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INSIDE

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Avoid a Lawsuit

ABSTRACT & COMMENTARY

By Joseph Varon, MD, FACP, FCCP, FCCM

Professor, University of Texas Health Science Center, Houston; Adjunct Professor of Medicine, University of Texas Medical Branch at Galveston

Dr. Varon reports no financial relationship to this field of study.

Synopsis: *Malpractice claims due to diagnostic errors in the ambulatory setting are common and are the result of multiple breakdowns and individual and system factors. Clinical knowledge and proper follow up are essential to avoid these claims.*

Source: Gandhi TJ, et al. *Ann Intern Med.* 2006;145:488-496

THIS RETROSPECTIVE STUDY WAS AIMED AT EVALUATING THE FACTORS involved in litigation proceedings involving diagnostic errors in the ambulatory setting. The study was designed as a retrospective review of 307 closed malpractice claims in which patients alleged missed or delayed diagnoses. Data was extracted from random samples of closed claim files of four malpractice insurance companies based in 3 regions of the United States. Each company insured approximately 21,000 physicians. A claim was defined as a written demand for compensation for medical injury. Those claims involving missed or delayed diagnoses were those alleging an error in diagnosis or testing that caused a delay in appropriate treatment or the failure to act or follow on the results of a diagnostic test. The claims were divided into 2 primary categories: those involving care in the emergency department (ED) and those in all other locations (ie, doctor's office, pathology laboratory, radiology suites). The operational definition of "error" was based on the Institute of Medicine definition. Throughout the study period (1984-2004) there were 307 diagnosis-related ambulatory claims closed. Seven hundred and thirty patients we studied. Of them, 181 claims (59%) were considered to truly have error in diagnosis and/or delay in initiation of therapy. Errors in 106 of these (59%), were associated with significant or major adverse outcome and 30% were associated with death. Cancer was the most common missed diagnosis (59% of cases), mainly breast cancer, followed by colorectal and skin cancer. Other missed diagnoses included infections, fractures, and myocardial infarctions. Most errors occurred in physicians' offices (85%). The mean interval between when diagno-

sis should have been made and when it was made (that is, in the absence of an error) was 465 days. The primary breakdown points found were the failure to order an appropriate diagnostic test (55%), failure to create a proper follow up (45%), failure to obtain an adequate history or physical examination (42%), and incorrect interpretation of the test (37%). Imaging studies were the most common diagnostic tests not ordered. The explanation for the failure to order a test was mainly a lack of knowledge of the proper test to request. Other factors that contributed to errors included failure in judgment (70%), vigilance or memory (59%), knowledge (48%), and patient-related factors (46%). The median number of factor contributing to a medical error was three (range 2-4).

COMMENTARY

Missed or delayed diagnoses in the ambulatory setting were common in this cohort. This study is interesting because it reaffirms that errors do occur for a variety of reasons and most of them are preventable. For example, over half of the diagnoses in this study were cancer-related and yet, lack of follow up was one contributing factor for a claim. This is particularly bothersome as primary clinicians are inundated with a variety of guidelines regarding the interpretation and follow up of abnormal results. Previous studies have shown that primary care clinicians do not follow up abnormal mammograms in up to one third of patients.[1] In addition, a delay in reviewing diagnostic test results has been reported in the primary care setting.[2]

Another problem noted by this study is a process breakdown. Clinicians need to find ways to safeguard their patients with mechanisms that allow them to review diagnostic test results in a timely fashion. Follow up is essential and could avoid litigation in many instances.

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1. Haas JS, et al. *J Gen Intern Med.* 2000;15:321-328.
2. Poon EG, et al. *Ann Intern Med.* 2004;164: 2223-2228.

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Questions & Comments

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Should patients with anemia and low normal or normal ferritin undergo colonoscopy?

ABSTRACT & COMMENTARY

By Malcolm Robinson, MD, FACP, FACG

Emeritus Clinical Professor of Medicine, University of Oklahoma College of Medicine, Oklahoma City.

Dr. Robinson reports no financial relationship to this field of study.

Synopsis: *In patients with anemia, serum ferritin levels below 100 ng/ml predict advanced neoplasia at colonoscopy.*

Source: Mandeep S, et al. *American Journal of Gastroenterology.* 2007;102:82-88.

