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INSIDE

High-Dose Vitamin E Increases All-Cause Mortality

ABSTRACT & COMMENTARY

Synopsis: *A meta-analysis of 19 clinical trials found that vitamin E intake greater than the recommended 400 IU/day found a statistically significant relationship between increased dosage and all-cause mortality when compared to both controls and lower doses.*

Source: Miller ER, et al. *Ann Intern Med*. 2005;142:37-46.

A COMPREHENSIVE REVIEW OF ALL CLINICAL TRIALS SINCE 1966 involving men and non-pregnant women using vitamin E supplementation for more than one year compared to randomized controls were analyzed for all-cause mortality. Nineteen trials were included involving 136,000 participants. Nine of the trials involved vitamin E supplementation alone, and the 10 others had combinations with other vitamins and minerals. Dosages of vitamin E ranged up to 2000 IU/day with a median of 400 IU/day.

While vitamin E overall did not affect mortality, there was a dose-response relationship between higher vitamin E amounts and increased mortality. The average death risk across all trials was 1022 per 10,000 persons; the pooled risk difference comparing vitamin E with controls was 10 per 10,000 persons. For low-dosage vitamin E the risk was actually lower, while for vitamin E in doses greater than 400 IU/day the pooled risk difference was 39 per 10,000 persons.

Miller and colleagues note that the trials that tested high dosages involved adults with chronic disease, and some involved multivitamin combinations so the exact effect of vitamin E could not be isolated. Nonetheless, they still felt that the conclusions were compelling enough to recommend against high-dosage vitamin E supplementation.

COMMENT BY MARY ELINA FERRIS, MD

The editorial that accompanies this article in the *Annals of Internal Medicine* is appropriately titled "Vitamin E Supplements: Good in Theory, but is the Theory Good?"[1] Widespread belief in the benefit of antioxidants has led to vitamin E being the most widely used of

VOLUME 27 • NUMBER 7 • APRIL 15, 2005 • PAGES 49-56

this group, estimated to be taken by 22% of US adults older than 55 years of age.[2] However, while both epidemiological evidence and laboratory experiments have supported a role for the oxidative process in the pathogenesis of many diseases, actual clinical trials of antioxidants have not shown a clear benefit. Nevertheless, the prevailing opinion has been that no harm would be done to take the supplements in the hope that morbidity could be prevented.

This new meta-analysis indicates that harm may actually ensue, particularly with doses higher than the recommended daily allowances. Miller et al's conclusions may be criticized because 10 of the 19 trials in their analysis also included other supplements (particularly beta-carotene which has been shown to be harmful) which may confound the results. However, the fundamental fact that no real benefit has been proven from antioxidants, in addition to possible harm, should lead physicians to recommend against increased vitamin E supplementation at this time. ■

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Does Periodontal Inflammation Produce CAD?

ABSTRACT & COMMENTARY

Synopsis: *This study provides evidence of a direct relationship between periodontal microbiology and subclinical atherosclerosis. This relationship exists independent of C-reactive protein.*

Source: Desvarieux, M et al. *Circulation*. 2005;576-582.

CARDIOLOGISTS HAD PREVIOUSLY THOUGHT THAT high-grade stenoses or complete obstruction were the cause of most acute coronary events but we now know that the majority of acute coronary syndrome (ACS) events occur in coronary arteries whose lumens have usually been narrowed by no more than 50% by atherosclerotic plaquing. Over the past several years it has been clearly demonstrated that inflammation is a critical factor in all aspects of the atherosclerotic coronary artery disease (CAD) process. When present in the coronary arterial wall, inflammation generates the formation of foam cells followed by plaque formation that, over time, may develop into a vulnerable plaque with subsequent fissuring, rupture and thrombosis resulting in any or all manifestations of the ACS. Recently published studies have suggested that patients with ACS often exhibit a significant degree of systemic inflammation and in fact, an emerging body of evidence supports a critical role for the leukocyte in the development of the vulnerable plaque, as well as in the adverse outcomes which often occur following acute myocardial infarctions. It has been suggested that activation of a leukocyte enzyme appears to be an important factor in the initiation and propagation of the inflammatory process in the vulnerable plaque.[1-6]

