next few years, poor diet will likely overtake tobacco as the leading cause of mortality."

In addition to premature death, years of lost life, diminished productivity, and decreased quality of life are strongly associated with the actual causes.

One important cause of death not directly related to obesity is the deficiency of calcium and vitamin D in the American diet. This leads eventually to death and disability as a complication of hip and other fractures.

Primary care clinicians bear a responsibility and opportunity to: 1) follow a healthy lifestyle themselves as an example to patients, and 2) to constantly encourage patients to do likewise. RTJ

3-2 THE IMMEDIATE VS THE IMPORTANT

"One of the most difficult challenges is to ensure that the urgent does not crowd out the important. That challenge is especially difficult because urgent matters can be so riveting."

Every death has a definable history that usually can be traced back to decades and sometimes even generations. Reporting of deaths, diseases and disabilities in traditional diagnostic categories tend to obscure the importance of factors that often play determinant antecedent roles in the occurrence of reported conditions. When it comes to ranking health problems and committing resources, attention seems more naturally drawn to the conditions most proximate to serious illness or death.

3-3 EVALUATION OF CARDIOVASCULAR EVENT RATES WITH HORMONE THERAPY IN HEALTHY, EARLY POSTMENOPAUSAL WOMEN

Two large randomized trials have evaluated effects of hormone replacement therapy **(HRT)** in postmenopausal women.

The average age of the subjects in these two studies was 63 years, well past onset of the menopause. Overall, the studies concluded that HRT results in net *harms*. . The greatest risk of adverse effects occurred in the first year.

This was contrary to older *observational* studies which reported considerable benefit in reducing cardiovascular morbidity and mortality. It led to reevaluation of the use of HRT.

It is important to determine if adverse events occur in *younger* women. Most women with menopausal symptoms take HRT at an earlier age, relatively soon after the menopause. This article reviewed 2 other large clinical trials of younger women (mean age 54). It asks—What is the risk of adverse events at this age?

Conclusion: In young, healthy postmenopausal women, the adverse effects of HRT *in the first year* of use were no greater than the expected harms in women not taking HRT.

What should primary care clinicians advise their patients about HRT?

A. *Risks of adverse events during the first few perimenopausal years are low in younger, healthier women taking combined HRT, and even lower in those taking estrogen alone.*
B. *These risks can be further reduced by therapy aimed at reducing cardiovascular risk: smoking cessation, low-dose aspirin; lipid, weight, and BP control; and using the lowest effective dose of estrogen and progesterone. Indeed, I believe it likely that women who, at the age of 50 adopt these protective measures and take HRT will be less likely to experience cerebrovascular events than women who do not take HRT and do not adopt these protective measures.*

I believe that recent reports overemphasized the adverse effects of HRT, and that many women who would benefit by symptom relief are being denied treatment. RTJ

3-4 CARDIOVASCULAR PROGNOSIS OF "MASKED HYPERTENSION" DETECTED BY BLOOD PRESSURE SELF-MEASUREMENT IN ELDERLY TREATED HYPERTENSIVE PATIENTS.

There are numerous criticisms of clinical BP measurement. Major inter- and intra-observer variability exist. There are difficulties with standardization of the measurement conditions, and insufficiency in the number of measurements. Office BP fails to recognize the patient's average daily BP.

In this study, home BP self-measurement defined the prognosis in terms of cardiovascular morbidity and mortality better than office measurement. This was due in part to the poor performance of office BP measurements.

The study reported a high prevalence of two classes of patients with hypertension not recognized by BP measurements confined to the office: 1) "White coat" hypertension (office BP higher than home BP); 2) "Masked" hypertension (the opposite - home BP higher than office BP). "The frequency of this double error, which is both diagnostic (with respect to the control of hypertension), and prognostic (with respect to the incidence of cardiovascular events), suggests that monitoring of patients being treated for hypertension must include home BP self measurement."

"Masked" hypertension was associated with a statistically significant increase in risk of adverse cardiovascular events. Indeed, the risk over 3 years was about the same as the group with uncontrolled hypertension. It remains to be seen, however, that adaptation of *treatment* to the results of home BP self-measurement allows better cardiovascular prevention than *treatment* based on office BP.

Although, as the authors state, there are no data reporting outcomes of patients treated for "masked hypertension", I believe it would be reasonable to treat them. What about "white coat"? Previous observations suggest that these patients are subject to development of sustained hypertension. They should be carefully observed. Some would advocate treatment.

I believe home BP will become more standardized as a method for following patients treated for hypertension. RTJ

3-5 SMOKING AND BLINDNESS

Age-related macular degeneration **(MD)** is related to smoking.

Three cross-sectional studies of over 12 000 patients reported that current smoking leads to a 3- to 4-fold incidence of MD compared with non-smokers. Indeed, the relative risk of smoking associated with MD is higher than the relative risk with ischemic heart disease. A dose-response relationship has been established.

Observational studies show a protective effect of smoking cessation on development of MD.

I was unaware of this association. Informing patients may be a powerful incentive to quit. RTJ

3-6 EFFECT OF INTENSIVE COMPARED WITH MODERATE LIPID-LOWERING THERAPY ON PROGRESSION OF CORONARY ATHEROSCLEROSIS. (REVERSAL)

Is there any benefit in lowering LDL-cholesterol below the recommended 100 mg/dL?

This study, in patients with established coronary atherosclerosis, compared the effect of *moderate* lipid-lowering by 40 mg pravastatin (*Pravachol*) with *intensive* lowering by 80 mg atorvastatin (*Lipitor*). Final mean LDL-c was 110 in the *Pravachol* group and 79 in the *Lipitor* group.

The main outcome (progression of coronary atherosclerosis as determined by intracoronary ultrasound) favored atorvastatin. Over 18 months, the atherosclerotic burden in the *Pravachol* group increased by +2.7% compared with – 0.4% in the atorvastatin group.

"These findings have considerable implications for treatment guidelines for patients with dyslipidemia and established CAD."

Note this was a study of lipid-lowering and atherosclerotic progression in patients with established CHD (a high risk group). It did not report any clinical benefits.

The larger problem of primary prevention is unanswered.

The benefit/harm-cost ratio of intensive statin therapy is not known.

We are becoming a nation of statin takers. Should the recommended dose be the highest demonstrated to produce surrogate end-point benefits? Should primary care clinicians now recommend 80 mg of atorvastatin for all? I believe not. The excess cost would be considerable. And, despite the report that the drug "was well tolerated", there will be serious adverse effects.

Note that LDL-c reached a level below 100 mg/dL in 65% of the group receiving 40 mg Pravachol. I believe it reasonable to start with a moderate dose and gradually increase if needed.

3-7 EFFECTS OF CHOLESTEROL-LOWERING WITH SIMVASTATIN ON STROKE AND OTHER MAJOR VASCULAR EVENTS IN 20 536 PEOPLE WITH CEREBROVASCULAR DISEASE OR OTHER HIGH-RISK CONDITIONS

In a large group of patients at *high risk* of vascular disese, statin therapy rapidly reduced risk of ischemic stroke with no apparent increase in risk of hemorrhagic stroke. Benefits occurred even among those who did *not*

have high cholesterol concentrations. Statin therapy also reduced the risk of major vascular events among people who had previously experienced a stroke or other cerebrovascular event.

A reduction in LDL-cholesterol from about 154 mg/dL to about 115 mg/dL reduced risk of stroke and other major vascular events by about one-quarter. Lowering it from about 115 mg/dL to about 77 mg/dL also reduced risk by about one quarter. "Current guidelines could, therefore, lead to substantial undertreatment of high-risk patients who present below, or close to, particular targets for LDL reduction."

"These results have important implications for revising treatment guidelines which do not currently take into account cerebrovascular disease risk reduction when considering the initiation of statin therapy."