Colon cancer is the second most common cause of cancer-related mortality in the U.S. Since iron deficiency anemia is often associated with colon cancer, colonoscopy in patients with iron deficiency is recommended. In the past, studies have demonstrated that serum ferritin less than 50 ng/ml is associated with a high prevalence of colon neoplasia. However, the potential association of advanced colon neoplasia with ferritin levels above 50 ng/ml is unknown. In this VA study, carefully selected populations (from a total of 6,885 patients having colonoscopy) included 414 anemic (Hemoglobin less than 13 grams) patients who underwent colonoscopy and 323 normal risk nonanemic individuals having screening colonoscopy. The study was intended to compare advanced colon neoplasia prevalence in anemic patients with ferritin levels less than or equal to 50 ng/ml, 50-100 ng/ml, or greater than 100 ng/ml with findings in a nonanemic population seen for screening colonoscopy. In the <50 ng/ml group, advanced colon neoplasia (invasive colon cancer, malignant or dysplastic polyps) was found

in 7.2% of exams vs 7.9% in patients who had >50 but <100 ng/ml ferritin. In the group with >100 ng/ml serum ferritin, 1.7% had advanced colonic neoplasia found as compared to 1.2% in the screening colonoscopy group. Of the patients in the <50 ng/ml group, 6.3% had invasive colon cancer. The authors point out that ferritin data were not available in the normal screening colonoscopy group. This study was summarized as indicating that there is a similarly high risk of colon neoplasia in patients with serum ferritin levels between 50-100 ng/ml as compared to ferritin levels below 50 ng/ml.

COMMENTARY

Although this study is mostly limited to the older male patients found in the Veterans Administration setting of this study, it is likely that the results can be generalized to broader population groups. Thus, serum ferritin levels under 100 ng/ml should be a strong indication for colonoscopic evaluation of anemic patients. However, it should not be forgotten that a small but significant number of nonanemic individuals and anemic patients with higher ferritin levels may still have advanced colonic neoplasia. The cutoff point for anemia at 13 grams is appropriate in the overall VA population but may not be as appropriate in the different gender mix of the general population. In any case, screening colonoscopy remains appropriate in the general population over age 50. The importance of these new VA data may be to help persuade otherwise reluctant patients to undergo procedures that may be lifesaving in a much higher than average risk setting. ■

An Aspirin a Day Keeps the Doctor at Bay

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington.

Dr. Phillips reports no financial relationship to this field of study.

Synopsis: *Aspirin, 325 mg every other day, reduced the risk of developing asthma by 25% (compared with placebo) over a 5-year period in a large group of healthy male physicians.*

Source: Garr RG, et al. Aspirin and decreased adult-onset asthma. Randomized comparisons from the Physician's Health Study. *Am J Respir Crit Care Med.* 2007; 175:120-125.

This report is a secondary analysis of a cohort of 22,040 physicians (mean age 54 years) who were free of asthma at enrollment, and who were randomized to take either aspirin 325 mg every other day or placebo. The study was terminated at 4.9 years of follow-up because the primary outcome measure (risk of first myocardial infarction) was very statistically and clinically reduced (by 44%!) in the group that was randomized to take aspirin. The onset of asthma was ascertained by self-report in this group of physicians, who are, as the authors put it, "unlikely to misrepresent their own medical diagnoses." At the termination of the study, there were 258 new cases of asthma altogether, but only 113 of them were in the aspirin group. This was statistically significant ($p = 0.045$), even after controlling for body mass index (BMI), age, and smoking. Aspirin's benefit in reducing asthma was greatest for those who were younger at enrollment and who had never smoked.

This report comes from a very large and very old dataset, the Physician's Health Study, which was actually begun in 1982 to test the hypotheses that aspirin or beta carotene prevent cardiovascular disease or cancer.[1] The aspirin arm of this study was terminated early in 1988 (because of the ethical need to allow all participants to take aspirin, given its benefits in reducing cardiovascular risk), and the beta carotene arm was terminated at its scheduled end in 1995. So these are old data, but still quite relevant and important.

