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INSIDE

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Magic Words for Smoking Cessation — Your Lungs Are 10 Years Older Than You Are

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Clinical Professor, University of California, San Diego

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

Synopsis: *In a British study telling the patient their lung age after spirometry doubled the likelihood of their stopping smoking at one year.*

Source: Parkes G, et al. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomized controlled trial. *BMJ.* 2008;336:567-568.

TELLING PATIENTS TO STOP SMOKING IS A VITALLY IMPORTANT step in smoking cessation although its effectiveness is limited. Smoking cessation programs go beyond this clinical recommendation yet depend on the patient's readiness and willingness to stop. What words might the physician use to motivate a patient to stop smoking?

Parkes, et al, performed a randomized controlled trial of 561 current smokers in five general practices in Hertfordshire, England. All were over age 35. All patients received spirometry to assess lung function and the study subjects were randomized. Smokers in the intervention group were told their "lung age" (the age of the average healthy person who would perform similar to them on spirometry). The control group was given the raw figures for forced expiratory volume at one second (FEV_1). Both groups were advised to stop smoking and referred to local National Health Service smoking cessation services.

One-year follow up was available on 89% of the subjects. The quit rate among the intervention group was 13.6% compared with 6.4% for the control group ($P = 0.005$). The number needed to treat was 14. Smokers with the worst spirometric findings and those

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with normal lung function were the least likely to quit. A new diagnosis of COPD was made in 16% of the subjects, with comparable findings in both groups.

In this local study in England, telling a person their lung age doubled their likelihood of stopping smoking compared with giving the spirometric results numerically.

COMMENTARY

The art of medicine includes using the right words in the right way to achieve therapeutic results. We all develop our way of saying things to motivate patients to change their lifestyle. Since smoking tobacco remains the leading cause of premature disease and death, counseling patients to stop smoking is of vital importance.

This study has potentially breakthrough information to aid in smoking cessation counseling. The day after reading this study I decided to try it. I work on a Mobile Health Unit in San Diego treating the homeless and uninsured. There is a high prevalence of smoking, even if the patients need to use cigarette butts on the street. I saw a middle-aged woman with longstanding smoking who quickly informed me that she was not going to quit. All the other doctors had asked her to quit to no avail. I suggested to her that her lungs may be 10 years older than she was. That got her attention. She said, "No one has said anything like that before." I do not know if this motivated her to stop, but the information seemed to make an impact, important in the pathway to behavior change.

Most spirometry results do not include a lung age. This can be requested, and based on this study is worth asking for. One local study does not prove that this intervention is successful, but it is certainly worth trying, and studying further in other settings.

Our words are powerful and we all want to improve them to achieve healing effects. I cannot think of any damage this information would have in an addicted smoker. Any longstanding smoker who thinks their lungs are healthy is in denial. Age is an easier concept to grasp than a per cent decline in lung function. I have been projecting the patient into the future, suggesting what they will look like and what their health is likely to be at important future milestones, such as at the wedding of their children or becoming a grandparent. Lung age today takes this concept and applies it to now. I like that. ■

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A Little DASH of Common Sense

ABSTRACT & COMMENTARY

By Barbara 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. *Middle-aged women who followed the DASH diet had a lower risk of stroke and coronary heart disease over a 24-year-period than comparable women who did not.*

Source: Fung TT, et al. Adherence to a DASH-Style Diet and Risk of Coronary Heart Disease and Stroke in Women. *Arch Intern Med.* 2008;168(7):713-720.