Desvarieux and associates in the INVEST study investigated whether or not periodontal infections may

predispose patients to the development of subclinical atherosclerosis and/or symptomatic CAD. They collected 4561 sub gingival plaque samples from 657 subjects and quantitatively assessed the samples for 11 known periodontal bacteria and then evaluated each patient for cardiovascular risk factor measurements, a white blood cell count, a C-reactive protein determination and finally they assessed the carotid intima-media thickness (IMT). They found that the overall periodontal bacterial burden was related to the degree of carotid arterial thickness and that this relationship was specific to the causative bacterial burden and the dominance of etiologic bacteria in the observed microbiological niche. C-reactive protein values were unrelated to the periodontal microbiological status. They concluded that there was evidence of a direct relationship between periodontal microbiology and subclinical atherosclerosis independent of the observed C-reactive protein values.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

Myeloperoxidase (MPO) is an abundant leukocyte enzyme that may serve as a central participant in the initiation and propagation of the inflammatory process in vulnerable coronary arterial plaques thereby promoting instability of the fibrous cap and rendering the plaque more susceptible to rupture.[1-6] An elevated MPO level has been demonstrated to be of prognostic value in patients presenting with chest pain and also has been found to be an independent predictor of adverse cardiac outcomes in patients with ACS.[1,2] These adverse events are probably due to leukocyte activation, which produces an increased propensity for thrombus formation in the setting of plaque instability. Multiple studies all point toward the emerging role of MPO as a central participant in the inflammatory cascade which leads to acute myocardial infarctions.

Increased carotid IMT measurements have been found to be associated with a 2.3-increased relative risk for nonfatal MI or coronary death.[7] Patients with a dominance of oral pathogens causally related to periodontal disease in the INVEST study demonstrated thicker carotid IMT measurements then did noninfected patients even after adjustment for conventional risk factors. The study provided the first direct evidence of a possible role of periodontal bacteria in the development of coronary atherosclerosis and the relationship appears to be independent of the C-reactive protein level. One must recognize that the results of the study may have been confounded by the effects of the hundreds of bacterial species that ordinarily colonize the oral cavity and that were not studied and therefore, additional carefully controlled population studies will have to be performed. If the findings of the INVEST study are confirmed in these subsequent studies, the relationship of periodontal disease to CHD could prove to be of great public health importance because of the possibility that premature coronary atherosclerotic damage could be reduced or perhaps even reversed through selective control of the appropriate pathogenic periodontal bacteria by antibacterial or immunologic means. ■

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Idiopathic Edema and Obstructive Sleep Apnea in Women

ABSTRACT & COMMENTARY

Synopsis: *In women, obstructive sleep apnea appears to be associated with idiopathic edema, even after controlling for obesity.*

Source: Blankfield RP, et al. *Sleep Medicine*. 2004;5:583-587.

This was a prospective study of patients from 2 private family practice offices in Ohio. A single physician recruited consecutive edematous obese patients to participate; nearly agreed. He also recruited nonedematous patients to serve as controls, about half of whom agreed to participate. Edema was defined as bilateral, pitting, pretibial swelling. Exclusion criteria included an ejection fraction of less than 50%, poorly controlled asthma, documented lung disease, hypoalbuminuria, proteinuria, pregnancy, nonambulatory state, cardiac disease, use of calcium channel blockers, unilateral edema, myxedema, or idiopathic cyclic edema. History and physical examination, spirometry, and overnight polysomnography (sleep studies) were done using established techniques.

Blankfield and colleagues enrolled 44 patients with

edema and 34 without. Most of the edema was an incidental finding, not a chief complaint. The edematous patients were heavier (body mass index [BMI], 47.0 vs 36.5), sleepier (Epworth Sleepiness Score, 11.2 vs 5.7), and more likely to be smokers (58 vs 15%). They also had more severe sleep apnea (apnea-hypopnea index [AHI], 34.1 vs 17.0), lower waking oxygen saturation (96.2 vs 97.1%) and slightly worse pulmonary function. After logistic regression to adjust for BMI, 63% of edematous women had sleep apnea (using an AHI > 15 as the criteria for diagnosing sleep apnea), but *only* 25% of the nonedematous women did ($P = 0.02$). A similar difference in the likelihood of sleep apnea in edematous vs nonedematous men did not emerge, probably because the numbers of men were too small.