The biologic basis by which aspirin might reduce asthma risk is that it might reduce COX-1, which blocks prostaglandin E2, which in turn inhibits Th1 lympocytes from releasing evil substances such as IFN-gamma.[2-4] There are several other proposed mechanisms as well, but frankly, I don't understand them. The background evidence that aspirin might reduce asthma risk includes the increase in asthma in the United States coincident with the reduction in aspirin use because of concerns about Reyes Syndrome.[2] Earlier work with a large cohort of women demonstrated a reduced rate of newly-diagnosed asthma in those who self-selected to take aspirin, as compared with other analgesics.[5] However, that kind of study does not have the power of a randomized controlled trial, such as is presented here. Other benefits of aspirin include the reduction in cardiovascular risk also demonstrated by the PHS, and a reduction in head and neck cancer.[6]

On the other hand, asthma is known to precipitate bronchospasm in as many as 10% of asthmatics.[7] Once asthma has developed, the horse is out of the barn, so to speak, and use of aspirin must be carefully considered in those with well-documented asthma.

Aspirin is an under rated drug, perhaps at least in part because it is cheap, unpatented, and over the counter;

direct-to-consumer marketing and physician detailing simply don't occur for aspirin. It's a good thing we can read journals! ■

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Driving Safety and Parkinson's Patients

ABSTRACT & COMMENTARY

By Charles P. Pollak, MD

Professor, Clinical Neurology, Weill College of Medicine

Dr. Pollak is a stockholder for Merck, and is on the speaker's bureau for Merck.

Synopsis: *Parkinson's patients with daytime sleepiness should drive with a companion.*

Source: Amick MM, et al. *J Neurol Sci*. 2007;252:13-15.

PATIENTS WITH PARKINSON'S DISEASE (PD) ARE vulnerable to a variety of sleep disorders and often have excessive daytime sleepiness (EDS), especially if they are treated with dopamine agonists (DAs) such as pramipexole or ropinirole. It has been suggested that "attacks" of sleepiness may occur without warning in such patients, putting themselves and others at risk. The present investigation was undertaken to assess the ability of patients with PD to drive safely, using a standardized on-road evaluation.

Twenty-one men and women with PD who were not demented and had valid drivers' licenses were administered a standardized road test by a professional driving instructor. Of the 21 subjects, 14 received a "safe" driving evaluation, whereas 7 were considered "marginal." Ratings were not explained by differences in EDS (which affected 5 subjects). Thirteen subjects were treated with a dopamine agonist (DA — pramipexole, ropinirole or pergolide). Those so treated had higher self-ratings of sleepiness (Epson sleepiness scale), but their road-test scores were not affected.

■ COMMENTARY

This small, preliminary study confirms that sleepiness is indeed common in patients with PD, especially those treated with DAs. Although 7 of the 21 PD patients were rated as "marginal" rather than "safe" drivers, neither EDS nor use of DAs accounted for their driving performance. It is a pity that a larger sample was not studied, as it might well have demonstrated an adverse effect of EDS on driving performance; even a small effect may prove fatal on the highway. The authors correctly suggest that the presence of a driving instructor may have kept the PD subjects alert. Longer drives (the duration of the road test that was administered was not specified) or tests of motor performance done with a driving simulator might have revealed alarming effects of EDS or of DAs that the present results only hint at. The authors themselves felt obliged to recommend that PD patients with EDS drive with companions, presumably to prod them awake whenever necessary. ■

Phenotypic Differences between Male Physicians, Surgeons, and Film Stars: Comparative Study

ABSTRACT & COMMENTARY

by John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver.

Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *A paper just emerged in the research section of the* British Medical Journal *that gives new meaning to scientific investigation. The authors noticed early in their training that the taller, better looking students tended to go into surgery, so these Spanish investigators set out to put their observations literally to the test.*

Source: Trilla A, et al. *BMJ.* 2006;333:1291-1293.

THE INVESTIGATORS ENTICED 14 MALE SURGEONS and 16 male physicians (internal medicine and subspecialists) to submit recent photographs of themselves to the investigators and to indicate how tall they were. In addition, photographs of 4 actors playing doctors were used as controls. They were George Clooney (E.R.), Patrick Dempsey (Grey's Anatomy), Harrison Ford (The Fugitive) and Hugh Laurie (House). Then, 8 women (5 nurses and 3 doctors) were chosen to review the photographs and to independently judge each according to a 1 to 7 "good-looking score" (7 being outstandingly handsome and 1 being ugly). Standard t tests were used for statistical analysis.