"Statin therapy should now be considered routinely for all patients at high risk of stroke, irrespective of their initial cholesterol concentrations. "

This study confirms the widely-held belief that statin therapy reduces risk of stroke as well as coronary disease. It also strengthens the observation that lowering LDL-cholesterol below levels usually considered "satisfactory" will further reduce risk of atherosclerotic disease.

The risk of events associated with cardiovascular risk factors increases linearly. There are no artificial cut-points dividing "satisfactory" levels vs "unsatisfactory" levels. RTJ

3-8 TEN YEAR'S EXPERIENCE WITH ALENDRONATE FOR OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

How long is the benefit of bisphosphonates sustained? This article reports results of a trial of postmenopausal women with osteoporosis who were treated for 10 years with alendronate (*Fosamax*).

Bone mineral density (**BMD)** continued to increase throughout the 10-year period. Lumbar spine density was increased by doses of 5 mg and 10 mg daily (+ 9% and +14%). The density of the femoral neck was increased by +3 and + 5%.

Even when alendronate is discontinued, the increased BMD persists for some time.

The drug was well tolerated over 10 years. There is some concern that bone may become more brittle as BMD increases due to prolonged therapy. No evidence, however, of an *increase* in fracture rate in this study.

The study reported a low calcium intake in these women. Deficient intake of calcium and vitamin D is common in the USA. Providing adequate calcium and vitamin D will retard development of osteoporosis. Women (and men) should maintain adequate intake of calcium and vitamin D throughout their lives. This can usually be attained only by supplementation. RTJ

3-9 A RANDOMIZED TRIAL OF EXEMESTANE AFTER TWO OR THREE YEARS OF TAMOXIFEN THERAPY IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER

Aromatase is the enzyme that catalyses the conversion of androgens to estrogens in females. Exemestane is a 3rd generation aromatase inhibitor. It inhibits aromatization almost completely.

Exemestane therapy, after 2 or 3 years of tamoxifen therapy, significantly reduced risk of metastatic recurrence and contralateral breast cancer as compared with continued tamoxifen.

[NNT (3 years exemestane to benefit one patient) = 21]

This is consistent with the hypothesis that BC frequently becomes resistant to tamoxifen within 5 years.

I included this abstract because I believe therapy with these aromatase inhibitors will continue to improve BC survival. Primary care clinicians should be aware of developments even though they may not be directly involved in this therapy. RTJ

3-10 PURINE-RICH FOODS, DAIRY AND PROTEIN INTAKE, AND RISK OF GOUT IN MEN.

This study prospectively investigated the association between dietary factors and *new* cases of gout.

Higher intakes of meats and seafoods were associated with *increased* risk of gout. Higher consumption of low-fat dairy products was associated with *decreased* risk. Those in the highest quintile of meat intake (beef, pork, and lamb as main dishes), compared with the lowest quintile, had an elevated risk of developing gout (relative risk = 1.4). Each additional daily serving of meat was associated with a 21% increase in risk.

Corresponding RR associated with seafood was 1.5. Each additional weekly serving was associated with a 7% increase in risk.

Higher intake of total protein and higher intake of purine-rich vegetables were *not* associated with increased risk.

The investigators speculate that the risk associated with increased meat and seafood may be greater in men who already have gout because they have impaired renal clearance of uric acid and the absorption of dietary purines causes a steeper increase in blood uric acid levels than in persons with normal uric acid concentrations. (Ie, diet is likely to be a secondary prevention measure.)

This was essentially a primary prevention study. It provides no information on risk of exacerbations due to dietary factors in men with established gout. The authors, however, speculate that increased intake of meat and seafood may increase risk of recurrence of acute gouty arthritis, and low-fat dairy products may decrease risk. I believe it prudent for primary care clinicians to advise these dietary limitations in patients with established gout. RTJ

3-11 URIC ACID AND DIET—INSIGHTS INTO THE EPIDEMIC OF CARDIOVASCULAR DISEASE.

The effects of diet are relevant to the epidemiology of hyperuricemia and gout. Gout and obesity have become epidemic among native people, such as the Maori of New Zealand, since the introduction of Western culture and diets. The immigration of non-Western peoples to Western countries—for example that of Filipino and Japanese to North America—has been associated with increases in the incidence of gout in parallel with the shift in diet to higher intakes of meat and saturated fats. Gout was rare among blacks in the USA until the 1940s when changes in diet led to the rapid development of obesity, diabetes, and hypertension. Now, gout is more common among blacks than in whites. It is also becoming more common in urban communities of Africa in association with an increasing frequency of hypertension and cardiovascular disease.

Gout is thus no longer a disease of the wealthy; rather its appearance reflects a worldwide increase in fatty meats and a decrease in intake of dairy products associated with Westernization.

Gout should be considered a part of the current epidemic of obesity, hypertension, and diabetes.

The preceding articles convincingly reinforce the view that lifestyle is indeed important in the pathogenesis of gout.

3-12 TAMSULOSIN (*FLOMAX*) IS EFFECTIVE FOR RENAL COLIC

In patients with renal colic due to juxtavesical stone**,** tamsulosin (*Flomax*) 0.4 mg given 3 times daily was associated with greater chance of passing the stone. And fewer hours to expulsion, fewer number of injections of diclofenac, lower hospitalization rate, and reduced need for endoscopic stone removal.

A therapeutic measure worth keeping in mind.

The major adverse effect of Flomax is postural hypotension. The PDR suggests the highest dose should be 0.8 mg daily. A daily dose of 1.2 mg (0.4 mg 3 times daily) will likely be associated with greater likelihood of hypotension. RTJ

3-13 THE BODY-MASS INDEX, AIRFLOW OBSTRUCTION, DYSPNEA, AND EXERCISE CAPACITY INDEX IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: The BODE Index

A simple multidimensional grading system predicted risk of death better than the FEV1 alone.

B Body mass index (Low BMI— weight in kg/height in meters ^{2}; cutpoint under 21)

O FEV1 as a percentage of predicted (Obstruction)

D Score on a dyspnea scale (Dyspnea scale 0 to 4)

E Distance walked in 6 minutes. (Exercise)

This simple grading system is a better predictor of death from any cause and death from respiratory causes than the FEV1 alone. Mortality increased progressively with quartiles of the score. The highest quartile (score = 7 to 10) was associated with a mortality of 80% over 4 years.

Despite its importance as a public health problem, COPD is vastly underappreciated. It is underdiagnosed, and when diagnosed, is commonly undertreated. Although it is not a single entity, all patients share a common physiological abnormality—limitation of expiratory airflow. It is a complex disorder, affecting far more than a single organ system. Patients with a similar FEV1 can have obvious and marked differences in body habitus, exercise performance, and oxygenation. Additional information complements the assessment by spirometry alone.

I believe primary care clinicians will rarely calculate this index. They will rely for prognosis on their general assessment of the patient. A patient who is wasted down from his normal weight to a BMI under 21 (probably, in old parlance, a "pink puffer"), who can do little without dyspnea, and who cannot walk even slowly for 6 minutes without stopping, has a very dim prognosis indeed. Assessment of the general condition may lead primary care clinicians to advise oxygen at an earlier stage, to treat more vigorously with inhalation therapy, and to use antibiotics earlier and more frequently. RTJ

==========

About Half Of All Deaths Can Be Attributed To A Limited Number Of Preventable Behaviors.

3-1 ACTUAL CAUSES OF DEATH IN THE UNITED STATES, 2000

This article defines the "actual" causes of death as underlying-modifiable-behavioral risk factors which predispose to the "disease" which is labeled as the cause of death.

A literature search identified epidemiological, clinical, and laboratory studies linking risk behaviors and mortality. The authors used a formula which calculated 'actual" causes of death from the percentage of deaths in those engaged in the risk behavior and the percentage *not* engaging in the risk behavior. (Eg, estimated the percentage of smokers dying of heart disease *vs* the percentage of non-smokers dying of heart disease. Then compared the relative risks of death in the two groups.)

