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INSIDE

Financial Disclosure: *Internal Medicine Alert's* editor, Stephen Brunton, MD, is a consultant for Abbott, Amylin, Boehringer Ingelheim, Eli Lilly, Endo, Novartis, and Novo Nordisk. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

Diagnosing UTI is as Simple as 1, 2, 3

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Residency Program Director, Associate Professor of Family Medicine, University of Alabama at Birmingham School of Medicine—Huntsville Regional Medical Campus, Huntsville

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

Synopsis: *Three criteria identify women who would benefit from empiric antibiotics for cystitis.*

Source: McIsaac WJ, et al. *Arch Intern Med.* 2007;167:2201-2206.

While the practice of using empiric antibiotics to treat women who present with symptoms of cystitis is common and recommended,[1] physicians are not adept at identifying which women actually need treatment. In a recent study,[2] physicians prescribed antibiotics 60% of the time that cultures were negative and did not prescribe them for 25% of women who had positive cultures. Building on and extending their previous work,[3] McIsaac and colleagues tested a 4-item decision aid. The four criteria were: burning or pain on urination, symptoms present for only 1 day, leukocytes on dipstick, and nitrites on dipstick. The presence of two or more criteria predicted a positive culture at least 70% of the time, and the rule recommended an antibiotic prescription and no culture. Women with only one or no criteria had a probability of infection of 30%. In this situation, the recommendation was for a urine culture and an antibiotic only if the culture were positive. The current validation study was conducted in April 2002 in the community practices of Canadian family physicians. Inclusion criteria were female gender and age 16 or greater with symptoms suggestive of acute cystitis. Women who were pregnant, living in nursing homes, immunocompromised, taking antibiotics, or who had renal tract abnormalities or indwelling catheters were excluded. The 331 subjects (average age 45.2 years) provided a clean-catch urine sample that was dipped for leukocytes and nitrites and sent for culture. The physicians recorded the subjects' signs and symptoms, their diagnoses, and whether they were prescribed antibiotics. They had the leukocyte and nitrite results and were asked to indicate whether they would normally have obtained a urine culture in each case.

VOLUME 30 • NUMBER 3 • FEBRUARY 15, 2008 • PAGES 17-24

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The patients rated the severity of their symptoms on a four-point scale (none, mild, moderate, severe). They were asked whether they would be willing to wait for the report of the urine culture before a decision was made on prescribing antibiotics. A urine culture was termed positive if it contained ≥ 10^2 colony-forming units (CFU)/ml.

Ninety-eight percent of women reported at least one urinary symptom (frequency, urgency, burning or pain). Two hundred eight (63%) cultures were positive. As the number of criteria increased, so did the percentage of positive cultures (0, 1, 2, 3, and 4 criteria and 24%, 41%, 68%, 76%, and 88%, respectively). The UTI signs and symptoms that were statistically significant were urgency, burning/painful voiding, voiding small amounts, flank pain/discomfort, greater than trace leukocytes, and positive nitrites. Only one day duration of symptoms was not associated with a positive culture. This criterion was dropped and the probabilities of positive culture were calculated with the remaining 3 criteria:

# of criteria	+ urine cultures
0	6/26 (23%)
1	35/81 (43%)
2	110/160 (69%)
3	57/64 (89%)

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

ASSOCIATE PUBLISHER: Lee Landenberger.

MARKETING PRODUCT MANAGER: Shawn DeMario.

MANAGING EDITOR: Iris Williamson Young

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

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Using this decision aid, 224 women (those with ≥ 2 criteria) would have been prescribed an antibiotic without getting a culture, and 107 women (≤ 1 criterion) would have been cultured and told to wait until the results were available before getting an antibiotic. Of the 224 women getting antibiotics, 57 (25%) would not have needed them ("unnecessary antibiotics"). Of the 107 women awaiting culture, 41 (38%) would eventually need them.

In reality, the physicians prescribed antibiotics to 292 women, 68 more than would have received them if the physicians had followed the decision rule. 95 women received "unnecessary antibiotics," 38 more than would have received them, again, if the rule had been followed. The physicians ordered 259 urine cultures, 152 more than the decision rule recommended.