THIS STUDY IS THE REPORT OF AN OBSERVATION OF 88,517 women who were part of the Nurses' Health Study. This analysis included participants for whom adequate dietary information was available and who had no history of coronary heart disease, stroke, or diabetes at baseline. Participants in this study were not instructed or counseled to use any particular diet, but the investigators retrospectively assessed their spontaneous use of the Dietary Approaches to Stop Hypertension (DASH) diet.[1] This was done by using analysis of food frequency ques-

tionnaires (FFQ), focusing on 8 components: high intake of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains, and low intake of sodium, sweetened beverages, and red and processed meats. DASH scores ranged from 8 to 40, with higher scores indicating closer adherence to the diet. The participants were divided into quintiles based on DASH scores. The authors collected data on incident coronary heart disease (nonfatal myocardial infarction [MI] or fatal CHD) and stroke for the next 24 years after the return of the first FFQ questionnaire in 1980. To reduce random within-person variation and to best represent long-term dietary intake, the investigators used cumulative means of the DASH score from the repeated FFQ administrations. For example, the DASH score in 1980 was used to predict risk from 1980 to 1984, and the mean DASH score from 1980 and 1984 was used to predict risk from 1984 to 1986. Cox proportional hazard modeling was used to assess the association between the DASH score and risk of CHD and stroke. Analyses were adjusted for age, smoking, BMI, menopausal status, postmenopausal hormone use, energy (calorie) intake, multivitamin intake, alcohol, family history of CHD, physical activity, and aspirin use. Most subjects also gave blood for measurement of C-reactive protein (CRP), interleukin 6 (IL-6) levels, total cholesterol, fasting triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

During the 24 years of follow-up, there were 2317 cases of CHD, and 2317 cases of stroke (1242 of these were ischemic). Women with higher DASH scores tended to use multivitamins, exercise more, and consume more fiber and omega-3 fatty acids but less saturated fat, trans fat, and total energy. They were also less likely to be current smokers but more likely to report a history of hypertension.

There was an inverse association between the DASH score and incident CHD and stroke. After statistical adjustment for confounders, women in the top quintile of the DASH score had a reduced relative risk (RR) of 0.76 ($P < .001$) for both fatal and nonfatal CHD compared with those in the lowest quintile. Further statistical adjustment for hypertension and high cholesterol did not change this finding. For stroke risk, those in the top quintile DASH score group had a lower relative risk of 0.82 ($P = .002$) compared with those in the bottom quintile, and the relationship was not affected by additional adjustment for hypertension and or diabetes. Of note, the inverse association between the DASH score appeared to be stronger among smokers ($P = .09$ for interaction) and those with hypertension ($P = .05$ for interaction) for the risk of stroke.

For those who had serum biomarkers of inflammation measured, a higher DASH score was associated with lower CRP and IL-6 levels but not for blood lipid levels.

COMMENTARY

This report received some attention in the lay press ("Blood pressure diet cuts heart, stroke risk"),[2] and your patients may ask you about it. While the findings of this study are not particularly surprising, what is new about this report is the duration of time over which the women were followed (nearly a quarter of a century!), and the ability to link improved cardiovascular outcomes to a specific named diet, the DASH diet. Because a randomized clinical trial of the DASH diet on cardiovascular end points is unlikely to occur, this study is probably about as good as it is going to get in terms of defining the long-term benefits of the DASH diet in the primary prevention of CVD among healthy subjects. It is notable that this study suggested people with hypertension (and thus at increased risk for stroke) seemed particularly likely to benefit from adherence to the DASH diet in terms of reduction in stroke.

The DASH diet has previously been reported to reduce both systolic and diastolic blood pressure among both those with hypertension and those without.[1] It has also been shown to reduce low-density lipoprotein cholesterol levels,[3] and is recommended by the National Heart, Lung, and Blood Institute (NHLBI) for the prevention and treatment of hypertension.[4] The total DASH score depends on including some things (fruits, vegetable, nuts) and excluding others (salt, sodas, red meat). Different components of the DASH score have been linked to lower blood pressure. Plant foods have been associated with lower blood pressure.[5-7] On the other hand, meat intake has been associated with higher blood pressure.[8] The DASH diet is not difficult to follow, and is available on the internet for your patients who are interested in lifestyle approaches to good health.[9] A typical daily DASH diet might include:

— At least 8 servings of fruits and vegetables (a serving is a ½ cup of cooked or a full cup of raw plant food, or a piece of fruit).