In a companion article, Blankfield et al found that of 8 men and women with sleep apnea and edema who complied with nasal continuous positive airway pressure, seven experienced a reduction in their edema, a result that was statistically significant.[1] The results of the second article indicate that sleep apnea can cause leg edema.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Lower extremity edema is a common finding in clinical practice. It is particularly prevalent in women. In fact, in a study of women attending a fracture clinic or their general practitioner, 28% and 33%, respectively, experienced non-menstrually related swelling symptoms in the month prior to interview.[2] Blankfield et al found that affective symptoms, a family history of swelling, and a BMI > 25 kg/m^2 were significantly associated with the presence of mild-to-severe swelling symptoms. Obesity is clearly a major risk factor for edema, and in obese patients the edema is often attributed to the obesity. Blankfield et al had previously noted[3] an association between edema and sleep apnea, but had been unable to control for obesity, a problem they rectified to some extent in the current paper. Although edematous patients were indeed heavier than nonedematous patients in this study, the association between edema and sleep apnea persisted even after controlling for obesity.

Why should sleep apnea be associated with edema? Clearly, sleep apnea is prevalent in heart failure,[4] but the edematous patients in this study had normal left ventricular ejection fractions. It is, of course, right heart failure that is associated with peripheral edema, and we really don't know about right ventricular function in these folks. There is a fair body of evidence to suggest that sleep apnea impairs right ventricular function and raises pulmonary artery pressures.[5]

What does this mean to us in clinical practice? When confronted with a person (especially of the female persuasion) with *idiopathic* edema, consider the possibility that she might have sleep apnea. It's treatable, and treatment improves multiple outcomes. ■

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The WHI Results on Urinary Incontinence

ABSTRACT & COMMENTARY

Synopsis: *Conjugated equine estrogen alone and CEE + MPA increased the risk of urinary incontinence among continent women and worsened the characteristics of urinary incontinence among symptomatic women after 1 year.*

Source: Hendrix SL, et al. *JAMA*. 2005;293:935-948.

Results from the 2 cancelled arms of the Women's Health Initiative (WHI) were reported for the presence of urinary incontinence after one year of treatment in those women without incontinence at baseline and for the severity of urinary incontinence in those who reported incontinence upon entry to the study. **Findings were as follows:**

	Estrogen+Progestin	Estrogen Alone
Women asymptomatic At baseline:		
Any incontinence	1.39 (1.27-1.52)	1.53 (1.37-1.71)
Stress incontinence	1.87 (1.61-2.18)	2.15 (1.77-2.62)
Urge incontinence	1.15 (0.99-1.34)	1.32 (1.10-1.58)
Older women and women most distant from menopause were at greater risk, but the confidence intervals were wider because of smaller numbers:		
Age 70-79	2.24 (1.17-4.30)	2.63 (1.32-5.25)
Worsening in women with Incontinence at baseline:		
Any incontinence	1.20 (1.06-1.36)	1.59 (1.39-1.82)

The use of hormone therapy for longer periods of time was examined in an 8.6% subset on treatment for 3 years, and there did not appear to be any meaningful changes in the relative risks.

COMMENT BY LEON SPEROFF, MD

This contribution from the WHI does not disagree with the overall results in previous literature. All of these results have been contrary to what seemed like a logical conclusion, that estrogen treatment would reduce or prevent incontinence by improving or avoiding the atrophy of the genito-urinary tract that follows menopause.