Three hundred nineteen women were asked whether they would be willing to wait for urine culture results before receiving a prescription for antibiotics. One hundred forty reported they definitely would not. These women reported more severe symptoms than women who were willing to wait. Applying the decision rule to this group of 319 women, 36 would have received a recommendation to wait. Only nine women in this group of 36 had a positive culture.

When the investigators looked at the strategy of prescribing empiric antibiotics based on symptoms alone (that is, women with at least two symptoms and without leukocyte and nitrite results), 294 of 327 women would have received antibiotics and 100 of these would have received them unnecessarily.

COMMENTARY

This seems like a relatively easy decision rule to remember and apply. Choosing the proper antibiotic may not be as easy. *Escherichia coli* is the most frequent offender in urinary tract infections, followed by *Staphylococcus* saprophyticus (especially in younger women), *Klebsiella* species, *Proteus* species, and enterococci. According to my hospital's microbiology laboratory, trimethoprim/ sulfamethoxazole (TMP/SMX, Bactrim®), the most common antibiotic ordered empirically for women with cystitis, was effective against *E. coli* only 79% of the time. Coincidentally, levofloxacin also earned a 79% rating. Amoxicillin fared far worse at 54%. My lab does not publish the susceptibilities for *S. saprophyticus*, but it is generally considered susceptible to TMP/SMX. Ordering TMP/SMX would be great if the culprit is Klebsiella species (96%), but not so great if it's *Proteus mirabilis* (78%). Nitrofurantoin is a good second-line drug. However, it has no activity against *Proteus*, and you generally cannot get away with anything less than seven days of treatment.

There are a couple of thoughts about this study that

gave me pause. The cutoff of 10^2 colony-forming units for a positive culture is lower than the one I generally use, but it is a one that shows up frequently in studies of urinary tract infections. The effect is to include many more women in the "culture-positive" group, including people that I probably would not have treated. The other thought is how to handle the patient who will not wait for culture results. One strategy would be to "cave-in", prescribe an antibiotic, and hope for the best, including no adverse drug reaction. My preferred strategy would be to discuss the risks, including adverse drug reactions and the development of antibiotic resistance, and the benefits of taking an antibiotic. If the patient symptoms were severe, one could turn to a urinary anesthetic such as phenazopyridine (Pyridium®). My impression, though, is that the recent news of community-based methicillin-resistant *Staphylococcus aureus* has made patients more receptive to thinking twice before taking an antibiotic. ■

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The Long-term Risk for Fatal Pulmonary Embolism after Discontinuing Anticoagulant Therapy for Venous Thromboembolism

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

Synopsis: Patients with a first VTE event occurring in association with a reversible or time-limited risk factor should be treated with anticoagulants for at least three months, whereas patients with a first PE should be treated for at least six to 12 months; in fact, a case can be made for indefinite anticoagulant therapy in PE patients who have a great concern about recurrent PE and/or who are minimally concerned about the bleeding risk of anticoagulant therapy and the need for frequent determinations of the INR.

Source: Douketis JD, et al. *Ann Inter Med.* 2007;766-772.

When deciding whether to discontinue anticoagulant therapy for venous thromboembolism (VTE), the subsequent risk for fatal pulmonary embolism (PE) is obviously among the most important prognostic considerations since knowledge of the annual risk for fatal PE will undoubtedly influence any decision about discontinuing anticoagulation despite the low overall risk of fatal PE in these patients. The risk of fatal PE can be expressed in absolute terms or in conditional terms as the risk of fatality if recurrent disease occurs.[1, 2]

Douketis and his international (Canada, Sweden, Italy) colleagues performed a prospective cohort study at academic medical centers in an attempt to provide reliable and precise estimates of the annual risk for fatal PE and the case-fatality rate of disease recurrence if anticoagulation was discontinued and then they assessed these outcomes according to the initial presentation (deep venous thrombosis (DVT), PE, or both) and its etiology (secondary or idiopathic).[3] They studied 2052 patients (1450 had DVT, 310 had PE, and 292 had DVT and PE) and determined the case-fatality rate of recurrent VTE, the incidence rates of any fatal PE and the rates of any definite or probable PE per 100 person-years of follow-up. The well defined and homogenous study population all had suffered a first episode of symptomatic VTE, had received similar initial anticoagulation and had completed, on average, six months of oral anticoagulant therapy. Careful follow-up revealed that in patients with a first episode of symptomatic VTE who had discontinued anticoagulant therapy, the risk for fatal PE was 0.19 to 0.49 events per 100 person-years and the case-fatality rate from recurrent VTE varied from 4% to 9%. This was contrasted with published data which reported that the annual risk for major hemorrhage if anticoagulation was continued at approximately 2%.