— One serving of nuts or legumes (a serving is a handful of nuts or half-cup of legumes).

— At least 2 servings of whole grains (a serving is a slice of bread, a cup of cereal, or ½ cup of cooked pasta or rice).

— About 2 servings of low-fat dairy products. (A serving is one cup).

— One-half serving of meat (a full serving is the size of a deck of cards). ■

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Should We Be Screening for Hepatitis C?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Synopsis: *Among veterans with risk factors for hepatitis C, a screening program yields results of limited value. The number needed to screen to yield a treatable case of hepatitis C was 451, but the number needed to screen for a successful outcome was more than 4000.*

Source: Mallette C, et al. Outcome of screening for hepatitis C virus infection based on risk factors. *Am J Gastroenterol.* 2008;103:131-137. Summary review by Essential Evidence Plus:Daily POEM: Screening for hepatitis C has minimal benefit (NNS = 4000). Wiley Subscriptions Services. April 10, 2008.

Hepatitis C is the most common viral hepatitis leading to chronic liver disease. Most patients with antibodies to hepatitis C do not develop liver disease even with positive RNA viral levels. The Centers for Disease Control and Prevention recommends screening high risk patients for hepatitis C (HCV) infection. The U.S. Preventive Services Task Force found insufficient evidence to support this recommendation. The current treatment for HCV is toxic and expensive, and the long term successful outcome as measured by clearing of the viral levels is less than 50%. Given all this, should we be screening high risk patients and who should we be referring for evaluation and treatment?

Two large VA studies have been published this year on outcomes of screening high risk patients (Mallette, et al and Groom, et al).[1] In the Mallette study review here, veterans at the Providence, RI Veterans Affairs Medical Center (VA) were given a questionnaire to assess for risk of hepatitis C. High risk factors were: serving in Vietnam, receiving blood products before 1992, intravenous drug or cocaine use, 5 or more alcoholic drinks per day for 10 or more years, 10 or more lifetime sexual partners, any male homosexual experience, blood exposure, hemodialysis, tattoo, current HIV or hepatitis B, or history of unexplained liver disease. Between October 1998 and May 2004, 25,701 patients were assessed and 8,471 had at least one risk factor. Of them, 5646 agreed to be tested, and 412 patients had a positive HCV test (7.3%). Of these, 260 were new diagnoses, and the authors used this number to support the screening program.

What happened to these 260 patients? One hundred forty-eight could not be reached for further evaluation reflecting the nature of this population with high levels of drug use and alcoholism. Among the 112 that did undergo a complete evaluation, about half (57) were treatment candidates. Only 18 underwent a full course of treatment and 6 had a sustained virologic response (less than 1 in 4000 screened). While the authors support the use of the screening program, the reviewers for Daily POEM (Wiley Subscription Services) consider screening for hepatitis C of minimal benefit. The results from a similar study at the Minneapolis VA by Groom, et al, yielded similar results.[1]

COMMENTARY

Screening, evaluation and treatment of hepatitis C is highly controversial. Given the high prevalence of this condition in the population, whether to screen or not and whom to evaluate and treat are vitally important questions. Enormous amounts of money are being spent on hepatitis C in a health care system strapped for funds.

I am the medical director of the indigent care program for San Diego County and am responsible for the medical policies, including screening and referral for evaluation and treatment of hepatitis C patients. We support

hepatitis C screening of at risk patients, mainly because we think that this knowledge is important to reduce risk of spread through sexual relations and the use of blood products. Our local liver clinics are willing to treat any patients with a positive viral load, which is about 50% of antibody positive patients. However, based on the toxicity, expense and limited success of treatment, we only support referral of patients with a positive ALT level (at least 50% above normal). This is because 85% of HCV patients will not develop hepatitis and waiting for early evidence of disease does not significantly change the outcome. Similar policies are used by other public health agencies in an effort to be cost effective.