The results bore out the authors' hunch. The surgeons were, on average, better looking than the physicians (4.39 versus 3.65; $p = 0.010$) and were taller (179 cm versus 172 cm; $p = 0.01$). The controls had an average

good-looking score of 5.96. A spin-off finding was that surgeons tended to have more hair.

In the Discussion Section, some very cogent points were made. Surgeons practice what the authors called "confidence based medicine" (something not quite similar to evidence based medicine), which requires boldness and an ability to tightly control their domain. The authors felt "being taller and better looking has several evolutionary advantages." Their extra height affords them more opportunity to be "masters and commanders, and gives them a better view of the operating room" (their designated kingdom). Also, their appearance may be enhanced by their environment. For example, there is more oxygen in the operating room, and, because they have a mask on much of the time, their faces are protected from "microtrauma" (a possible anti-aging trick). Many surgeons even wear clogs to add at least two inches to their height.

On the other hand, the authors indicate that physicians tend to have heavy stethoscopes around their necks, which causes them to stoop, thereby making them appear shorter and less attractive. In addition, the mental weight of having to keep up with the voluminous amount of evidence-based literature "grinds them down" and can play havoc on their demeanor and, in turn, their appearance.

COMMENTARY

The major drawback to this study is that surgeons were only pitted against internists—an unfair comparison—and not against OB/GYNs. Also, who said you have to be tall to be called good looking? Last, who is George Clooney? ■

Reference

1. Trilla A, et al. *BMJ.* 2006;333:1291-1293.

Pharmacology Update

Dasatinib Tablets (Sprycel®)

By William T. Elliott, MD, FACP, and James Chan, PhD, PharmD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationship to this field of study.

An orally active kinase inhibitor is available for patients with chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia who are intolerant or resistant to prior therapy with imatinib. Dasatinib, in contrast to imatinib, binds to numerous kinase domains (multi-targeted). It is marketed by Bristol-Myers Squibb as Sprycel.

Indications

Dasatinib is approved for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic, myeloid leukemia and Philadelphia chromosome-positive acute lymphobastic leukemia (Ph+ ALL) who are intolerant or resistant to prior therapy with imatinib.[1]

Dosage

The recommended initial dose is 70 mg twice daily (morning and evening). The tablet may be taken with or without food and should be taken whole, not crushed or cut.[1]

Dose adjustments are required for neutropenia, thrombocytopenia, and other adverse reactions.

Dasatinib is available as 20 mg, 50 mg, and 70 mg.

Potential Advantages

Dasatinib has been shown to produce hematologic and cytogenetic response in patients intolerant to or resistant to imatinib.[1, 2, 3, 4] It is more active against the wild-type BCR-ABL, but also active against most of the imatinib-resistant BCR-ABL mutants.[5]

Potential Disadvantages

Myelosuppression is the primary adverse reaction. The frequency of grade 3 or 4 neutropenia ranged from 49% in patients with chronic-phase disease; 74% with accelerated phase disease, 83% myeloid blast phase, and 81% with lymphoid blast phase and Philadelphia positive acute lymphoblastic leukemia.[1] The frequencies of thrombocytopenia are roughly similar. Other serious adverse reactions include bleeding events, fluid retention, and QT prolongation. Dasatinib is an inhibitor of CYP3A4 and may increase plasma levels of drug metabolized by this pathway.

Comments

CML is the result of translocation of parts of two chromosomes (Philadelphia chromosomes) leading to a fused BCR-ABL protein that leads to abnormal cell growth. This abnormal protein is a tyrosine kinase. Dasatinib is a multi-targeted kinase inhibitor of BCR-ABL and SRC family kinases. It is more active against the wild-type BCR-ABL as well as all but one the imatinib-resistant BCR-ABL mutants tested.[5] It has been shown to be effective in CML resistant to

imatinib or in patients intolerant of imatinib. Major hematologic responses (complete hematologic response and no evidence of leukemia) ranged from 31% to 59% and cytogenetic response [complete (0% Ph + cells) and partial (> 0% -35%) responses] from 30% to 58%.[1] The median duration of major hematologic response was 3.7 months in lymphoid blast CML and 4.8 months in Ph+ ALL. Major toxicities are myelosuppression and bleeding events (e.g., CNS and GI). Most bleeding events are associated with thrombocytopenia. Myelosuppression is generally reversible and managed by reducing or withdrawal of the drug. Other common adverse reactions include diarrhea, headache, skin rash, fatigue, and nausea. The wholesale cost of a 30-day supply of dasatinib (70 mg twice daily) is $4205.