■ COMMENTARY

Douketis and his associates[3] have provided important information required by every clinician who treats patients with VTE or PE. The case-fatality rates which they carefully studied measures the clinical impact of disease recurrence if anticoagulation is discontinued, which can be compared with the case-fatality rate of bleeding if anticoagulation is continued.[4,5] These findings become important when applied to advising patients with a first symptomatic VTE about their prognosis after discontinuing anticoagulation therapy[6] The reported rate of fatal PE should reassure patients that their prognosis is good after stopping anticoagulation with a low (less than 1% per year) risk for future fatal PE that is further reduced if the initial VTE occurred after exposure to a transient risk factor or if they had already discontinued anticoagulants for more than one year. Of course, it should be recognized that these findings are less pertinent to patients with active cancer, permanent immobili-

ty, or high risk thrombophilia, who should not be identified with the study cohort because these patients usually receive lifelong anticoagulation therapy.[6] A potential limitation of the Douketis study[3] is that the duration of anticoagulant therapy was not standardized before entry into the inception cohort which theoretically could affect the incidence of fatal PE after anticoagulant treatment was stopped; however, in prespecified regression analyses, they found that the duration of anticoagulation, which ranged from three months to more than 12 months did not affect the incidence of fatal PE after discontinuation of therapy.

It has been demonstrated that the annual risk for disease recurrence if anticoagulation is discontinued is about 10%[7] among patients with a first idiopathic VTE and that the annual risk for major bleeding if anticoagulation is continued is only about 2%.[8] The calculated annual risk for death from bleeding is 0.16% to 0.18%, whereas the annual risk for death from recurrent VTE if anticoagulation is discontinued is 0.40 percent to 0.90% (ie, 10% recurrence risk times 4% to 9% case fatality rate), suggesting that the balance of risks seem to favor continuing anticoagulant therapy. However it is critically important to recognize that because the absolute difference in risk for death with either approach is extremely small, other individual patient factors (the D-dimer levels after discontinuing anticoagulant therapy,[9] the estimated risk for nonfatal outcomes for example, postthrombotic syndrome, chronic pulmonary hypertension,[10,11] and patient preferences) should be factored into the clinical decision about whether to continue or stop anticoagulants in each individual patient.

In summary, it would appear that the duration of the anticoagulant therapy in patients with VTE varies with the clinical setting as well as with patient preferences. Patients with a first VTE occurring in association with a reversible or time-limited risk factor should be treated with anticoagulants for at least three months whereas patients with a first PE should be treated for at least six to 12 months; in fact, a case can be made for indefinite anticoagulant therapy in PE patients who have a great concern about recurrent PE and/or who are minimally concerned about the bleeding risk of anticoagulant therapy and the need for frequent determinations of the INR. Finally, the results of the Douketis study[3] would suggest that consideration should be given to continuing anticoagulants indefinitely in all patients with VTE; however, since the risk of death is extremely small whether or not anticoagulants therapy is continued after 3-12 months of therapy, clinical judgment will play an important role in the final decision. ■

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Special Feature

Female Physicians at Greater Risk for Suicide

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center, Section Editor, Updates, Section Editor, HIV

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

This article first appeared in the January 2008 issue of Infectious Disease Alert.

Source: *Peterson MR, Burnett CA. The suicide mortality of working physicians and dentists. Occupational Medicine Advance Access published October 27, 2007*

FEMALE PHYSICIANS HAVE MORE THAN TWICE THE rate of suicide as other professional women and are proportionally at greater risk compared with their male physician counterparts. That was the unhappy conclusion of these authors who examined the National Occupational Mortality Surveillance Data for 26 states in the United States from 1984-1992. Age-standardized suicide rates were calculated for male and female physicians and male dentists (there were too few female dentists to assess); data for white vs non-white workers were also examined.