It has been argued that genuine stress incontinence is not affected by treatment with estrogen, whereas others have contended that estrogen treatment improves or cures stress incontinence in more than 50% of patients due to a direct effect on the urethral mucosa.[1-3] However, a meta-analysis concluded that improvement was reported only in nonrandomized studies.[4] Two randomized trials dedicated to this clinical problem failed to demonstrate a beneficial effect of estrogen treatment.[5,6] Most cases of urinary incontinence in elderly women are a mixed problem with a significant component of urge incontinence that clinicians believed to be improved by estrogen therapy. However, the Heart and Estrogen-progestin Replacement Study (HERS) randomized trial indicated a worsening of incontinence with hormone therapy for both urge and stress incontinence, and the Nurses' Health Study reported a small increase of incontinence in hormone users.[7,8]

These results seem somewhat surprising, and indicate that the mechanism for stress incontinence is not only unresponsive to estrogen's beneficial effects on epithelium, but even worsened. Although the adverse effects were more prominent in the oldest women in the WHI, the impact was observed in younger women as well. This certainly challenges the urogynecologists to study this mechanism and understand the physiology behind these epidemiologic results.

One could nitpick this report from the WHI. For example, the participants in the 2 trials were not identical (more reported daily incontinence in the estrogen only arm, and the estrogen only arm had more elderly women), and current users of hormone therapy upon entry to the study did not have an adverse effect on incontinence (but the numbers were small). It is intriguing to wonder why the women who were currently using hormone therapy at baseline did not report this adverse effect. However, the overall results are consistent with the literature on this subject, and we should accept that postmenopausal hormone therapy carries a small increase in worsening or onset of incontinence. Most importantly, the reason why needs understanding. ■

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Dr. Speroff is Professor of Obstetrics and Gynecology, Oregon Health Sciences University, Portland.

Pharmacology Update

Palifermin Injection (Kepivance™)

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

AMGEN HAS RECEIVED APPROVAL TO MARKET PALIFermin. The drug is approved to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies undergoing chemotherapy, with or without radiation, followed by a bone marrow transplant. Palifermin is a protein produced by recombinant DNA technology that is a truncated copy of the keratinocyte growth factor which stimulates proliferation, differentiation, and migration of epithelial cells. Palifermin is marketed as Kepivance™.

Indications

Palifermin is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematologic stem cell support.[1]

Dosage

The recommended dose is 60 µg/kg/day, given as an intravenous bolus for 3 consecutive days before and 3 consecutive days after myelotoxic therapy. The third dose should be given 24-48 hours before myelotoxic

therapy. Administration within 24 hours may increase the severity and duration of oral mucositis.[1]

Potential Advantages

Palifermin has been shown to reduce the incidence of grade 3 and grade 4 oral mucositis, use of total parenteral nutrition, use of opioid analgesics, incidence of febrile neutropenia, and patient-reported soreness of the mouth and throat.[1,2]

Potential Disadvantages

Adverse events include rash, pruritus, erythema, mouth and tongue disorders and altered taste.[1,2] Palifermin has shown evidence of stimulation of tumors in cell cultures (eg, epithelial tumor cell lines) and animal models of non-hematopoietic human tumors.[1]

Comments

Palifermin is a truncated version of the endogenous human keratinocyte growth factor (KGF) produced by recombinant DNA technology. Twenty-three amino acids in the N-terminal chain were deleted to improve stability but retain activity.[1-3] The KGF receptor is present on epithelial cells including the tongue, the GI tract, salivary gland, lung, liver, pancreas, kidney, bladder, mammary gland, and skin. Efficacy was reported in one published study (n = 212).[2] Patients enrolled in this study were scheduled to undergo autologous stem-cell transplantation after receiving fractionated total-body irradiation and high-dose etoposide and high-dose cyclophosphamide for non-Hodgkin's lymphoma, Hodgkin's disease, acute myelogenous leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and multiple myeloma. All patients received filgrastim (G-CSF). Oral mucositis was assessed for 28 days after transplantation. WHO grade 3 was defined as inability to swallow solid food and grade 4 as no form of oral alimentation possible. Palifermin reduced days of WHO grade 3/4 oral mucositis from a median of 9 days for placebo to 3 days. Incidence of mucostitis vs placebo was 63% vs 98. Grade 4 mucositits was 20% vs 62%. The use of opioid analgesics was reduced from a median of 535 mg of morphine equivalent per day to 212 mg, incidence of total parenteral nutrition was 31% vs 55% for placebo, and incidence of febrile neutropenia 75% vs 92%. There was also a lower score of patient-reported soreness of the mouth and throat. All the above were statistically significant at $P < 0.001$. Similar reduction in grade 3 and 4 mucositis was reported for a similar study that varied the schedule of palifermin who received the same dose and schedule. Adverse events were generally related to skin and epithelium. These tended to be mild to moderate in severity and occurred approximately 3 days after the last dose, lasting about 3 days.2 Transient elevations of serum amylase and lipase have also been observed.[2] The wholesale cost for a 6 doses of palifermin is $8250.