Clinical Implications

CML is most common in the middle-aged and elderly with an annual incidence of 1 to 2 per 100,000 individuals. There are three phases of the disease; chronic, accelerated, and blast phases. The majority of patients (85%) are diagnosed in the chronic phase. While imatinib is considered first line therapy, resistance is becoming more problematic at the later stages of the disease due to mutations of BCR-ABL. Dasatinib is an important addition to the treatment CML.

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CME Questions

5. In the study by Gandhi and coworkers, one of the factors that were noted to be the cause of a medical error was:
a. performing too many diagnostic tests
b. lack of referral to a subspecialist
c. failure to act or follow up on diagnostic results
d. failure to obtain a second opinion on a biopsy sample
e. age of the patient

6. Which of the following statements is false?
a. Advanced colon neoplasia does not occur in anemic patients with ferritin levels above 50 ng/ml.
b. Serum ferritin levels of < 50 ng/ml and 50-100 ng/ml have similar risks for advanced colon neoplasia.
c. Nonanemic otherwise normal risk patients have less than 2% likelihood of colon neoplasia at colonoscopy.
d. More than 6% of anemic patients with ferritin < 50 ng/ml were found to have invasive colon cancer in this VA study.
e. The cutoff point for anemia in this VA study was 13 grams of hemoglobin.

Answers: 5 (c); 6 (a)

CME Objectives

The objectives of *Internal Medicine Alert* are:
- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Alendronate: How Much of a Good Thing?

The most popularly used pharmacotherapy for prevention and/or treatment of osteoporosis (OSPS) is bisphosphonate (BIS), specifically alendronate and risedronate. Once an appropriate treatment candidate is identified, therapy is usually employed on "indefinite" basis, since an optimum duration of treatment remains to be elucidated. Black, et al compared 5 years vs 10 years of BIS in a large population of patients (n = 1,099) by following all patients on BIS for 5 years, and then discontinuing BIS in half of the population and following the entire group for an additional 5 years.

As might be intuitively obvious, subjects who discontinued BIS during the second 5-year phase of the study did show declines in BMD (bone mineral density) and increases in markers of bone turnover compared with persons continuing BIS. More importantly, there was NOT an increase in fracture occurrence among persons who discontinued BIS after 5 years. All in all, even with 5 years of BIS treatment followed by 5 years with no active agent, BMD remained better than at baseline.

Long term use of BIS is generally considered safe, and the optimum duration of treatment remains unknown. This data suggests that for persons who have convincing rationale to discontinue BIS (eg, expense, inconvenience, intolerance), a hiatus of as long as 5 years may not increase risk of osteoporotic fracture. ■

Black DM, et al. JAMA. 2006;296:2927-2938.

Early Localized Prostate Cancer: Does Intervention Make a Difference?

PSA screening is utilized by most clinicians for men at age 50 and beyond. As a result, the distribution of prostate cancers discovered in middle-aged men has evolved to include a disproportionate number of early, localized tumors. There have been conflicting data about the impact on survival of intervention (radiation therapy or radical prostatectomy) in persons with localized disease.

The SEER database (Surveillance, Epidemiology, and End Results) provides observational data on US cancer registry patients representing 14% of the US population. From this database, men aged 65-80 (n = 111,640) with a new diagnosis of prostate cancer in the 1991-1999 time period were classified as either receiving active intervention or observation.

At the end of a 12-year study period, the hazard ratio for death was 31% greater in men in the observation group ($p = < 0.05$) than in men who received active intervention. Active intervention was associated with increased frequency of incontinence and erectile dysfunction compared to observation, although the latter population had more obstructive voiding symptoms.