Specialty physicians want to treat and stamp out disease in their organ system, and gastroenterologists/hepatologists are no exception. Much has been learned about the treatment of chronic HCV, and the treatment regimens will improve with time and experience. However, mass evaluation and treatment of HCV today is not the best use of limited health care resources. We need to be selective in our use of screening and treatment. Many of the veterans in these studies voted with their feet and did not pursue evaluation and treatment. I think we need to stay very selective in our screening, evaluation and treatment of HCV. If I were HCV positive and had a normal ALT, I would sit tight and not undergo a liver biopsy or treatment at this time. ■

Reference

1. Groom H, et al. *J Clin Gastroenterol.* 2008;42:97-106.

Pharmacology Update

Sumatriptan Succinate and Naproxen Sodium Tablets (Treximet™)

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.

A PRODUCT CONTAINING A COMMONLY USED ANTIMIgraine drug (sumatriptan) and a NSAID (naproxen) has been approved for the treatment of acute migraine attacks. This fixed-dose combination is marketed by GlaxoSmithKline as Treximet™.

Indications

Sumatriptan-naproxen (SUM/NAP) is indicated for the acute treatment of migraine attacks with or without aura in adults.[1]

Dosage

The recommended dose is 1 tablet and may be taken without regard to meals. No more than 2 tablets should be taken within 24 hours and should be at least 2 hours apart. The efficacy of a second dose has not been established.[1]

Each tablet contains sumatriptan 85 mg and naproxen sodium (500 mg) and they are supplied as compact containers of 9 tablets.

Potential Advantages

The combination provides two drugs with different mechanisms of action. SUM/NAP is more effective than sumatriptan monotherapy in terms of headache relief and pain free response at 2 hours post dosing, sustained (2 to 24-hour) headache relief and pain-free response, and less use of rescue medications.[1,2]

Potential Disadvantages

SUM/NAP is a fixed-dose combination and does not permit titration of either component.

Serious cardiovascular events have been reported with 5-HT_1 agonists (triptans), and whether the addition of a NSAID, which carries its own cardiovascular risk, adds additional risk is not known.

Comments

The rationale of a sumatriptan/naproxen combination is to provide drugs with different mechanisms of action as well as different pharmacokinetics to treat an acute migraine headache. Sumatriptan is absorbed rapidly and the absorption of naproxen is delayed and along with its long elimination half-life contributes to sustained pain relief.[2] In two identical studies (n = 2911) subjects were randomized to SUM/NAP, sumatriptan 85 mg, naproxen sodium 500 mg, or placebo. SUM/NAP was better than sumatriptan monotherapy in terms of 2-hour pain relief and sustained (2-24 hr) pain free response, and use of rescue medication.[2] SUM/NAP was more effective than sumatriptan in terms of the absence of photophobia and phonophobia at 4 hours.[2] Subjects reported returning to normal function earlier.[3] There was no difference in terms of relief of nausea. While SUM/NAP was more effective than sumatriptan (85 mg) alone overall, it was no more effective than sumatriptan alone in subjects with severe migraine. Adverse events were similar between SUM/NAP and sumatriptan. In a 12-month, open-label study, 69% of attacks were treated with one dose and did not require a second dose and 28% of attacks were treated with a second dose that did not require other rescue medication.[4] The estimated proba-

bility of patients taking a second dose or rescue medication is about 40% for sumatriptan alone.[5] It is not known how SUM/NAP differs in effectiveness from sumatriptan and naproxen taken as two separate tablets. The wholesale cost of SUM-NAP is $18.37 per tablet compared to $15.67 for sumatriptan (100 mg) and $1.13 for a generic naproxen sodium (500 mg) tablet.