	Causes of death as reported in death certificates (No. per 100 000 population)
Heart disease	258
Malignant neoplasms	200
Cerebrovascular disease	61
Chronic lower respiratory disease	44
Unintentional injuries	36
Diabetes	25
Influenza and pneumonia	24
Alzheimer disease	18

"Actual" causes of death	No. in 1990 (thousands)	No. in 2000 (thousands)
Tobacco	400	435
Poor diet and physical inactivity	300	400
Alcohol	100	85
Microbial agents	90	75
Toxic agents	60	55
Motor vehicle	25	43
Firearms	35	29
Sexual behavior	30	17
Illicit drug use	20	17

About half of all deaths could be attributed to a limited number of largely preventable behaviors.

Interventions to prevent and increase cessation of smoking, improve diet, and increase physical activity must become a much higher priority in the public health and health care systems.

The most striking finding is the substantial increase (to about 400 000) in the number of estimated deaths attributable to poor diet and physical inactivity. The gap between deaths due to poor diet and inactivity and those due to smoking has narrowed substantially. "It is clear that if the increasing trend of overweight is not reversed over the next few years, poor diet will likely overtake tobacco as the leading cause of mortality."

The most disappointing finding may be the slow progress in reducing tobacco-related mortality.

In addition to premature death, years of lost life, diminished productivity, and decreased quality of life are strongly associated with the actual causes.

JAMA March 10, 2004; 291: 1238-45 "Special Communication", commentary, first author Ali H Mokdad, Centers for Disease Control and Prevention, Atlanta. GA. www.jama.com

Comment:

One important cause of death not directly related to obesity is the deficiency of calcium and vitamin D in the American diet. This leads eventually to death and disability due to hip and other fractures.

Primary care is the specialty which bears the greatest responsibility and opportunity to reduce prevalence of unhealthy lifestyles. Clinicians must: 1) follow a healthy lifestyle themselves as an example to patients, and 2) to constantly encourage patients to do likewise. RTJ

=========

The Urgent Crowds Out The Important

3-2 THE IMMEDIATE VS THE IMPORTANT

(This editorial comments and expands on the preceding article.)

"One of the most difficult challenges is to ensure that the urgent does not crowd out the important. That challenge is especially difficult because urgent matters can be so riveting."

At the policy level, medical care expenditures often drive decisions in which *cost cutting* is aimed at discretionary investments, such as those in prevention and public health, that offer the greatest prospects for overall health improvement.

Every death has a definable history that usually can be traced back for decades, and sometimes even generations. Reporting of deaths, diseases and disabilities in traditional diagnostic categories tend to obscure the importance of factors that often play determinant antecedent roles in the occurrence of the reported conditions. When it comes to ranking health problems and committing resources, attention seems more naturally drawn to the conditions most proximate to serious illness or death.

Another important category not included in the articles is medical error, which, according the Institute of Medicine, are estimated to account for 44 000 to 98 000 deaths annually.

Refining insights into the root causes of illness and injury, presenting those insights in a fashion that can motivate and guide effective action, and marshalling the effort to monitor the results of these actions will require steady improvements in the knowledge base and commitment at the policy level.

JAMA March 10, 2004; 291: 1263-64 Editorial, first author J Michael McGinnis, Robert Wood Johnson Foundation, Princeton, NJ www.jama.com

==========

HRT Is Safer In Younger Postmenopausal Women

3-3 EVALUATION OF CARDIOVASCULAR EVENT RATES WITH HORMONE THERAPY IN HEALTHY, EARLY POSTMENOPAUSAL WOMEN

Two large randomized trials [1,2] have evaluated effects of hormone replacement therapy **(HRT)** in postmenopausal women with and without established cardiovascular disease **(CVD).** HRT consisted of oral conjugated equine estrogens + medroxyprogesterone acetate (**CEE**; *Premarin*—0.625 daily + **MPA**; *Provera* – 2 .5 mg daily). The average age of the subjects was 63 years, well past onset of the menopause. The greatest risk of adverse effects occurred in the first year.

Overall, the studies concluded that HRT results in net harms. This was contrary to older *observational* studies which reported considerable benefit in reducing cardiovascular morbidity and mortality. It led to reevaluation of the use of HRT.

It is important, however, to determine if adverse events occur in *younger* women. Most women with menopausal symptoms take HRT at an earlier age relatively soon after the menopause. This article asks - What is the risk of adverse events at this age?

Conclusion: In young, healthy postmenopausal women, the adverse effects of HRT in the first year of use were low.

STUDY

1. Evaluated results of 2 large clinical trials [3,4] of over 3500 healthy women, mean age 53. They were an average of 5 years past their last menstrual period.
2. Some received varying doses of CEE—0.3 mg to 0.625 mg, with and without MPA at varying doses. Some received placebo.
3. Determined adverse effects during the *first* year of use, and compared them with expected risks in women not taking HRT.

RESULTS

1. In the first year of treatment with HRT no cardiovascular deaths occurred. No myocardial infarct was diagnosed.
2. There were 7 vascular events among HRT treated women: stroke (3); TIA (1); pulmonary embolism and venous thrombosis (3).
3. Overall incidence of vascular events in women using HRT for the first year = 2/1000 patient-years. This compares with the expected annual rate of events (4/1000) in women *not* taking HRT.

DISCUSSION

1. During the first year of HRT use, the incidence of vascular events in healthy women age 50-60 (mean age = 53) was low.
2. This contrasts markedly with the risks reported by the Woman's Health Initiative (**WHI**). Women in the WHI, however, were older and not as close to the menopause as women in this study.

3. "The CHD and stroke data suggest that there is *no* increased risk in young symptomatic women compared with reported annual rates."
4. "The data seem to suggest that the results of early CHD risk observed in the WHI may not be applicable to healthy, younger postmenopausal women who seek treatment for menopausal symptoms." Indeed, in the WHI, women who had experienced menopause within the past 10 years, the hazard ratio of HRT was only 0.89, compared with 1.22 and 1.71 respectively for women who had experienced menopause between 10 to 19 years previously, and women who had experienced it more than 20 years previously.

CONCLUSION

"For patients who seek HRT for symptoms early in the menopause, these data suggest that the benefits may outweigh the risks."

Archives Int Med March 8, 2004; 164: 482-84 Commentary by Rogerio A Lobo, Columbia University College of Physicians and Surgeons, New York www.archinternmed.com

1 *The Heart and Estrogen/progestin Replacement Study (HERS)* JAMA 1998; 280: 605-13

2 *The Women's Health Initiative (WHI) Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women* JAMA 2002; 288: 321-33

3 *Relief Of Vasomotor Symptoms And Vaginal Atrophy With Lower Doses Of Conjugated Equine Estrogens And Medroxyprogesterone Acetate* Fertil Steril 2001; 75: 1065-79

4 *Bleeding Patterns In Postmenopausal Women Taking Continuous Combined Or Sequential Regimens Of Conjugated Equine Estrogens With Medroxyprogesterone* Obstet Gynecol 1994; 83:686-92

Comment:

Practical Pointers has abstracted 6 reports relating HRT to vascular complications over the past 2 years. I will try to clarify and condense important points:

1. The main message is that HRT does not lower risks, and that it should not be used for that purpose. HRT does not protect against vascular disease. This is a complete reversal of past observational studies which suggested a large protective effect.

2. HRT is more risky in women with established vascular disease than in women free of vascular disease.

3. Risks are higher in elderly women than in perimenopausal women.

4. Estrogen alone is safer than estrogen/progestin.

5. Risks are especially high in the first year of use. (I believe these risks can be reduced by smoking cessation, low dose aspirin, lipid and BP control, and by using lowest effective dose of estrogen and progesterone. Indeed, I believe it likely that women who, at the age of 50 adopt these protective measures and take HRT will be less likely to experience vascular events than women who do not take HRT and do not adopt these protective measures.)

6. There is some evidence that, once the 1-year period of increased vulnerability is past, and HRT is continued, risk of vascular disease is reduced to match that of women who do not take HRT.