Observational data cannot provide conclusive answers to questions about outcomes related to particular interventions. Results from randomized interventional trials to more conclusively address the question of whether active treatment improves outcomes in senior men with localized prostate cancer are pending. ■

Wong YN, et al. JAMA. 2006;296:2683-2693.

CV Biomarkers: The More Is Not Always the Merrier

Initiated in 1948, the Framingham Heart Study is the longest ongoing epidemiologic study in the United States. Thanks to reports stemming from this observational data set, we have come to recognize "conventional" risk factors for cardiovascular disease (CVD): smoking, hypertension, and cholesterol. Although attributable risk for CVD from these risk factors is substantial, emerging biomarkers—eg CRP, brain natriuretic peptide (BNP), plasma rennin, homocysteine, urinary albumin-to-creatinine ratio—might provide greater risk prediction.

Wang, et al followed 3,209 Framingham Heart Study participants who were free of known cardiovascular disease at baseline for 7.4 years (mean) to evaluate the relationship between 10 biomarkers (individually and in aggregate) and CVD.

After adjustment for conventional risk factors, each individual biomarker was associated with an incremental increase in CVD risk, most prominent of which was BNP (hazard ratio = 1.25). However, even though biomarkers did independently predict risk for CVD, the incremental amount added in addition to conventional risk factors was reported to be only "modest." Although biomarkers are associated with CVD risk, conventional risk factors are responsible for the majority of attributable risk. ■

Wang TJ, et al N Engl J Med. 2006;355:2631-2639.

Tell Me A Story

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*
Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

Dr. Grauer reports no financial relationship to this field of study.

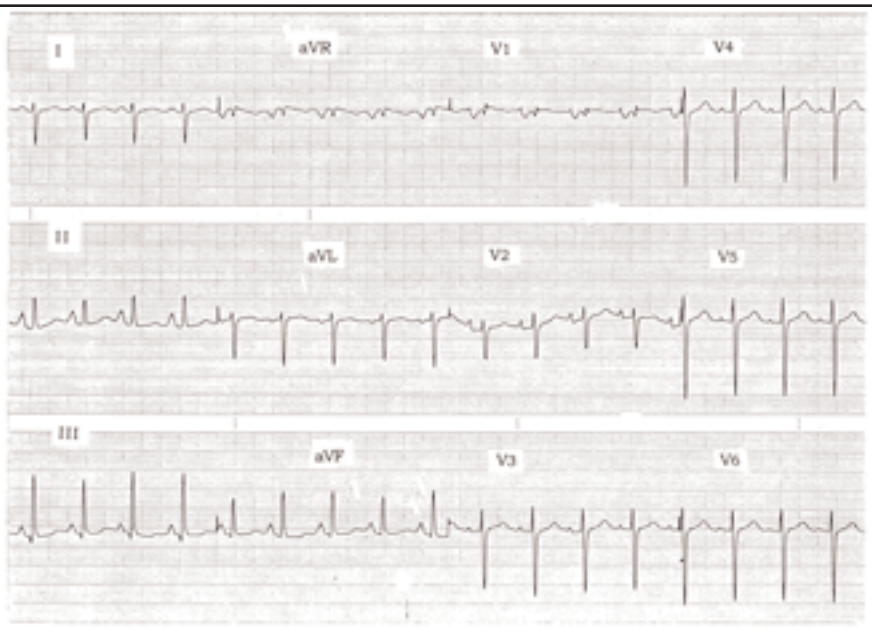

Figure. 12-lead ECG obtained from a middle-aged heavy smoker.

Clinical Scenario: The ECG in the Figure was obtained from a middle-aged woman with shortness of breath. She is a long-time heavy smoker. How would you interpret her 12-lead ECG?

Interpretation/Answer: The story told by this ECG is that of significant pulmonary disease. The rhythm is sinus tachycardia at a rate of about 110/minute. There is definite RAD (right axis deviation), as the QRS complex in lead I is predominantly negative. There is ECG evidence of bilateral atrial abnormality—tall peaked P waves in the inferior leads consistent with RAA (right atrial abnormality); and a very deep, negative component to the P wave in lead V1 consistent with LAA (left atrial abnormality). There is an r prime addition to the end of the small QRS complex in lead V1. Finally, deep terminal S waves persist across the precordial leads, such that transition never occurs.