Clinical Implications

Oral mucositis is a common adverse event resulting from radiation as well as chemotherapy. The incidence is estimated to be about 40% with standard chemotherapy and increases with subsequent cycles.[4] For patients undergoing bone marrow transplantation who received high dose chemotherapy the incidence is about 76% up to 100%.[5] Mucositis with neutropenia increases the risk of life-threatening infections and prolonged hospitalization.[6] Palifermin is approved for severe oral mucositis in patient with hematologic cancers receiving myelotoxic chemotherapy and requiring hematopoietic stem cell support. Effective alternatives for these patients are limited.[5] Low-level laser therapy is being studies with some encouraging evidence.[5] ■

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CME Questions

19. Idiopathic edema:

a. is more prevalent in men than in women.
b. is uncommon in general practices.
c. is not associated with obesity.
d. is associated with sleep apnea.
e. is not seen in patients with normal left ventricular ejection fractions.

20. Inflammation is an important factor:

a. in all aspects of the atherosclerotic coronary artery disease process.
b. generates the formation of foam cells followed by plaque formation in the atherosclerotic process.
c. promotes instability of the fibrous cap rendering the cap more susceptible to rupture.
d. All of the above

Answers: 19 (d); 20 (d)

By Louis Kuritzky, MD

Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

ALTHOUGH ALL STROKES ARE potentially debilitating, intracerebral hemorrhage (ICH) is often the most disabling. Encouraging medical advances offer promise for ischemic stroke, but no known medical interventions convincingly alter the consequences of ICH (30-day mortality greater than 30%, 80% of survivors losing functional independence). After the initial bleed, hematoma growth is felt to influence adverse outcome; hence, limiting hematoma progression or rebleed could favorably alter the course of ICH. Since activated factor VII (aF7) has proven efficacy as a pro-coagulant not only in hemophilia, but also in patients without known coagulopathy, it is a rational option for study.

Patients who had confirmed ICH within 3 hours of onset of symptoms (n = 399) were randomized to recombinant aF7 or placebo. Followup CT scans were obtained 24 and 72 hrs after IV administration of one of three dosage intensities of aF7. The primary outcome measure was percent increase in ICH volume.

ICH volume increase was significantly less in subjects who received the highest aF7 dose; and the closer to time of admission aF7 was administered, the greater the beneficial impact. Additionally, 3-month mortality was reduced by 38% in the aF7 group compared with placebo.

Serious arterial thromboembolic events (MI, Ischemic Stroke) were more frequent in persons who received aF7, but fatal or disabling thromboembolic events were not significantly different between the groups. These data are promising for the future of aF7 in ICH. ■

Mayer SA, et al. N Engl J Med. 2005; 352:777-785.

Amoxicillin-Clavulanate vs Ciprofloxacin for the Treatment of Uncomplicated Cystitis in Women

EMERGING PATHOGEN RESISTANCE, particularly that of *E. coli*, has influenced the choice of treatment for urinary tract infection (UTI). Trimethoprim-Sulfamethoxazole (TMP-SMX) has probably been the most commonly used urinary antibacterial, often administered as a 3-day course. *E. coli* remains the most frequent pathogen, but is increasingly resistant to beta lactams and TMP-SMX. Although most organisms responsible for UTI retain sensitivity to quinolones, we desire to retain the long-term use of quinolones by avoiding overuse; hence we seek appropriate non-quinolone alternatives to TMP-SMX.

This trial compared amoxicillin/clavulanate 500/125 (AM/C) b.i.d. to ciprofloxacin (CIP) 250 mg b.i.d. for 3 days in adult women (n = 322) with uncomplicated acute cystitis. Culture data reflected a pathogen distribution similar to what is seen in many ambulatory settings: *E coli* in 82%, Group b Streptococcus in 8%, *Staphylococcus saprophyticus* in 8%, and others (Klebsiella, Proteus) in 2%.