7. Risks should not be overemphasized. They are less than 1 in 1000 women per year.

8. HRT does improve lipid profiles. The increased risk of vascular disease is likely due to an increased thrombotic potential.

What about breast cancer?

Reports are consistent. HRT over time does increase risk. But estrogen alone carries less risk than estrogen/progestin.

I believe that recent reports overemphasized the adverse effects of HRT, and that many women who would benefit by symptom relief are being denied treatment. Individual informed consent should be obtained after explanation of the risk/benefit ratio. RTJ

==========

Monitoring Of Patients Being Treated For Hypertension Must Include Home BP Self Measurement."

3-4 CARDIOVASCULAR PROGNOSIS OF "MASKED HYPERTENSION" DETECTED BY BLOOD PRESSURE SELF-MEASUREMENT IN ELDERLY TREATED HYPERTENSIVE PATIENTS.

The reference method for BP measurement is the auscultatory method with a mercury sphygmomanometer. This has demonstrated the relationship between BP and cardiovascular risk. For each increase of 10 mm Hg in systolic BP **(SBP),** or 5 mm HG of diastolic BP **(DBP),** the average risk of cerebrovascular mortality increases by 40%, and the risk of mortality from ischemic heart disease increases by 30%.

But, there are numerous criticisms of *clinical* BP measurement. Major inter- and intra-observer variability exist. There are difficulties with standardization of the measurement conditions, and insufficiency in the number of measurements. It fails to recognize "masked" hypertension (home hypertension) as well as "white-coat" hypertension (office hypertension).

Many guidelines recommend replacement of the office BP measurement with physician-independent methods (ambulatory 24-hour BP monitoring or self-measurement at home). Home BP has a high degree of quality and is cheaper and better accepted by patients than ambulatory (24 hour) monitoring.

This cohort study evaluated the prognostic value of home BP measurement *vs* office BP measurement in a population being treated for hypertension.

Conclusion: Home BP measurement had better prognostic value than office BP measurement.
It uncovered masked hypertension as well as white coat hypertension.

STUDY

1. Prospective study entered over 4900 patients (mean age 70). All had treated hypertension. The study was designed to compare the prognostic value of home BP *vs* office BP.
2. The first phase measured office BP by a mercury sphygmomanometer 3 times on two separate visits over 2 weeks. (Average of 6 readings.) Home BP was determined over a 4-day period by 3 measurements of BP in

the AM and 3 in the PM with an Omron 705 CP device. (Average of 24 determinations.) The device had been previously validated against a mercury sphygmomanometer.

3. The second phase periodically measured both office and home BP at intervals for 3 years.
4. The mean of all home BP measurements was used for comparison with the mean office BP. The threshold defining uncontrolled hypertension was 140/90 for office BP and 135/85 for home BP.
5. Primary end point = cardiovascular mortality. Secondary end points = total mortality, and the combination of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, hospitalization for angina or heart failure, and coronary angioplasty or coronary bypass surgery.
6. There were no specific recommendations concerning management of hypertension, including frequency of visits, drug treatment, or BP goal.

RESULTS

1. At 3 years, at least one cardiovascular event occurred in 324 patients. (6.5%)
2. For home BP, each 10 mm increase in systolic increased risk of a cardiovascular event by 17%; each 5 mm increase in diastolic increased risk by 12%.
3. 3-year hazard ratios for cardiovascular outcomes:

	HR	Number of patients
A. Both home and office normal	1.00 (referent)	685 (14%)
B. Both high (Uncontrolled hypertension)	1.96	3125 (64%)
C. Normal office; high home* (“Masked” hypertension)	2.06	462 (9%)
D. High office; normal home (“White-coat” hypertension)	1.18	656 (12%)

(* Note the main conclusion of the study: Masked hypertension was associated with a statistically significant increase in risk. Indeed, the risk over 3 years was about the same as the group with uncontrolled hypertension.)

DISCUSSION

1. In this study, home BP self-measurement defined the prognosis in terms of cardiovascular morbidity and mortality better than office measurement.
2. Home BP identified a subgroup of 9% who had poor control at home, but apparently controlled in the office. (“White coat hypertension”). And a group of 12% with apparently controlled BP in the office, but not controlled at home. (“Masked” hypertension).
3. Home BP is the mean BP trough (morning) and peak (evening) values. Since office BP was obtained during normal working hours, it is likely that every possible timing of measurement is represented in this sample.
4. The large number of morbidity and mortality events demonstrated the prognostic superiority of standardized home BP measurements. Superiority was related to the reduced variability of home BP compared with the office BP measurement. This was due, in part, to the increased number of measurements (24), which defined home BP, compared with only 6 measurements which defined office BP.
5. This is also due in part to the poor performance of office BP measurement.
6. The study confirms the high prevalence of the “white coat” effect.

7. The new element of the study relates to “masked hypertension” (elevated home BP; normal office BP).
8. The authors state home BP has excellent feasibility and is the method preferred by patients. It remains to be seen, however, that adaptation of *treatment* to the results of home BP self-measurement allows better cardiovascular prevention than *treatment* based on office BP.

CONCLUSION

Home BP self measurement had a better prognostic value than office BP. Office BP failed to identify patients with elevated BP in the office, but not at home (“white coat hypertension”) and those with elevated BP at home but not in the office (“masked hypertension”).

“The frequency of this double error, which is both diagnostic (with respect to the control of hypertension), and prognostic (with respect to the incidence of cardiovascular events), suggests that monitoring of patients being treated for hypertension must include home BP self measurement.”

JAMA March 17, 2004; 291: 1342-49 Original investigation by the “Self Measurement of Blood Pressure at Home in the Elderly: Assessment and Follow-up” (SHEAF) Study, first author Guillaume Bobrie, Hopital Europeen Georges Pompidou, Paris France. www.jama.com

Comment:

An article abstracted in the February 2004 issue of Practical Pointers (2-1) reported that self-measured home BP (SMHBP) led to less intensive drug therapy and to discontinuation of drug therapy in twice as many patients as office BP measurement. It mentioned that SMHBP will detect patients with “masked hypertension”.

Although, as the authors state, there are no data reporting outcomes of patients treated for “masked hypertension”, I believe it would be reasonable to treat them.

I believe home BP will become more standardized as a method for following patients treated for hypertension. RTJ

==========

Smoking Is The Prime Modifiable Risk Factor

3-5 SMOKING AND BLINDNESS

Patients (*and physicians)* remain largely unaware of the link between smoking and blindness. Smoking is a risk factor for age-related macular degeneration (**MD**).

Three cross-sectional studies of over 12 000 patients reported that *current* smoking leads to a 3- to 4-fold incidence of MD compared with non-smokers. Indeed, the relative risk of smoking associated with MD is higher than the relative risk with ischemic heart disease.

A dose-response relationship has been established. The risk of early MD increases with the number of pack years. MD develops about 10 years earlier in smokers. About ¼ of all cases of age-related MD are attributable to smoking.

The relationship is biologically plausible. Age-related MD may reflect accumulated oxidative damage in the retina. Smoking is known to impede the protective effects of antioxidants and to reduce macular pigment density.

The editorialist estimates that over 50 000 residents in the UK older than age 69 may have visual impairment because of MD attributable to smoking, and over 17 000 are blind.

Observational studies show a protective effect of smoking cessation on development of MD. Former smokers have only a slightly increased risk compared to never smokers. In patients with MD in one eye, cessation may prevent development of MD in the other eye. Smoking is associated with poorer outcomes after photocoagulation.

Primary smoking prevention is even more important.

BMJ March 6, 2004; 32 8: 537-38 Editorial, fist author Simon P Kelly, Bolton Hospital, Bolton UK www.bmj.com

Comment:

I was unaware of this association. Informing patients may be a powerful incentive to quit. RTJ

==========

Intensive Lipid-Lowering Therapy Stopped Progression of Coronary Atherosclerosis

3-6 EFFECT OF INTENSIVE COMPARED WITH MODERATE LIPID-LOWERING THERAPY ON PROGRESSION OF CORONARY ATHEROSCLEROSIS. (REVERSAL)

The optimal approach to lipid control in patients with established coronary heart disease **(CHD)** remains uncertain.