Clinical Implications

Migraine is a chronic, intermittently disabling condition. The prevalence of migraine is 18.2% among females and 6.5% among males.[6] First line pharmacotherapies include NSAIDs, analgesic combinations, dihydroergotamine nasal spray, and triptans. The US Headache Consortium recommends NSAIDs and analgesic combinations for mild-to-moderate migraine attacks or severe migraine that have responded in the past.[7] Triptans and dihydroergotamine nasal spray should be considered for moderate-to-severe attacks and in those that have responded poorly to NSAIDs or combination analgesics. Triptans are recommended for more severe attacks. SUM/NAP appears to provide an incremental and measurable improvement in acute and sustained headache relief compared to sumatriptan 85 mg monotherapy. It may be an alternative for patients with moderate-to-severe migraine who have not achieved adequate relief with a triptan alone. ■

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CME Questions

19. The DASH diet:
a. improves blood pressure in the short run, but not for periods longer than 18 months
b. recommends consumption of at least 2 servings of red meat daily
c. recommends consumption of at least 8 ounces of water daily
d. reduces risk of strokes and myocardial infarction

20. Which of the following statements about screening for hepatitis C is true?
a. All high risk patients for hepatitis C should be screened because the majority of patients have some evidence of liver disease that can be effectively treated.
b. Hepatitis C screening programs have a high yield of antibody positive patients that are willing to undergo evaluation and treatment.
c. The majority of HCV patients have an elevated ALT level indicating some level of hepatitis.
d. Screening for hepatitis C has limited value since the number needed to screen in order to achieve a long term treatment success is more than 4000.

21. Telling smokers their lung age with their spirometry results had what impact on their likelihood to stop smoking at one year?
a. No difference
b. A 10% increase in smoking cessation
c. A doubling of the smoking cessation rate
d. Lung age had a negative impact on the stop smoking rates

Answers: 19(d); 20(d); 21(c)

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.

Looking at CAD through the PERISCOPE

Coronary artery disease (CAD) is the most common cause of death in America, and diabetics suffer a disproportionate burden of risk from cardiovascular disease. Although glucose control has consistently demonstrated a favorable impact upon microvascular diabetic consequences (retinopathy, nephropathy, neuropathy), clinical trials have not been able to convincingly prove favorable effects upon macrovascular endpoints, most importantly CAD.

The PERISCOPE Trial (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) prospectively compared the impact of a sulfonylurea (glimepiride) with a thiazolidinedione (pioglitazone) upon coronary atherosclerosis as measured by intravascular ultrasound (IVUS). To that end, adult type 2 diabetics were randomized to glimepiride or pioglitazone and followed for 18 months.

Percent atheroma volume progressed modestly with glimepiride, and regressed modestly with pioglitazone (p = .002). During the trial, the pioglitazone subjects had a slightly more favorable A1c and HDL than the glimepiride group.

For the first time, it has been demonstrated that a thiazolidinedione has more favorable effects on coronary atherosclerosis than a sulfonylurea. These promising findings about surrogate markers are encouraging, but do not satisfy the remaining uncertainty about whether either class of agent can reduce macrovascular endpoints. ■

Source: *Nissen SE, et al. JAMA. 2008;299(13):1561-1573.*

Addressing Agitation and Aggression in Persons with Advanced Dementia

Agitation, aggression, and psychosis are predictably problematic in persons with progressive dementia—over 90% of dementia patients will experience one or more of these during the course of their illness. Indeed, such affective changes are quite often the "straw that breaks the camel's back," resulting in institutionalization because of the unmanageability of such problems in the home setting. Agitation and aggression (A&A) are more commonplace than psychosis, but treatment interventions to prevent or modulate A&A are limited. In addition, the presence of A&A is predictive of a more rapid progression of dementia.

The Neuropsychiatry Inventory (NPI) is a scoring system that contains subitems addressing agitation and psychosis. Study subjects with moderately-severe to severe Alzheimer's disease (n=983) were randomized to memantine (MEM) or placebo and a post-hoc analysis assessed the impact among dementia patients with prevalent A&A.