White male physicians > 45 years of age had two times the rate of suicide as their white female physician counterparts. But when proportional risk assessments to other working groups were made, women were at far greater risk relative to their working professional female colleagues. In contrast, because the overall rate of suicide for men in the general population is 5 times higher than that for women, the proportional rate for male physicians relative to their male counterparts were significantly less than the

proportional rate for female physicians relative to their female counterparts. (White male dentists had similar suicide rates to white male physicians). Suicide rates for male physicians was similar to that for other male professionals, but lower than non-professionals. In addition, suicide rates for men < 45 years of age were lower than then their older colleagues, and clearly increased with age. Suicide rates in women were not age-related.

Similar results were observed by the AMA in the 1960s-1970s. That earlier data also found a higher risk of suicide in female physicians, but also found that location may be an important factor, as may the physician speciality, neither of which was examined in the current study. ■

Pharmacology Update

Nebivolol Tablets (Bystolic™)

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

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.

THE FDA HAS APPROVED ANOTHER BETA-ADRENERgic blocker. Nebivolol is a selective β_1 adrenergic receptor antagonist, and seems to possess additional pharmacologic action that is related to the L-arginine/nitric oxide pathway.[1] It is licensed from Mylan Laboratories, Inc. and marketed by Forest Pharmaceuticals Inc as Bystolic.

Indications

Nebivolol is indicated for the treatment of hypertension as monotherapy or in combination with other antihypertensive agents.[2]

Dosage

The recommended initial dose is 5 mg once daily. If further blood pressure reduction is required, the dose may be increased at 2-week intervals up to 40 mg daily. Patients with severe renal impairment (creatinine clearance less than 30 mL/min) or moderate hepatic impairment should be initiated at 2.5 mg daily and titration should be done with caution. Nebivolol may be taken without regard to meals.[2]

Nebivolol is available as 2.5 mg, 5 mg, and 10 mg tablets.

Potential Advantages

Nebivolol does not appear to negatively affect lipid or carbohydrate metabolism. It does appear to benefit endothelial function and may reduce systemic oxidative stress.[1,3] Compared to atenolol, nebivolol was less likely to negatively affect insulin sensitivity and erectile dysfunction.[4,5]

Potential Disadvantages

Nebivolol is metabolized by CYP2D6 therefore drugs that inhibit or induce this enzyme would be expected to affect its plasma level. In patients who are poor metabolizers, β_1 selectivity is reduced. As monotherapy, nebivolol was somewhat less effective in African Americans compared to Caucasians.[2]

Comments

Nebivolol is a selective b1 adrenergic receptor inhibitor at lower doses (5 mg to 10 mg) and inhibitor both β_1 and β_2 receptors at higher doses or in patients that are poor metabolizers.[2] Nebivolol is a racemic mixture-and both enantiomers appear to contribute to its pharmacologic effect. The d-nebivolol is a selective β_1 adrenergic blocker and l-nebivolol cause vasodilation via the L-arginine-nitric oxide pathway. The efficacy as monotherapy was demonstrated in three placebo controlled randomized studies in patients with mild to moderate hypertension with baseline diastolic blood pressure of 95 to 109 mm Hg (n = 2016). Patients were randomized to doses of nebivolol ranging from 1.25 mg to 40 mg or placebo for 12 weeks.[2,6] At the recommended starting dose of 5 mg the least square placebo-subtracted reduction of sitting trough blood pressure ranged from -3.3 to -5.5 for diastolic blood pressure (SiDBP) and -2.6 to -8.1 for systolic blood pressure (SiSBP). All the differences in SiDBP were statistically different at $p < 0.05$. A dose dependent trend was generally observed. Blood pressure reduction was seen within 2 weeks and was maintained over 24 hours.[2] Nebivolol is effective as monotherapy in African American patients but may be less effective in

magnitude of effect compared to Caucasian.[2,7] In a number of comparative studies, nebivolol (5 mg daily) was similar to atenolol (50 mg to 100 mg daily), bisoprolol (5 mg daily), and metoprolol (100 mg twice daily) as well as to other classes of antihypertensives.[8] Nebivolol has shown benefit (all cause mortality or cardiovascular hospitalization) compared to placebo in heart failure[9] but it is currently not FDA approved for this use. Nebivolol is well tolerated with the most common adverse effects (2-7%) including headache, fatigue, dizziness, diarrhea, and nausea.[2] The monthly cost of nebivolol is $45, which is about 3 times that of generic atenolol.