The clinical cure rate (determined at the 2-week follow-up visit) was 58% for AM/C vs 77% for CIP ($P \leq 0.001$). Even when evaluating the population of women whose urine sensitivity testing indicated AM/C susceptibility, cure rates were superior for CIP. A 3-day course of AM/C is less effective than CIP for uncomplicated acute cystitis in adult women. ■

Hooton TM, et al JAMA. 2005;293: 949-955.

Why do Patients with Erectile Dysfunction Abandon Effective Therapy with Sildenafil (Viagra)?

THE AVAILABILITY OF HIGHLY effective safe oral agents for erectile dysfunction (ED) has immeasurably improved the management of male sexual health. Typically, studies indicate that 60-80% of men are satisfied with the efficacy of phosphodiesterase 5 inhibitors (PDE5i). Consistently, surveys of men with ED indicate a strong preponderance of preference for oral agents over other methodologies such as surgical, urethral pellets, injections, or vacuum constriction devices. Whether men who respond favorably to PDE5i continue long-term treatment with these agents has not been well studied.

Klotz et al prospectively studied men, mean age 63, with ED who had successfully used sildenafil. If men did not renew a prescription within 6 months, they were considered to have abandoned treatment and were surveyed by telephone to find the reason(s) why.

Almost one-third (31%) of subjects had not sought a refill within 6 months. The most common reason cited was *lack of opportunity or desire for intercourse*, in 45%. Next most common was *failure of partner to show interest in sex* (23%), followed by cost (12%).

Men who receive PDE5i generally initially report successful ability to have intercourse, but a substantial minority does not continue the medication. Whether the same results would be seen in populations of younger men has not been determined ■

Klotz T, et al. Int J Impot Res. 2005;17(1):2-4.

When to Pace Sick Sinus?

By Ken Grauer, MD

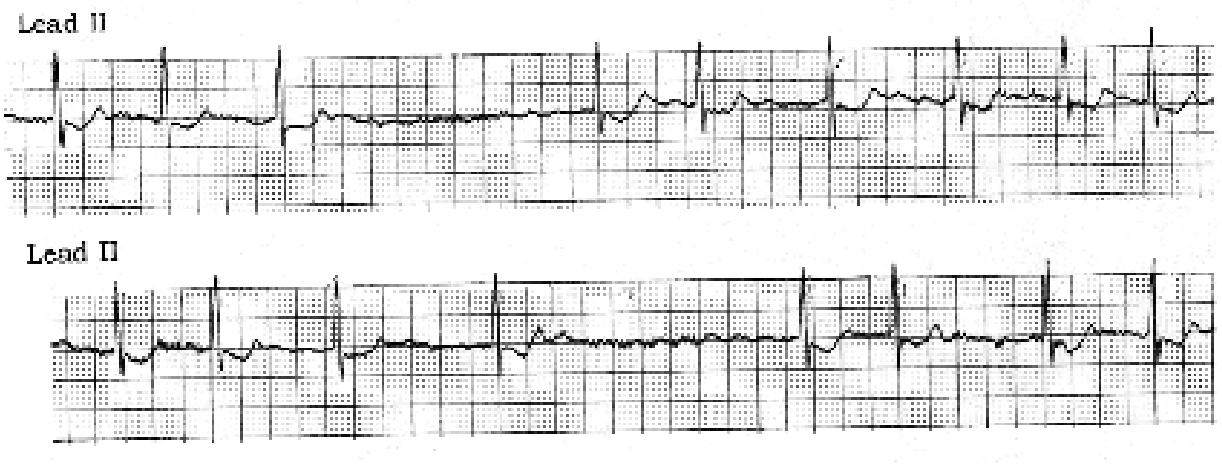

Figure. Non-consecutive lead II rhythm strips obtained from a 76-year-old woman. Does she have sick sinus syndrome?