This study compared the effect of *moderate* lipid-lowering with pravastatin (*Pravachol*) with *intensive* lowering with atorvastatin (*Lipitor*). Is there any benefit in lowering LDL-cholesterol below the recommended 100 mg/dL?

Conclusion: High dose atorvastatin was associated with lower LDL-c levels, and stopped progression of coronary atherosclerosis. There was no data on clinical benefits.

STUDY

1. Double-blind, randomized trial entered over 650 patients (mean age 56). All had established CHD which required coronary angiography for a clinical indication. All had a luminal narrowing of more than 50% in a "target" segment of an artery.
2. Measured coronary atherosclerotic progression with a miniaturized ultrasound transducer which generates detailed images of the vessel wall. This allows precise quantification of the atherosclerotic burden.
3. Randomized to: 1) pravastatin 40 mg daily, or 2) atorvastatin 80 mg daily.
4. Primary efficacy parameter was percentage change in atheroma volume. Follow-up = 18 months.

RESULTS

1. Lipid changes (means)	Total cholesterol	LDL-c	HDL-c	Triglycerides
Baseline	232	150	42	197
Final pravastatin	187	110	45	166
Final atorvastatin	151	79	43	148

2. LDL-c reached levels under 100 mg/dL in 65% of the pravastatin group vs 97% in the atorvastatin group.
3. C-reactive protein and apolipoprotein levels were decreased much more in the atorvastatin group (-36% vs – 5%; and – 39% vs – 22%)
4. Progression of coronary atherosclerosis occurred in the pravastatin group (+2.7%); but did not occur in the atorvastatin group (-0.4%). Significant differences favoring atorvastatin occurred in total atheroma volume.
5. Both regimens were well tolerated. About 6% withdrew in each group.

DISCUSSION

1. In comparison with moderate lipid control, intensive control resulted in significantly reduced progression of coronary atherosclerosis. "These findings have considerable implications for treatment guidelines for patients with dyslipidemia and established CAD."
2. The clinical significance of the large reduction in C-reactive protein by atorvastatin is not known. The reduction in triglycerides and apolipoprotein B may add to the benefit in reducing atherosclerotic burden.
3. The clinical benefits of high-dose atorvastatin are not known. The authors believe, however, that halting progression of the atherosclerotic process will translate into clinical benefit.

CONCLUSION

High-dose atorvastatin in patients with established CHD halted progression of atherosclerosis, whereas moderate therapy with pravastatin was associated with significant disease progression.

"A more intensive lipid-lowering therapy is required than is currently recommended by the national guidelines to obtain maximal reduction in the progression of coronary atherosclerosis."

JAMA March 3, 2004; 291: 1071-80 Original investigation by the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study, first author Steven E Nissen, Cleveland Clinic Foundation, Cleveland, Ohio www.jama.com

Cost: *www.mydrugstore.com* quotes $95 for 30 tablets of 80 mg *Lipitor*; $120 for 30 tablets 40 mg *Pravachol*

Comment:

Note this was a study of lipid-lowering and atherosclerotic progression in patients with established CHD (a high risk group). It did not report any clinical benefits. (Ie, the benefit of intensive LDL-c lowering in secondary prevention of CHD events was not known.)

The larger problem of primary prevention is unanswered as well.

The benefit/harm-cost ratio of intensive statin therapy is not known.

We are becoming a nation of statin takers. Should the recommended dose be the highest demonstrated to produce surrogate end-point benefits? Should primary care clinicians now recommend 80 mg of atorvastatin for all? I believe not. The excess cost would be considerable. And, despite the report that the drug "was well tolerated," there will be serious adverse effects.

Note that LDL-c reached a level below 100 mg/dL in 65% of the group receiving 40 mg Pravachol. I believe it reasonable to start with a moderate dose and gradually increase if needed. RTJ

==========

Statin Therapy Rapidly Reduced The Risk Of Ischemic Stroke.

3-7 EFFECTS OF CHOLESTEROL-LOWERING WITH SIMVASTATIN ON STROKE AND OTHER MAJOR VASCULAR EVENTS IN 20 536 PEOPLE WITH CEREBROVASCULAR DISEASE OR OTHER HIGH-RISK CONDITIONS

Lower cholesterol concentrations have consistently been found to be strongly associated with lower risks of coronary disease, but not stroke. Previous small trials, have suggested, however, that statin therapy does reduce risk of stroke. This large prospective study was designed to provide confirmation of the association.

Conclusion: Statin therapy rapidly reduced the risk of ischemic stroke.

STUDY

1. Entered over 3200 adults (mean age = 65) with established cerebrovascular disease, and another 17 000 with other occlusive arterial diseases or diabetes. (Ie, high risk groups.)
2. Randomized to: 1) 40 mg simvastatin (*Zocor*) daily, or 2) matching placebo.
3. Outcomes: first "major vascular event" (non-fatal MI or coronary death, stroke of any type, or any revascularization procedure).
4. Follow-up = 5 years.

RESULTS

1. Overall, there was a highly significant 25% reduction in rate of stroke (simvastatin 4.3% vs placebo 5.7%). (Absolute differences = 1.4%; NNT (5 years to prevent one stroke) = 71.
2. The benefits were limited to ischemic stroke; no difference in hemorrhagic stroke.
3. In addition, simvastatin was associated with a reduction in transient ischemic attacks (2.0% vs 2.4%), and those requiring carotid endarterectomy or angioplasty (0.4% vs 0.8%)
4. The reduction in risk did not occur until the 2nd year. Continuation of therapy beyond 5 years would eventually produce an even larger absolute reduction in risk.
5. In the subset with preexisting cerebrovascular disease there was no apparent reduction in stroke rate, but a highly significant reduction in rate of other vascular events (24.7% vs 29.8%).
6. Risk of stroke was reduced by about ¼ in subcategories of patients: those with coronary disease; diabetes; age over 70; and those with different levels of lipids and blood pressure. Benefit was evident even in those with a baseline LDL-cholesterol below 116 mg/dL.
7. There was no evidence of an excess risk of hemorrhagic stroke.

DISCUSSION

1. In these high risk groups, statin therapy rapidly produced a substantial reduction in risk of ischemic stroke regardless of the patient's age, sex, or lipid concentrations. "These results have important implications for revising treatment guidelines which do not currently take into account cerebrovascular disease risk reduction when considering the initiation of statin therapy."

2. Statin therapy also reduced the risk of major vascular events among people who have previously had a stroke or other cerebrovascular event.
3. When published results of large-scale randomized trials of statins are considered together, an average reduction of LDL-cholesterol of 39 mg/dL is associated with a 21% reduction in incidence of stroke.
4. A reduction in LDL-cholesterol from about 154 mg/dL to about 115 mg/dL reduced risk of stroke and other major vascular events by about one-quarter. Reducing it from about 115 mg/dL to about 77 mg/dL also reduced risk by about one quarter. "Current guidelines could, therefore, lead to substantial undertreatment of high-risk patients who present below, or close to, particular targets for LDL reduction."
5. The lack of observed benefit in the subgroup with history of ischemic stroke at baseline could be due to the play of chance. (Numbers of subjects with pre-existing cerebrovascular disease were small.)
6. "Statin therapy should now be considered routinely for all patients at high risk of stroke, irrespective of their initial cholesterol concentrations."

CONCLUSION

In a large group of patients at high risk of vascular disese, statin therapy rapidly reduced risk of ischemic stroke with no apparent increase in risk of hemorrhagic stroke even among those who did not have high cholesterol concentrations.