Clinical Implications

Nebivolol is the newest β-adrenergic blocker and is the 19th drug in this class approved in the US. Beta-blockers in general, and atenolol in particular, have fallen out of favor as first line therapy as they may be less effective in reducing strokes compared to other classes of antihypertensives.[10] Whether nebivolol's additional vasodilatory effect make it unique within this class remains to be established. ■

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CME Questions

6. The acute cystitis decision rule uses three criteria to determine which women require empiric antibiotics. The criteria include all the following, except:
a. duration of symptoms.
b. presence of nitrites on dipstick.
c. burning or pain on urination.
d. presence of leukocytes on dipstick.

7. Warfarin therapy being given to patients with venous thromboembolic pulmonary emboli:
a. should be discontinued in all patients after 12 months of therapy.
b. should be continued indefinitely in selected patients.
c. may safely be discontinued after three months of therapy.
d. is not associated with an increased risk of hemorrhage.

Answers: 6 (a); 7 (b)

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.

Testosterone in Older Men: Is Low Normal Too Low?

After attaining peak adult testosterone levels, men experience a continuous decline in testosterone (TST) of about 1% per year. Concomitant changes with aging such as sarcopenia, cognitive decline, reduced strength, and increased abdominal fat mass have been associated with this loss of TST. The definition of "normal" testosterone includes a wide range, and since most late-life males who have TST levels checked do not have an available early-life TST level for comparison, it is difficult to know whether or not low-normal levels represent a significant pathologic contrast from levels in youth.

Emmelot-Vonk et al studied the effects of TST supplementation among Dutch men with low-normal TST levels. Outcomes measured included functional mobility, handgrip strength, leg strength, cognitive function, BMD, lipids, glucose and quality of life (scored by SF-36). In this randomized double-blind trial, men (n=237) received either 80 mg testosterone undecenoate p.o. b.i.d. or placebo for 6 months.

Although TST did produce meaningful increases in lean body mass, and a corresponding decrease in fat mass, there was no concomitant functional mobility or strength change. Of concern, TST was associated with a 20% decline in HDL, without any measurable benefits in QOL or cognitive function.

This study does not support benefit from supplemental TST in men with low-normal TST levels. ■

Emmelot-Vonk, et al. JAMA. 2008;299(1):39-52.

CT Pulmonary Angiography as Good as Ventilation-perfusion Scanning for Suspected Pulmonary Embolus

Pulmonary embolism (PEM) is responsible for over ¼ million deaths in the US each year, but accurate and timely diagnosis can sometimes prove elusive. The "gold standard" noninvasive test for at least 3 decades has been the ventilation-perfusion scan (VQS), which has an extraordinarily high specificity: a negative VQS essentially excludes PEM. Unfortunately, the majority of VQS results are reported as low-intermediate PEM probability, leaving a great deal of diagnostic uncertainty.

CT pulmonary angiography (CTPA), because it can be read simply as either positive or negative, is not hampered by this same uncertainty. Additionally, it can detect other chest pathology, although historically it has been considered less sensitive than VQS.

In this study, patients suspected of having PEM (n=1417) were randomized to PEM or CTPA. It is critical that PEM diagnostic tests not falsely exclude individuals who actually have the disorder (false negatives). Hence, the primary endpoint of the study was the number of individuals developing symptomatic proximal deep vein thrombosis (DVT) or PEM in the 3 months following an initial negative investigation.

There was no statistically significant difference in the accuracy of PEM vs CTPA. Using standard protocols which employ d-Dimer and leg venous ultrasound, CTPA and VQS have similar predictive value. ■

Anderson DR, et al. JAMA. 2007;298(23):2743-2753.

Vertebral Fracture Begets Vertebral Fracture

Vertebral fracture may be defined as a decrease of at least 20% in vertebral height, amounting to a height decrement of at least 4 mm. The Study of Osteoporotic Fractures offers a long-term observation of risk of osteoporotic vertebral fracture (VFX) in women with and without VFX at baseline. This study population was comprised of 9,704 midlife Caucasian women (mean age = 68.8, range 65-99 years) recruited within the United States from 1986-1988 and followed for an average of 14.9 years.