Memantine was associated with a statistically significant reduction in risk for agitation and aggression. This was not at the expense of functionality, since the Alzheimer Disease Cooperative Study Activities of Daily Living Inventory also showed improvements with memantine compared to placebo. Memantine is promising as a tool for management of aggression and agitation in persons with advanced dementia. ■

Source: *Wilcock GK, et al. Clin Psych. 2008;69:341-348.*

It Used To Be Easier To Treat Sinusitis

In the last decade, advice from consensus groups on management of acute sinusitis ranges from exhortation to wisely choose among antibiotics and/or nasal steroids all the way through admonitions against utilization of either. This literature inconsistency helps little to balance the requests of patients who supplicatingly report a history of protracted sinusitis surrendering only to well-chosen antibiotics.

In the United States, more than three-fourths of patients with a clinical diagnosis of sinusitis are prescribed an antibiotic. Young, et al obtained individual patient data from numerous clinical trial databases, including the Cochrane Central Register of Controlled Trials. All trials compared antibiotic to placebo, and reported the percentage of patients cured at trial end. (n=2,547).

The odds ratio for attaining cure by trial end favored antibiotics, but the margin was not large. The number needed to treat (NNT) with antibiotics to be beneficial was 15. The authors suggest that because the benefit of antibiotics is small, a watch-and-wait posture is appropriate for most patients with sinusitis. ■

Source: *Young J, et al Lancet 2008;371:908-914.*

A "Pressure" Phenomenon

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.

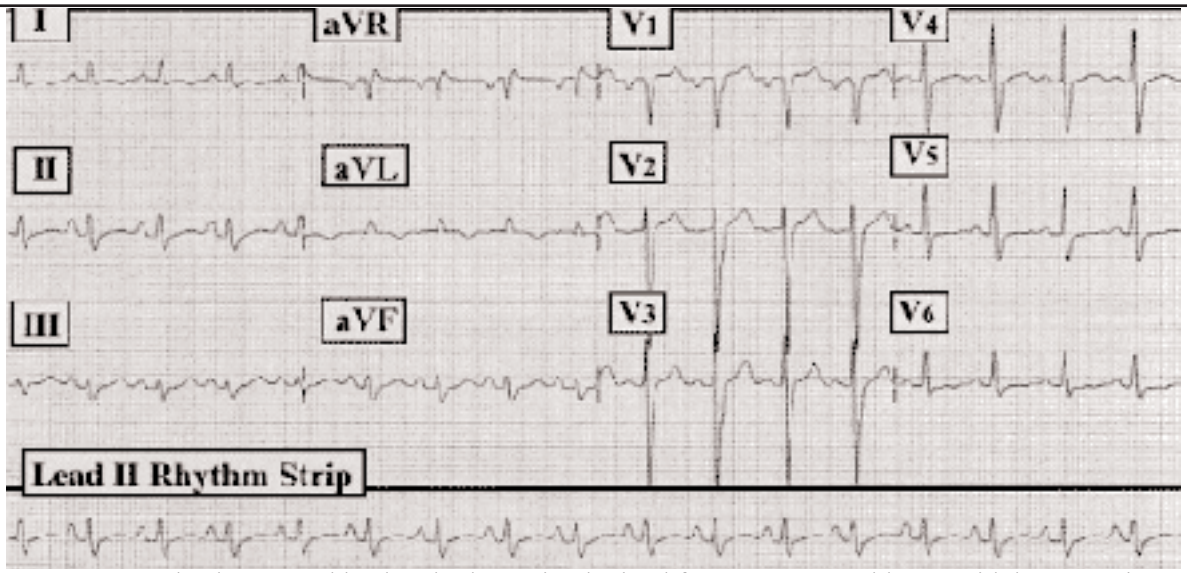

Figure: 12-lead ECG and lead II rhythm strip obtained from a 72-year-old man with hypertension, ESRD, and heart failure. Which one lead is of most concern to you?