The ECG diagnosis of RVH (right ventricular hypertrophy) is often difficult to make. This is because there is no single finding that establishes this diagnosis with certainty. Instead, a combination of findings in the right clinical setting suggests the presence of RVH. This is the case here, in which this middle-aged, long-term smoker manifests RAD, RAA, an r prime pattern in lead V1, and persistent deep, S waves across the precordium. The marked degree of RAD and the very tall and peaked P waves in the inferior leads suggests significant RVH and/or pulmonary hypertension. In view of this patient's shortness of breath occurring in the setting of tachycardia and RVH on ECG, consideration should be given to the possibility that an acute event (ie, pulmonary embolism) may have precipitated her symptoms. ■

In Future Issues: **Colonoscopic Withdrawal Times during Screening Colonoscopy**

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

This Month's Issue Focuses on Women's Health

Breast Cancer Rates Have Dropped Since WHI of 2002

Several important papers have been published in the last 2 months, none more important than the realization that breast cancer rates have dropped precipitously since the publication of the Women's Health Initiative (WHI) in 2002. The issue of estrogen-alone (not in combination with a progestin) and the risk of breast cancer is addressed in a new paper, as is the use of herbal supplements to treat postmenopausal vasomotor symptoms in women who have stopped HRT. Finally the duration of treatment of bisphosphonates for osteoporosis gains some clarity with publication of new data from the Fracture Intervention Trial.

The WHI study of combined estrogen and progesterone was halted in 2002 when it was found that women on the drug combination were at increased risk of breast cancer. Prior to the publication of the study, it was estimated that 30% of American women over the age of 50 were taking HRT. Within 6 months of the publication of WHI, half of those women had discontinued HRT. Now preliminary data suggests that breast cancer rates dropped precipitously in 2003 compared to 2002. The decline was most pronounced in women over the age of 50, and the biggest decline was in estrogen-receptor-positive breast cancer. Breast cancer rates had been rising steadily in this country at an average of 1.7% per year until 1998 when the rate began declining at 1% per year. The 7% drop seen in 2003 was the largest single decrease ever seen within a single year. The data was presented at the 29th Annual San Antonio Breast Cancer Symposium by researchers from MD Anderson. In a separate study, researchers from Northern California presented their own data that showed a decrease in hormone use of 68% between 2001 and 2003, and a decrease in breast cancer rates of 10-11%, which was sustained to 2004 (*J Clin Oncology* 2006;24:e49-50). The implication is that the sudden decrease in HRT use is responsible for the decrease rate of breast cancer, a conclusion supported by the dramatic decrease in ER positive cancers in postmenopausal women.

In contrast to the findings of the estrogens/progesterone wing of the Women's Health Initiative, the estrogen-only wing showed no increased risk of breast cancer (*JAMA*. 2004;291:1701-12). This was in contrast to several European studies, including the Million Woman Study, which showed an increased rate of breast cancer with unopposed estrogen (*Lancet*. 2003;362:419-427). Now a new study also suggests that estrogen-only is associated with a slightly increased risk of breast cancer. The study from Finland looked at nearly 85,000 women using oral or transdermal estradiol, 8,000 women using oral estriol (widely used in Europe but uncommonly used in the United States), and 18,000 women using vaginal estrogens for least 6 months were followed from 1994 through 2001. There was no increase risk for breast cancer for estradiol use of less than 5 years. Women who used estradiol for more than 5 years had a relative risk of breast cancer of 1.44 (1.29-1.59). Oral and transdermal estradiol conveyed similar risk. Oral estriol and vaginal estrogens did not increase breast cancer risk. The authors con-

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clude that the use of estradiol for more than 5 years is associated with a increased risk of breast cancer (*Obstet and Gynecol*. 2006;108:1354-1360).