At the 15-year follow-up clinic visit, overall 18.2% of women had a new VFX, but the disproportion of incident VFX was markedly skewed towards those had had a prevalent VFX at baseline: 41.4% of the 394 women with baseline VFX at study enrollment had experienced one or more incident VFX, as compared with 14.2% of the 2,286 women without baseline VFX.

Currently recognized risk factors were associated with VFX including low body weight, BMD, smoking history, and age.

Pre-existing VFX was the most potent predictor of future VFX, and was also associated with increased risk for nonvertebral fracture. The predictive capacity of pre-existing VFX was independent of BMD, corroborating the current philosophy that BMD is a major contributor to, but not the only factor involved in, bone fragility. ■

Cauley JA, et al. JAMA. 2007;298(23)2761-2767.

Chest Pain After Bypass

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.

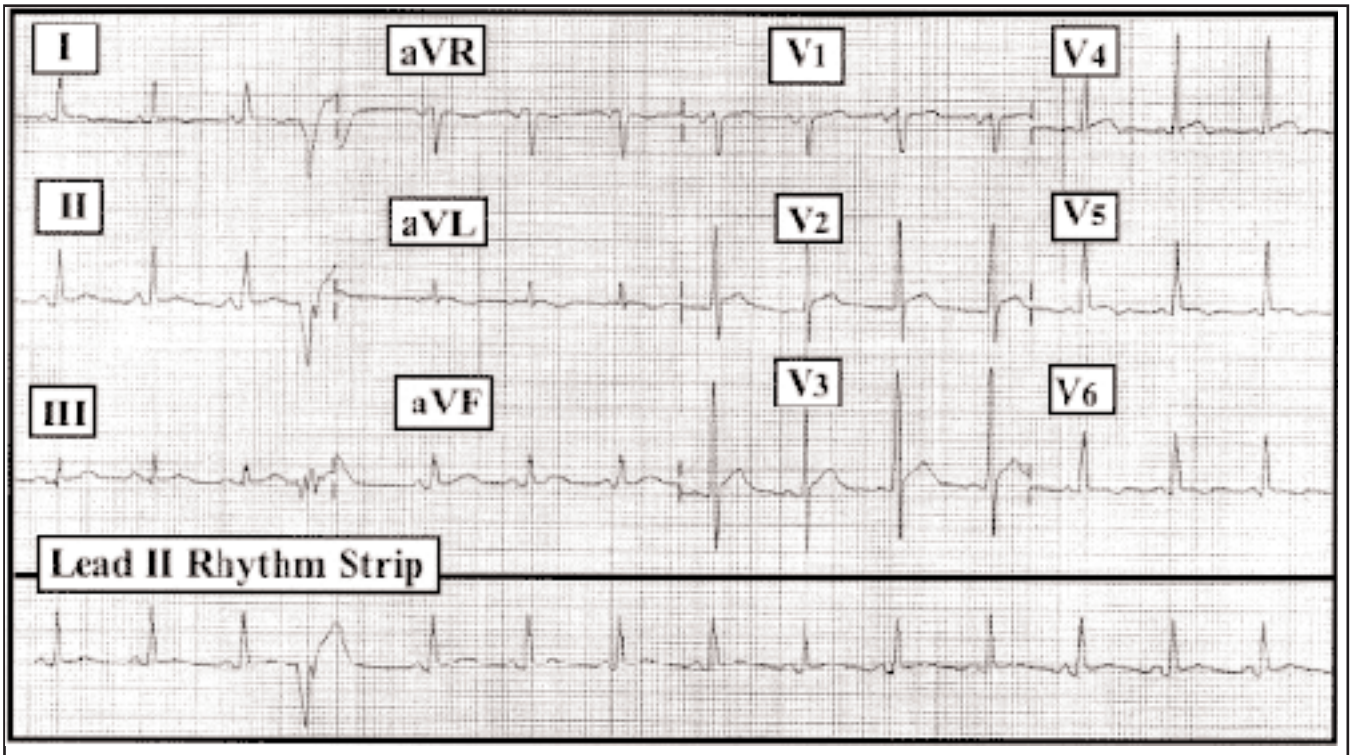

Figure: 12-lead ECG and lead II rhythm strip obtained from a 59-year-old man after coronary bypass.