Clinical Scenario: The non-continuous lead II rhythm strips shown in the Figure were obtained from an asymptomatic 76-year-old woman. Are these rhythms diagnostic (or at least consistent) with sick sinus syndrome (SSS)? Is permanent pacemaker implantation indicated? On what does your answer depend?

Answer: The QRS complex is narrow and the rhythm is irregularly irregular. No P waves are seen. The rhythm is therefore atrial fibrillation. Although the overall ventricular response is controlled (if not moderately rapid), a pause of slightly more than 2 seconds is seen in each tracing.

A variety of rhythms may be seen with sick sinus syndrome (SSS). Among these are sinus bradycardia, sinus arrhythmia, sinus pauses, SA (sino-atrial) node exit block, and/or sinus arrest, which may then result in atrial fibrillation or an AV (atrio-ventricular) nodal escape rhythm. Because conduction system disease generally affects not only the SA node, but also the AV node, the ventricular response to either atrial fibrillation or AV nodal escape rhythms is typically slow. In addition to bradyarrhythmias, a "tachy-brady" syndrome is often seen in which brief episodes of tachyarrhythmias (most commonly rapid atrial fibrillation) are followed by relative pauses. This is the situation here, where the two rhythm strips shown in the Figure manifest relatively rapid atrial fibrillation with two brief pauses.

Essential to the diagnosis of SSS is the *ruling out* of other potential causes of bradycardia, such as medication effect from rate-slowing drugs (ie, digoxin, beta-blockers, verapamil/diltiazem), hypothyroidism, and/or recent myocardial infarction. It is important to appreciate that the two principle indications for permanent pacing of SSS are: i) symptomatic bradycardia (*not* symptomatic tachycardia); and ii) tachycardia for which rate-slowing medication is needed that then produces symptomatic bradycardia. In general, pauses are not of concern until they exceed 3 seconds in duration. Thus, while the 76-year-old woman in this case may indeed have SSS, permanent pacing is not yet indicated because her pauses are brief and she is still asymptomatic. ■

In Future Issues: Vitamin E—Good or Bad?

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.*

Preparing for the Possibility of a Bird Flu Pandemic

The possibility of a bird flu pandemic has health officials worldwide in a high state of alert. The highly pathogenic avian influenza A virus is responsible for the death of more than 100 million birds in Southeast Asia, but less than 100 cases have been documented in humans, and only 2 of those have been from human-to-human contact. Still, influenza A viruses are known to undergo an antigenic shift periodically, marking an abrupt change in the viral genome. It is the possibility of a mutation that has health officials concerned. If the virus suddenly became infectious in human populations, the resulting pandemic could kill millions, as similar avian influenza virus pandemics did in 1968, with one to four million deaths, and 1918, when the avian flu pandemic killed as many as 50 million people. The World Heath Organization is urging all countries to develop or update their influenza pandemic preparedness plans. From a pharmaceutical perspective, the WHO has singled out oseltamivir (Tamiflu) as the treatment of choice to reduce symptoms and prevent spread of avian influenza. Roche Holding AG, the makers of oseltamivir, recently announced that Britain and the United States are discussing large purchases of the drug, with the intent of stockpiling supplies for a potential avian influenza outbreak. Other governments around the world have been stockpiling the drug as well, and Roche is increasing its production capacity to meet the additional demand.

Amoxicillin-Clavulanate vs Ciprofloxacin

The search for effective antibiotics to treat common infections is a high priority, given increasing resistance patterns for many commonly used antibiotics. This was the basis for a new study by researchers at the University of Washington, in which they compared ciprofloxacin to amoxicillin-clavulanate in women with uncomplicated cystitis. The study was driven by an increasing rate of resistance to trimethoprim-sulfa and other antimicrobials among *E. coli* strains causing acute cystitis in women. While ciprofloxacin is a common alternative, amoxicillin-clavulanate has not been well studied. In a randomized, single-blinded trial, 370 women aged 18 to 45 with symptoms of acute uncomplicate cystitis with a positive urine culture were randomized to amoxicillin-clavulanate 500/125mg twice daily or ciprofloxacin to 250 mg twice daily for 3 days. Clinical cure was observed in 58% of women treated with amoxicillin-clavulanate, compared with 77% of women treated with ciprofloxacin ($P < .001$). Amoxicillin-clavulanate was not as effective as ciprofloxacin, even among women infected with *E. coli* strains suscepti-