Lancet March 6, 2004; 363: 757-67 Original investigation by the Heart Protection Study Collaborative Group, correspondence to Heart Protection Study, Clinical Trials Service Unit and Epidemiological Studies Unit, Radcliffe Infirmary, Oxford, UK. www.thelancet.com

Comment:

This study confirms the widely-held belief that statin therapy reduces risk of stroke as well as coronary disease. It also strengthens the observation that lowering LDL-cholesterol below levels usually considered "satisfactory" will further reduce risk of atherosclerotic disease.

The risk of events associated with risk factors increases linearly. There are no artificial values dividing "satisfactory" levels vs "unsatisfactory" levels. RTJ

==========

Therapeutic Benefits Were Sustained Over A 10-Year Period.

3-8 TEN YEAR'S EXPERIENCE WITH ALENDRONATE (*FOSAMAX*) FOR OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

Postmenopausal osteoporosis is a chronic, progressive disorder in which bone resorption exceeds bone formation. The resultant decrease in bone strength increases susceptibility to fractures.

Previous trials reported that the increased bone mineral density (BMD) resulting from bisphosphonate therapy is associated with a substantially reduced risk of fracture.

How long is the benefit sustained? This article reports results of a trial of women with osteoporosis who were treated for 10 years with alendronate (*Fosamax*).

Conclusion: Therapeutic benefit was sustained over a 10-year period.

STUDY

1. Double-blind study followed 78 women receiving alendronate 5 mg daily and 86 receiving 10 mg daily for 10 years. Mean age of women = 63 at baseline. Daily calcium intake averaged below 850 mg daily.

(*The study included several sub-groups of subjects receiving placebo and varying doses of alendronate for varying durations. This abstract is limited to the groups receiving alendronate daily for 10 years. RTJ*)

2. Determined bone mineral density at baseline and at 10 years.

RESULTS

1. Outcomes at 10 years compared with baseline:

	Alendronate 5 mg	Alendronate 10 mg.
Changes in bone mineral density		
Lumbar spine	+ 9%	+14%
Trochanter	+5%	+ 10%
Femoral neck	+ 3%	+ 5%
Total hip	+3%	+7%
Total body	+1%	+3%
Distal forearm	-1%	+1%

2. Bone mineral density at the lumbar spine continued to increase throughout the 10-year period.
3. Non-vertebral fracture rate and loss of height were less in the 10 mg group. The groups were too small to permit detection of rate of vertebral fracture.

DISCUSSION

1. Alendronate appeared to be effective over a 10-year period. Bone turnover was reduced by more than 50%.
2. Even when alendronate is discontinued, the increased BMD may persist for some time. This contrasts to the effect of estrogen discontinuation which results in a relatively rapid decline in BMD.
3. The drug was well tolerated over 10 years. There is some concern that bone may become more brittle as BMD increases due to prolonged therapy. In this study, however, no evidence of an *increase* in fracture rate.

CONCLUSON

Continuous treatment of osteoporosis with daily alendronate for 10 years was associated with sustained therapeutic effects on bone density and remodeling. There was no indication that the anti-fracture efficacy of the drug was diminished.

NEJM March 18, 2004; 350: 1189-99 Original investigation, first author Henry G Bone, Michigan Bone and Mineral Clinic, Detroit, Michigan. www.nejm.org

An editorial in this issue of NEJM (pp 1172-74) by Gordon J Strewler, Harvard Medical School, Boston Mass comments and expands on the study:

"Osteoporosis is, to a remarkable degree, a disease of Western civilization." A 50 year old woman in the U.S. has a 40% lifetime risk of an osteoporotic fracture. One woman in 9 older than age 80 will sustain a hip fracture, and up to 20% of these die from attendant complications.

Bisphosphonates are bound to bone mineral and are slowly released as bone is resorbed. They are then taken up by osteoclasts and inhibit formation of the ruffled border of osteoclasts, the organelle of active bone resorption.

In clinical trials, alendronate increases bone mineral density, decreases bone turnover, and reduces risk of vertebral fracture.

Why does slowing *resorption* of bone by bisphosphonates lead to an *increase* in bone mass? This is because bone formation and bone resorption are separate processes. Bisphosphonates do not reduce new bone formation, new bone formation continues. This results in a net gain in bone mass.

Is the increase in mineralization good or bad? It is good up to a point. The higher the bone mineral content, the stiffer bone becomes, and the more stress it will tolerate. But, when bone is highly mineralized, it becomes brittle and cracks. (No evidence of this adverse effect in this study.)

The study presents convincing evidence that the benefits of alendronate on BMD remain stable over 10 years. The optimum duration of therapy has not been established.

Comment:

Osteoporosis is an "actual" cause of death. (See preceding article.) Given the almost universal incidence of osteoporosis and the high burden of complications from fractures, I wonder why low-dose anti-resorptive drugs are not given routinely to women at the time of menopause and for 10 years thereafter instead of waiting for evidence of decreased BMD. Would not this delay the onset of osteoporosis and ultimately reduce fracture rate?

Note the low calcium intake in these women. Deficient intake of calcium and vitamin D is common in the USA. Women (and men) should maintain adequate intake of calcium and vitamin D throughout their lives. This can usually be attained only by supplementation.

The editorialist also comments on the benefit of treatment with parathyroid hormone (teriparatide), and possible benefit of strontium. RTJ

==========

The Aromatase Inhibitor Exemestane Significantly Improved Disease-Free Survival.

3-9 A RANDOMIZED TRIAL OF EXEMESTANE AFTER TWO OR THREE YEARS OF TAMOXIFEN THERAPY IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER

The anti-estrogen, tamoxifen (*Nolvadex*), taken for 5 years, is the standard adjuvant therapy for postmenopausal women with primary estrogen-receptor-positive breast cancer (**BC**). (Tamoxifen blocks the receptor for estrogen on cells.) In the first 5 years after surgery, it reduces risk of recurrence in women with estrogen-receptor-positive cancers, by 47%.

Its risk-benefit beyond 5 years remains unclear.

Aromatase is the enzyme that catalyses the conversion of androgens to estrogens in females. There are 2 classes of 3rd generation oral aromatase inhibitors:

Irreversible steroidal inactivators

Exemestane

Reversible non-steroidal inhibitors

Anastrozole

Letrozole.

Exemestane inhibits aromatization almost completely. It has antitumor effects in patients who have no response to non-steroidal inhibitors. Preliminary results show that it is superior to tamoxifen as first-line therapy for metastatic BC. This phase 3 study compared efficacy and safety of continued tamoxifen therapy with exemestane in postmenopausal women with BC who remained free of disease after receiving adjuvant tamoxifen.

Conclusion: Exemestane significantly improved disease-free survival.

STUDY

1. Double-blind, randomized trial entered over 4700 postmenopausal women (mean age 64) with primary BC. All had unilateral BC which had been completely resected and which was positive for estrogen receptors, or for which estrogen-receptor status was not known. All had received adequate treatment of their primary tumor and remained free of disease after receiving 2 or 3 years of tamoxifen.
2. Randomized to: 1) continued tamoxifen [20 mg daily], or 2) oral exemestane [25 mg daily].
3. Study continued to complete a total of 5 years on adjuvant therapy.
4. Primary end-point = local or metastatic recurrence of BC at any site, contralateral BC, or death from any cause.

RESULTS

1. After a median follow-up of 31 months, the primary end-point was reached in 266 in the tamoxifen group and 185 in the exemestane group. (Hazard ratio = 0.68; a 32% reduction in risk.)
2. Absolute reduction was 4.7% at 3 years after randomization. [NNT (3 years exemestane to benefit one patient) = 21]
3. Contralateral BC occurred in 20 in the tamoxifen group and 9 in the exemestane group.
4. Adverse effects: Exemestane was associated with a higher incidence of arthralgia and diarrhea, but a lower incidence of vaginal bleeding, and muscle cramps. Thromboembolic events were less common in the exemestane group. There was a suggestion of more osteoporosis, more fractures and visual disturbance in the exemestane group.

DISCUSSION

1. Switching to adjuvant therapy with exemestane after 2 or 3 years of tamoxifen was associated with a clinically significant improvement in disease-free survival and a reduced risk of metastatic disease, development of contralateral BC, and endometrial cancer. This is consistent with the hypothesis that BC frequently becomes resistant to tamoxifen within 5 years.