Clinical Scenario:

The 12-lead ECG and lead II rhythm strip in the Figure were obtained from a 59-year old man several days after coronary bypass. He complained of postitional chest pain. How would you interpret his ECG given this clinical context?

Interpretation/Answer:

The rhythm is sinus at a rate of 90/minute. One PVC (premature ventricular contraction) is seen. All intervals are normal. The mean QRS axis is +40°. There is no sign of chamber enlargement. A small, narrow q wave is seen in leads III and V6. Transition is early (occurring between leads V1 to V2). However, the most interesting finding on this tracing is the subtle ST segment elevation that is seen in virtually all leads except aVR, aVL, and V1. There is beginning T wave inversion in leads V5, V6.

The finding of diffuse (albeit subtle) ST segment elevation in the absence of ST segment depression and only minimal (beginning) T wave inversion as seen here should strongly suggest acute pericarditis as the diagnosis. This is consistent with the clinical scenario in this case (ie, occurrence shortly after coronary bypass surgery and positional nature of the chest pain). Even though no pericardial friction rub was heard, the history, negative troponins, and serial ECGs obtained in this case were felt to confirm the diagnosis. ■

In Future Issues: **The Mystery of Warts: Duct Tape, Moleskin, or What?**

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.

Another Study Implicates Avandia

In this issue: *Rosiglitazone (Avandia) implicated in yet another study; Prilosec and Nexium not associated with cardiac events; Anastrozole (Arimidex) shown more effective than tamoxifen for treatment of early-stage breast cancer; antibiotics show no effect on sinusitis; FDA actions.*

THE HANDWRITING MAY BE ON THE WALL FOR GlaxoSmithKline's rosiglitazone (Avandia) with yet another study implicating the drug with an increased risk of heart failure, cardiovascular events and mortality when compared to other oral hypoglycemic agents. The study was a nested case-control analysis of a retrospective cohort study using health care databases in Ontario. The patient population was nearly 160,000 older (>65 years of age) type 2 diabetics on at least one oral agent. The primary outcome was emergency visit or hospitalization for congestive heart failure, while secondary outcomes were AMI and all-cause mortality. After a mean follow-up of 3.8 years, monotherapy with rosiglitazone was associated with an increased risk of CHF (RR 1.60; 95% CI 2.10; *P*<.001), AMI (RR 1.40; 95% CI, 1.05-1.86; *P*=.02), and death (RR 1.29; 95% CI, 1.02-1.62; *P*=.03). Thiazolidinediones in general were evaluated in the study, but the adverse effects were limited to rosiglitazone. Adverse effects were found in patients who took the drug as a single agent or in combination with other hypoglycemic drugs (*JAMA*. 2007;298:2634-2643). Meanwhile, two large pharmacy benefit managers, Prime Therapeutics and HealthTrans, have dropped rosiglitzone from their formularies and the Department of Veterans Affairs is severely limiting the drug's use. Sales of the drug dropped 27% in the second quarter of 2007 and 39% in the third quarter.

Prilosec and Nexium Cleared

Omeprazole (Prilosec) and esomeprazole (Nexium) are not associated with increased rates of cardiac events, according to statements on the FDA web site. Concern was raised after AstraZeneca submitted data from two long-term studies in patients with severe gastroesophageal reflux to assess treatment with either drug vs surgery. Evaluation of secondary outcomes raised the question of whether long-term use of these drugs increased risk of cardiovascular events including sudden death. In a statement published on the FDA web site (www.fda.gov) on December 10, the agency states that it has completed a comprehensive scientific review of known safety data for both drugs. Based on review of the two studies presented by AstraZeneca and analysis of 14 comparative studies of omeprazole, no evidence of increased rate of cardiac events was seen. "Therefore, FDA continues to conclude that long-term use of these drugs is not likely to be associated with an increased risk of heart problems. The FDA recommends that health-care providers continue to prescribe, and patient's continue to use, these products as described in the labeling for the two drugs."

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: iris.young@ahcmedia.com.