Clinical Scenario:

The 12-lead ECG and lead II rhythm strip in the Figure were obtained from a 72-year old man with severe hypertension and end-stage renal disease (ESRD), on dialysis. He presented in heart failure. How would you interpret his ECG given this clinical context? Which cardiac chambers are enlarged by ECG criteria? Which one lead is of *most* concern to you in interpreting this tracing?

Interpretation/Answer:

The ECG shows sinus rhythm at a rate just under 100/minute. All intervals are normal. There is LAD (left axis deviation), but not enough to meet criteria for LAHB (left anterior hemiblock), since the QRS complex is isoelectric in lead II (we estimate the axis to be right at -30°). Regarding chamber enlargement, LVH (left ventricular hypertrophy) is strongly suggested by the very deep S wave (nearly 25 mm) in lead V2, especially given the age of this patient with ESRD and heart failure. In addition, ECG criteria are met for both LAE (left atrial enlargement) and RAE (right atrial enlargement). RAE is suggested by the tall (•2.5 mm) peaked P wave in lead II, and LAE by the very deep (•1 mm) negative component of the P wave in lead V1. Regarding QRST changes—only a tiny q wave is seen (in lead aVL), transition is slightly delayed (occurs between lead V4 to V5), and ST-T wave changes are relatively subtle and most consistent with LVH (ST segment flattening in lead V6 and T wave inversion in leads I and aVL).

The ECG lead of most concern to us is lead I. Although there is no ST segment elevation, the ST segment is definitely *coved* in this lead. This is not usually seen simply with LVH. ST segment coving in a single lead without ST elevation is clearly not a specific finding. However, given the clinical context described here, comparison with a previous ECG on this patient, repeating his ECG the next day, and obtaining serial troponins should be considered to ensure that there is no acute infarction.

Finally — we titled this ECG Review, *"A Pressure Phenomenon"* in reference to increased P wave amplitude seen in this tracing. P wave amplitude was *dynamic* in this patient, typically becoming *much* greater during episodes of fluid overload that resulted in heart failure (presumably reflecting increased intra-atrial volume and pressure during such episodes). ■

In Future Issues: **Poverty's Role in Global Antimicrobial Resistance**

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.

FDA Drug Approval to Change its Ways?

In This Issue: FDA drug approval to change? Urinary incontinence in women; how metabolism of certain drugs can be predicted by genetic analysis; bowel preps may compromise renal function especially in the elderly according to a new study; FDA Actions.

Should the FDA change the way it approves drugs? With the number of drug withdrawals and black box warnings in the last 10 years, the FDA's approval process has come under scrutiny. Many have focused on the Prescription Drug User Fee Act (PDUFA), originally enacted in 1992 which transformed the FDA's drug approval process. At that time the FDA was underfunded and understaffed. PDUFA was negotiated with the pharmaceutical industry to help defray the cost of new drug approvals. Under this plan drug manufacturers would pay a user fee for each drug review to help cover the costs of FDA staff; however the FDA would be required to make a decision on each application within a fixed date after submission. Some have argued that this arrangement makes the FDA too beholden to the industry that it regulates. There has also been concern that the required deadline for approval has accelerated the approval process, perhaps at the expense of drug safety. A new study from Harvard in the March 27 *New England Journal of Medicine* looks at the relationship between drug review deadlines and safety issues—specifically whether drugs approved immediately before their deadlines are associated with a higher rate of post-marketing safety problems. As compared with drugs approved at other times, drugs approved within the two months before their PDUFA deadlines were more likely to be withdrawn for safety reasons (odds ratio 5.5; 95% CI, 1.3 to 27.8), and more likely to carry a subsequent black box warning (OR 4.4; 95% CI, 1.2 to 20.5), and more likely to have one or more dosage forms voluntarily discontinued by the manufacturer (OR 3.3; 95% CI, 1.5 to 7.5). The authors conclude that PDUFA deadlines have appreciably changed the approval decisions of the FDA, and drugs approved immediately before their deadline are more likely to have subsequent safety problems. They also state, "A plausible hypothesis is that relying more on staffing and less on deadlines could result in the same degree of review efficiency without increasing the risk (and resulting greater cost) of unanticipated drug-safety problems." (NEJM 2008; 358:1354-1361).