2. Exemestane seemed to be equally effective in both progesterone-receptor-negative subgroups as in progesterone-receptor-positive patients, and in node-positive and node-negative groups.
3. The data and safety monitoring committee recommended early release of the results.
4. Another study reported that anastrozole alone was superior to tamoxifen alone. Nevertheless 5 years of tamoxifen alone remains the widely recommended standard adjuvant therapy. The FDA has recently approved anastrozole monotherapy as an alternative.

CONCLUSION

Exemestane therapy, after 2 or 3 years of tamoxifen therapy significantly improved disease-free survival as compared with standard 5 years of tamoxifen therapy.

NEJM March 11, 2004; 350: 1081-92 Original investigation by the Intergroup Exemestane Study, first author R Charles Coombes, Imperial College and Charing Cross Hospital London, UK www.nejm.org
An editorial in this issue of NEJM by Martine J Piccart-Gebhart comments and expands on the study:
We have learned 4 major lessons during anti-estrogen strategies for treatment of BC:

1. They work *only* for estrogen-receptor-positive tumors. (2/3 of BCs)
2. .As adjuvant therapy, tamoxifen has had unprecedented success in reducing BC-related mortality worldwide.
3. Tamoxifen and probably other agents can *prevent* BC.
4. Cross-resistance can be circumvented in advanced disease. (Tamoxifen-resistant tumors are generally *not* resistant to aromatase inhibitors.)

Tamoxifen eventually switches from antagonist to agonist.
Aromatase inhibitors are superior to tamoxifen as first-line endocrine therapy for metastatic BC.

Exemestane is effective in women whose BC has progressed despite both tamoxifen and anastrozole or letrozole therapy.

What should clinicians do now? More years will be required to fine-tune the risk/benefit of adjuvant aromatase inhibitors. But, physicians should discuss use of these agents to suitable candidates. Patients should be informed about the limitations of current data and lack of definitive data on adverse effects.

Comment:

I included this abstract because I believe therapy with these aromatase inhibitors will continue to improve BC survival. Primary care clinicians should be aware of developments even though they may not be directly involved in this therapy. RTJ

==========

Higher Intakes Of Meats And Seafoods Were Associated With Increased Risk Of Gout.

3-10 PURINE-RICH FOODS, DAIRY AND PROTEIN INTAKE, AND RISK OF GOUT IN MEN.

Various purine-rich foods and high protein intake have long been thought to be risk factors for gout.

Patients with gout are typically advised to avoid habitual intake of purine-rich foods such as meats, seafood, purine-rich vegetables, and animal protein (as a proxy for purines). The association has not been confirmed by prospective studies.

This study prospectively investigated the association between these dietary factors and *new* cases of gout.

Conclusion: Higher intakes of meats and seafoods were associated with *increased* risk of gout. Higher consumption of low-fat dairy products was associated with *decreased* risk.

STUDY

1. Health Professionals Follow-up Study is an ongoing longitudinal study involving over 51 000 male health-care professionals. All were age 40-75 in 1986.
2. The study assessed dietary intake using a food-frequency questionnaire inquiring about the average consumption of more than 130 foods during the previous year. (Updated in 1990 and 1994.)
3. Over a 12-year period prospectively examined the relationship between purported dietary risk factors and *new* cases of gout among over 47 000 men who had no history of gout at baseline.

RESULTS

1. Over 12 years, documented 730 confirmed new cases of gout.
2. Those in the highest quintile of meat intake (beef, pork, and lamb as main dishes), compared with the lowest quintile, had an elevated risk (relative risk = 1.4). Each additional weekly serving of meat was associated with a 21% increase in risk.
3. Corresponding RR associated with seafood was 1.5. Each additional weekly serving was associated with a 7% increase in risk.
4. Increasing intake of dairy products (highest quintile vs lowest) was associated with *less* risk. (RR = 0.56). The associating was limited to *low-fat* dairy products. Skim milk (2 glasses daily as compared with less than one glass daily), and low-fat yogurt were the only diary products associated with lower risk. (Dairy products are low in purine content.)
5. Higher intake of total protein was *not* associated with increased risk. Higher intake of purine-rich vegetables was *not* associated with increased risk.
6. The associations with increased risk did *not* vary according to body-mass index or whether men drank alcohol.[1]

DISCUSSION

1. The study found increased risk of gout with higher meat consumption and higher seafood consumption, but *not* with higher consumption of animal or vegetable protein, purine-rich foods, or alcohol. [1]
2. There was a strong *inverse* association between intake of dairy products and incidence of gout.
3. The suspicion that there is a link between purine-rich diets and gout has been based on metabolic experiments that examined the effects of artificial short-term loading of purified purine on serum uric acid levels (not on gouty arthritis). Although this provides a theoretical basis for the effects of a purine-rich diet on hyperuricemia, and, conceivably, on eventual development of gout, several important hurdles remain before

these data can be applied to clinical practice. Little is known about the precise identity and quantity of individual purines in most foods, and about the bioavailability of various purines contained in different foods. The outcome examined in these metabolic studies was hyperuricemia rather than gouty arthritis. A substantial proportion of people with hyperuricemia will not have gout.

4. The investigators speculate that the risk associated with increased meat and seafood may be greater in men who already have gout because they have impaired renal clearance of uric acid and the absorption of dietary purines causes a steeper increase in blood uric acid levels than in persons with normal uric acid concentrations. (Ie, an opportunity for secondary prevention.)
5. "These data support our findings that the consumption of protein does *not* increase risk of gout but, rather, may actually decrease the risk and that protein content of foods may not be a good surrogate for their purine content."

CONCLUSION

Meat and seafood consumption were associated with an increased incidence of gout. Consumption of dairy products, especially low-fat dairy, was associated with a substantially reduced incidence of gout. Moderate intake of purine-rich vegetables or protein was not associated with increased risk of gout.

NEJM March 11, 2004; 350: 1093-1103 Original investigation, first author Hyon K Choi, Massachusetts General Hospital, Boston, Mass. www.nejm.org

Comment:

1 *The null effect of alcohol was surprising. And, I believe, misleading. Another recent investigation, "Alcohol Intake and Risk of Incident Gout in Men" (Lancet April 17, 2004;363: 1277-81) reported that alcohol intake is strongly associated with increased risk of gout. Beer confers a larger risk than spirits. Moderate wine drinking does not increase risk.*

In respect to alcohol, the studies diverge. This is another good example of how well-done investigations can reach different conclusions. Which one is correct? I would vote for the Lancet study. The relation between alcohol and gout is time-honored. Indeed, centuries of anecdotal experiences have attested to the relationship.

The NEJM study provides no information on risk of exacerbations due to dietary factors in men with established gout. The authors, however, speculate that increased intake of meat and seafood may increase risk of recurrence of acute gouty arthritis, and low-fat dairy products may decrease risk. I believe it is prudent for primary care clinicians to advise these dietary limitations in patients with established gout. RTJ

==========

Gout Should Be Considered A Part Of The Current Epidemic Of Obesity, Hypertension, And Diabetes.

3-11 URIC ACID AND DIET—INSIGHTS INTO THE EPIDEMIC OF CARDIOVASCULAR DISEASE.

(This editorial comments and expands on the preceding study.)

Gout, a “disease of kings and a king of diseases”, has been known since antiquity. It has been associated with the wealthy and educated. It has had a penchant for those with habits that bordered on overindulgence, gluttony, and intemperance.

Humans are the only mammals in which gout develops spontaneously, probably because humans are the only species in which hyperuricemia develops (serum uric acid levels above 6.5 to 7.0 mg/dL). Humans do not have the enzyme uricase, which converts uric acid to allantoin.

Among humans, serum uric acid levels vary markedly. Premenopausal women have lower levels because estrogen stimulates urinary urate excretion. Genetic differences regulate uric acid synthesis and excretion. Racial differences exist.