Herbal Supplements to Treat Vasomotor Symptoms

Many women who have stopped HRT have tried herbal supplements to treat vasomotor symptoms. A new study compares the effectiveness of black cohosh, multibotanicals, and soy with HRT and placebo. Researchers from the University of Washington enrolled 351 women who were in menopausal transition or were postmenopausal. They were given black cohosh 160 mg daily, multibotanical with black cohosh 200 mg plus 9 other ingredients, multibotanical plus dietary soy counseling, HRT with conjugated equine estrogen 0.625 mg daily with or without medroxyprogesterone 2.5 mg daily, or placebo. There was no difference in vasomotor symptoms between the herbal interventions and placebo at 3, 6, or 12 months or for the average over-all follow-up time points ($P > 0.05$ for all comparisons), with the exception that symptom intensity was significantly worse with the multibotanical plus soy compared with placebo ($P = 0.016$). Hormone therapy was effective at reducing vasomotor symptoms ($P < 0.001$). The authors conclude that black cohosh alone or as part of a multibotanical regimen was ineffective at treating menopausal vasomotor symptoms (*Ann Int Med*. 2006; 145: 869-879). As pointed out in an accompanying editorial, even though herbal supplements were found to be ineffective, the good news is that women in the placebo group had a 30% reduction in the severity and frequency of vasomotor symptoms during the 12-month follow up, a number that probably reflects the natural history of postmenopausal symptoms (*Ann Int Med*. 2006;145:924-925).

Bisphosphonates to Treat LBD, After 5 Years?

Since WHI, bisphosphonates have become the drugs of choice for many women with low bone density. Treatment with bisphosphonates for 5 years is safe and effective; however, treatment beyond 5 years has been debated with some experts recommending a "drug holiday" after 5 years because of a concern about diminished bone strength and microfractures. A new study suggests that there is no harm in extending treatment beyond 5 years, although there is minimal benefit. In the Fracture Intervention Trial (FIT), 1,099 postmenopausal women who had used alendronate for 5 years were randomized to 5 more years of alendronate 5 mg per day, 10 mg per day, or placebo. Outcomes were hip bone mineral density (BMD) with an exploratory outcome measure of fracture incidence. Compared to women who continued alendronate, those who were switched to placebo at 5 years had declines in BMD at the total hip (-2.4%; 95% CI, -2.9% to -1.8%; $P < 0.001$) and spine (-3.7%; 95% CI, -4.5% to -3.0%; $P < 0.001$). Still, despite discontinuing alendronate, BMD remained at levels above pretreatment levels 10 years earlier. The cumulative risk for non-vertebral fractures was not significantly different between those continuing or discontinuing alendronate (19% vs 18.9%). Those who continued alendronate had significant lower risk of clinically recognized vertebral fractures, however, (5.3% placebo vs 2.4% alendronate) but no significant reduction in morphometric vertebral fractures. Of the women continuing alendronate, 18 underwent bone biopsies and none showed any qualitative abnormalities. The authors conclude that discontinuing alendronate after 5 years results in a moderate decline in BMD, a gradual rise in biochemical markers, but no higher fracture risk other than for clinical vertebral fractures compared to women who continued alendronate. The data also suggests that stopping alendronate at 5 years is safe, although the authors suggest that high-risk women may want to continue beyond 5 years (*JAMA*. 2006;296:2947-2953). Interestingly, no cases of osteonecrosis of the jaw were reported in women who took alendronate for 10 years.

FDA Actions

The FDA has approved a new estradiol gel for the treatment of moderate to severe vasomotor symptoms assisted with menopause. The gel, which is applied daily, supplies the lowest dose of estradiol approved by the FDA for this indication. Estradiol gel will be marketed as "Elestrin" by Kenwood Therapeutics.

The FDA has approved Novartis' combination antihypertensive "Exforge." The drug combines valsartan and amlodipine in one pill that is dosed once daily. It is expected to be marketed by September 2007.

The FDA has approved the first generic ondansetron injection (Zofran) for the prophylaxis of postoperative nausea and vomiting, and nausea and vomiting associated with cancer chemotherapy. The generic is manufactured by Teva pharmaceuticals.

The FDA has also approved generic oxybutynin extended release tablets (Ditropan XL). 'The new generics will be available in 5 mg and 10 mg extended-release tablets made by Mylan, and 50 mg extended-release tablets manufactured by Impax Laboratories. Oxybutynin is indicated for once daily treatment of overactive bladder in patients with urge incontinence, urgency, and frequency.

A generic bupropion extended-release tablet has been approved by the FDA. The generic version of Wellbutrin XL for the treatment of depression will be available in 150 mg and 300 mg tablets. The new generic is manufactured by Anchen Pharmaceuticals. ■