Anastrozole over Tamoxifen for Breast Cancer

Anastrozole (Arimidex) is more effective than tamoxifen as adjuvant treatment for early-stage breast cancer according to a study published online as an early release in the *Lancet Oncology*. The study looked at 6241 women with locally invasive breast cancer who were randomized to anastrozole or tamoxifen and followed for a median of 100 months. Primary endpoints were disease-free survival, and secondary endpoints were time to recurrence, incidence of new contralateral breast cancer, time to distant recurrence, overall survival, and death after recurrence. Endpoints were evaluated in the total population and in the hormone-receptor-positive subpopulation. The primary endpoint and all secondary endpoints favored anastrozole except for deaths after recurrence and overall survival for which there is no significant difference. Fracture rates were higher in patients receiving anastrozole compared to tamoxifen. There was no difference in cardiovascular morbidity or mortality between the two treatment groups. The authors conclude that the study "establishes long-term efficacy of anastrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with hormone sensitive, early breast cancer, and provide statistically significant evidence of a larger carryover effect after five years of adjuvant treatment with anastrozole." (*Lancet Oncology* early online publication, 50 December 2007).

Antibiotics and Steroids Not for Sinusitis

Antibiotics and topical nasal steroids are of no benefit for patients with acute maxillary sinusitis according to a new randomized controlled trial of 240 adults. Patients with acute non-recurrent sinusitis were randomized to treatment with antibiotics and nasal steroids, placebo antibiotic and nasal steroid, antibiotic and placebo nasal steroids, or placebo antibiotic and placebo nasal steroid. Amoxicillin 500 mg three times a day for seven days and budesonide spray once daily were the active drug use in the study. The main outcome was proportion of clinically cured at 10 days and the duration of symptoms. Antibiotics made no difference in the proportion of patients with symptoms lasting 10 days or more (29% with antibiotics, 33.6% with no antibiotics). Use of nasal steroid also made no difference for the same measure (31.4% with budesonide, 31.4% with no budesonide). The authors conclude that neither an antibiotic nor topical steroid alone or in combination was effective as the treatment for acute sinusitis in the primary care setting (*JAMA*. 2007;298:2487-2496).

FDA Actions

An expert advisory panel of the FDA has recommended against approving Merck's petition to take lovastatin (Mevacor) over-the-counter. This was the third request in 7 years for OTC status for the cholesterol-lowering drug. The advisers voted 10-2 against approval citing concerns whether patients were capable of determining if they are appropriate candidates for the medication. The FDA generally follows the advice of its advisory panels.

The FDA has approved yet another beta-blocker for the treatment of hypertension. MylanBertek's nebivolol (Bystolic) is a selective beta-1-adrenoreceptor blocker with vasodilating effects. The drug is the 19th beta-blocker approved in the United States.

Wyeth has received an approvable letter for bazedoxifene, a new selective estrogen receptor modulator (SERM) for the prevention of osteoporosis in postmenopausal women. In issuing the letter, the agency asked for more data on the risk of blood clots and stroke, problems that have plagued the other marketed SERM for this indication (raloxifene-Evista). The agency did not ask for new studies however. Wyeth is also seeking the indication for treatment of osteoporosis in postmenopausal women. When approved, bazedoxifene will be marketed as Viviant.

The FDA has issued a safety warning on fentanyl skin patches after several reports of deaths and life-threatening side effects associated with inappropriate use. The warning stresses that the patches are only for patients who are opioid-tolerant and have poorly controlled pain on other narcotic pain medications. The patches are not for postoperative pain or sudden or occasional pain. Patients who used the patch should be aware of the signs of fentanyl overdose. Patients and physicians should be aware of potential drug interactions and physicians and pharmacists need to instruct patients on appropriate use of the patch. Patients also need to be aware that heat sources such as heating pads, electric blankets, saunas, heated waterbeds, hot baths, sunbathing and even fever may result in sudden increases in blood levels of fentanyl.

The FDA has approved a new volume expander for the treatment of volume loss during surgery. German drugmaker Fresenius Kabi's Voluven utilizes a new synthetic starch that is insoluble in water. In clinical trials the product was found to be as safe and effective as Hespan, a currently approved starch solution volume expander. ■