It has been postulated that a major mechanism underlying the development of gout is the excess ingestion of purine-rich foods and alcohol. Indeed, in the late 1600s, John Locke proposed a diet low in meat and high in dairy products as a means of prevention. The effects of diet are relevant to the epidemiology of hyperuricemia and gout. Gout and obesity have become epidemic among native people, such as the Maori of New Zealand, since the introduction of Western culture and diets. The immigration of non-Western peoples to Western countries—for example that of Filipino and Japanese to North America—has been associated with increases in the incidence of gout in parallel with the shift in diet to higher intakes of meat and saturated fats. Gout was rare among blacks in the USA until the 1940s when changes in diet led to the rapid development of obesity, diabetes, and hypertension. Now, gout is more common among blacks than in whites. It is also becoming more common in urban communities of Africa in association with an increasing frequency of hypertension and cardiovascular disease.

Gout is thus no longer a disease of the wealthy; rather its appearance reflects a worldwide increase in fatty meats and a decrease in intake of dairy products associated with Westernization.

Gout should be considered a part of the current epidemic of obesity, hypertension, and diabetes.

Diets rich in fruits, vegetables, and low-fat dairy, such as the “Dietary Approach to Stop Hypertension” (DASH) diet may reduce not only the blood pressure, but also the frequency of gout.

NEJM March 11, 2004; 350: 1071-72 Editorial, first author Richard J Johnson, University of Florida, Gainesville. www.nejm.org

Comment:

Note that the association with alcohol was not stressed in either of the preceding articles. The editorial commented briefly—“It has been postulated that a major mechanism underlying the development of gout is the excess ingestion of purine-rich foods and alcohol.” RTJ

==========

Tamsulosin (*Flomax)* Is Effective For Renal Colic

3-12 EFFICACY OF TAMSULOSIN IN THE MEDICAL MANAGEMENT OF JUXTAVESICAL URETERAL STONES

(*This brief report was published in BMJ March 20, 2004 as a POEM [Patient-oriented Evidence that Matters]. It was abstracted from J Urology 2003; 170: 22-02-05, first author Dellabella M.*

Although the original was not available to me, I abstracted the abstract because it suggests a helpful practical point for primary care. RTJ)

Medical management of renal colic includes reduction of ureteral edema and spasm, and the prevention of co-infection. Alpha 1 antagonists reduce ureteral contractions and spasm, and may hasten passage of retained stones.

This study followed 60 patients presenting to an emergency department in Italy with renal colic. All had unilateral, juxtavesical stones (mean size 6 mm).They were randomized (unblinded) to receive: 1) a corticosteroid to control edema; a prophylactic antibiotic; diclofenac (*Voltarin*) 75 mg on demand for pain control; and a locally prescribed spasmolytic drug* 3 times daily or 2) similar treatment with substitution of tamsulosin 0.4 mg for the spasmolytic drug.

In group 2), the expulsion rate was 100% compared with 70% in group 1). [NNT = 3]

Mean hours to expulsion, mean number of injections of diclofenac, hospitalization rate, and need for endoscopic stone removal were all lower in group 2).

(Not in my PDR. Apparently not used in the USA, RTJ)*

BMJ March 20, 2004; 328 "This week in the BMJ " www.bmj.com

Comment:

A therapeutic measure certainly worth keeping in mind.

The major adverse effect of Flomax is postural hypotension. The PDR suggests the highest dose should be 0.8 mg daily. A daily dose of 1.2 mg (0.4 mg 3 times daily) will likely be associated with greater likelihood of hypotension. RTJ

==========

Low BMI, Low FEV1, Dyspnea, and Impaired Exercise Tolerance Predict Risk of Death

3-13 THE BODY-MASS INDEX, AIRFLOW OBSTRUCTION, DYSPNEA, AND EXERCISE CAPACITY INDEX IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: The BODE Index

COPD is predicted to be the third most frequent cause of death in the world by 2020. It is characterized by an *incompletely* reversible limitation of airflow. The forced expiratory volume in one second (**FEV1**) is often used to grade severity of COPD. Patients with COPD, however, have systemic manifestations that are not reflected by the FEV1.

This study hypothesized that a multifactorial grading system assessing the systemic expression of COPD as well as the respiratory expressions, would better categorize and predict outcomes.

Conclusion: A simple multidimensional grading system predicted risk of death better than the FEV1 alone.

STUDY

1. Entered a total of over 850 outpatients (mean age 66) with a wide range of severity of COPD. All were clinically stable and were receiving appropriate therapy.
2. Defined COPD as a history of more than 20- pack-years of smoking, and a ratio of FEV1 to forced vital capacity of less than 0.7 measured 20 minutes after inhalation of albuterol (*Proventil*; *Ventolin*; *generic*). Excluded patients with asthma, defined as an increase of FEV1 of more than 15% above baseline after a bronchodilator.
3. Determined mortality associated with a group of four variables: (BODE index)
   - B Body mass index (BMI— weight in kg/height in meters ^{2}; cutpoint = 21)
   - O FEV1 as a percentage of predicted (Obstruction)
   - D Score on a dyspnea scale (Dyspnea scale 0 to 4)
   - E Distance walked in 6 minutes. (Exercise)
4. The index contains one measure of obstruction (O), one of patient's perception of symptoms (D), and two of systemic consequences (B and E).
5. The index score is determined by adding severity of the 4 factors. (Possible range = 0 to 10.)

Variable	Points on scale			
	0	1	2	3
FEV1 (% of predicted	>65	50-64	36-49	<35
Distance walked in 6 min	> 350	250-350	150-249	< 150
Dyspnea scale*	0-1	2	3	4
BMI				< 21

(* 4 indicates patient is too breathless to leave the house, or becomes breathless when dressing

6. Follow-up for up to 52 months.

RESULTS

1. The BODE score was higher among those that died than among survivors (5.9 vs 3.7).
2. Mortality increased progressively with quartiles of the score. The highest quartile (score = 7 to 10) was associated with a mortality of 80%.
3. For each one-point increase in the score, the hazard ratio for death from any cause was 1.3 and the hazard ratio for death from respiratory causes was 1.6.
4. The ability of the BODE index to predict risk of death exceeded that of FEV1.

DISCUSSION

1. This simple grading system is a better predictor of death from any cause and death from respiratory causes than the FEV1 alone.
2. Although the FEV1 is essential for the diagnosis and quantification of the respiratory impairment, it does not adequately reflect all the systemic manifestations of the disease.

CONCLUSION

The BODE Index is superior to FEV1 alone in prediction risk of death in patients with COPD.

NEJM March 4, 2004; 350: 1005-12 Original investigation, first author Bartlolme R Celli, Tufts University School of Medicine Boston Mass. www.nejm.org

An editorial in this issue of NEJM by Stephen I Rennard, University of Nebraska Medical Center, comments and expands on this study: Cigarette smoking is the major risk factor in 80% of patients with COPD—20% are lifelong non-smokers. Despite its importance as a public health problem, COPD is vastly underappreciated. It is underdiagnosed, and when diagnosed, is commonly undertreated. Although it is not a single entity, all patients share a common physiological abnormality—limitation of expiratory airflow. It is a complex disorder, affecting far more than a single organ system. Patients with a similar FEV1 can have obvious and marked differences in body habitus, exercise performance, and oxygenation. Additional information is needed to complement the assessment by spirometry. "This index is desperately needed."

Comment:

I believe primary care clinicians will rarely calculate this index. They will rely for prognosis on their general assessment of the patient. A patient who is wasted down from his normal weight to a BMI under 21 (probably, in old parlance, a "pink puffer"), who can do little without dyspnea, and who cannot walk even slowly for 6 minutes, has a very dim prognosis indeed. Assessment of the general condition may lead primary care clinicians to advise oxygen at an earlier stage, to treat more vigorously with inhalation therapy, and to use antibiotics earlier and more frequently. RTJ