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ble to amoxicillin-clavulanate. At follow-up visits 2 weeks after treatment, 45% of women in the amoxicillin-clavulanate group had vaginal colonization with *E. coli*, compared to only 10% in the ciprofloxacin group ($P <$ .001). The authors point out that *E. coli* resistance is an increasing problem worldwide, especially with trimethoprim-sulfa. However, resistance is also been seen with fluoroquinolones including ciprofloxacin. Amoxicillin-clavulanate was chosen in the study in the hopes of finding an effective fluoroquinolone-sparing antibiotic for the treatment of uncomplicated cystitis. Unfortunately, amoxicillin-clavulanate is not a reliable option and alternatives will need to be found (*JAMA.* 2005;293:949-955).

AD Therapy and Cognitive Function

Men with prostate cancer who note worsening cognitive function in the early stages of androgen deprivation (AD) therapy should consider that the change is due to the treatment not the disease, according to new study published online in the "Early View" section of *Cancer*. Researchers from Finland followed 23 men undergoing AD for prostate cancer. Thirty-one cognitive tests were performed at baseline, 6 months, and 12 months into therapy. Testosterone and estradiol locals were followed throughout treatment. Visual memory of figures in recognition speed of numbers were significantly impaired at 6 months. Surprisingly, some men with the lowest change in estradiol levels had an improvement in verbal fluency and 12 months. The author suggests that cognition may be adversely affected during androgen deprivation (*Cancer*-published online 2/16/05).

LDL Lowering in CHD Patients

An LDL target in the 70s for CAD patients may become the standard, as evidence continues to mount for the benefit of intensive cholesterol lowering. The latest study from the "Treating to New Targets" or TNT investigators looked at 10,000 patients with stable coronary disease and LDL levels less than 130. Patients were randomized to atorvastatin 10 mg/day (low dose) or 80mg/day (high dose) and were followed for an average of 4 years. Mean LDL cholesterol was lowered to 101 mg/dL in the low-dose group and to 77 mg/dL in the high-dose group. Persistent elevations in liver enzymes was more common in the high-dose group (0.2% low dose, 1.2 % high dose [$P <$ .001]). The study end points were cardiovascular events including death from CHD, nonfatal MI, resuscitation after cardiac arrest, or stroke (fatal or nonfatal). A primary event occurred in 548 patients in the low-dose group (10.9%) and 434 patients in the high-dose group (8.7%) for a 2.2% absolute rate reduction (HR, 0.78; 95% CI, 0.69-0.89; $P <$ .001). There was a higher death rate from noncardiovascular causes in the high-dose treatment group, and no difference in overall mortality. There were no trends in the noncardiovascular deaths, specifically no higher rate of cancer or violent deaths. The authors conclude that aggressive LDL lowering is warranted in CHD patients (*N Engl J Med*-published online March 2005). An accompanying editorial suggests more caution, stating, "Patients and their physicians will need to carefully weigh the benefits or a reduction in the risk of cardiovascular events. . . against the uncertainty of an increase in the risk of death from noncardiovascular causes" (*N Engl J Med*-published online March 2005).

FDA Actions

The FDA and federal marshals from the Department of Justice have seized Paxil CR and Avandamet tablets manufactured by GlazxoSmithKline at its plants in Knoxville, TN, and Puerto Rico. The FDA stated that the seizures were prompted by violations of manufacturing standards that resulted in the production of poor quality drug products, including tablets that could split apart and tablets that had inaccurate doses of the active ingredient.

In late February, the FDA issued a public health advisory regarding nataluzimab (Tysabri), Biogen's recently approved drug for the treatment of relapsing forms of multiple sclerosis. Marketing of the drug has been suspended while the agency and the manufacturer evaluate 2 cases of progressive multifocal leukoencephalopathy in MS patients who were using the drug, one of which resulted in death. Nataluzimab received accelerated approval in November 2004, and 8000 patients have received the drug, including 3000 who received it during clinical trials. ■