Help for Women with Urinary Incontinence

Urinary incontinence is a common problem in women, affecting one third of women over the age of 65, and up to 25% of younger women. The NIH has published a systematic review of nonsurgical treatments for urinary incontinence in women, reviewing the most commonly used modalities. Pelvic floor muscle training (Kegel exercises) plus bladder training resolved urinary incontinence

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compared with regular care. Different injectable blocking agents and medical devices all had similar improvement rates, while electrical stimulation failed to resolve urinary incontinence. Oral hormone administration improved urinary continence, however transdermal or vaginal estrogen results were inconsistent. Adrenergic drugs were ineffective. Oxybutynin (Ditropan) and tolterodine (Detrol) were both effective at resolving urinary incontinence compared with placebo, however duloxetine improved but did not resolve incontinence. The authors conclude that pelvic floor muscle training and bladder training are effective interventions for women with incontinence as are oxybutynin and tolterodine. Duloxetine improved but did not resolve incontinence and electrostimulation, medical devices, injectable blocking agents, and local estrogen therapy were inconsistent (*Annals Int Med.* 2008; 148: 459-473).

Human Genome Study Affects Pharmacology

Phamacogenetics and pharmacogenomics are terms that practicing physicians will have to get use to the next few years. The study of the human genome has led to many breakthroughs, not the least of which is the realization that metabolism of certain drugs can be predicted by genetic analysis. The FDA has recently altered the labels of both warfarin and carbamazepine to incorporate language encouraging health professionals to consider pharmacokinetic testing prior to prescribing these drugs in some situations. Some are calling this personalized medicine, but there are concerns ranging from the cost/benefit of these analyses to the potential for abuse of this information, including genetic discrimination. The March 19 issue of *JAMA* is entirely devoted to medical genomics (the study of how genes interact and influence the biology and physical characteristics of living things) and includes articles reviewing genetic analysis for cardiovascular risk, osteoporosis, post-traumatic stress disorder, deep venous thrombosis, and cancer. The issue includes a patient page "Genetics: the Basics" with a glossary of terms (good for patients and doctors alike!).

Bowel Preps and Renal Function in Elderly

Oral sodium phosphate solution (OSPS) bowel preps may compromise renal function especially in the elderly according to a new study. Researchers in Texas retrospectively reviewed 286 patients who received phosphorus containing bowel preps (Fleet Phospho-Soda, Accu-Prep, Visicol) for colonoscopy or sigmoidoscopy and 125 controls. Both groups had similar baseline characteristics, the mean age was 68, 85% were white, and 64% female. In patients treated with OSPS, the baseline glomerular filtration rate was 79 mL/min/1.73 m2 which declined to 73 mL/min/1.73 m2 at 6 months after exposure to OSPS. The GFR in the control group was stable at six months. A drop in GFR in the treatment group was still present one year later although to a lesser degree. Concomitant use of ACEIs or ARBs or the presence of diabetes were significant determinants of the fall in GFR after OSPS preps. The authors conclude that use of oral sodium phosphate solution bowel preps is an under-diagnosed cause of acute kidney injury and that if patients are to receive these preps, physicians should focus on adequate hydration and avoidance of ACEIs and ARBs, especially in diabetic patients (*Arch Int Med.* 2008; 168:593-597). The authors state that their health-care system has banned the routine use of OSPS as bowel cleansing agents for colonoscopies and has switched to polyethylene glycol agents for any patient with stage 3-5 CKD. An accompanying editorial points out that of the two most commonly used methods for colon preps, oral sodium phosphate solutions are often preferred over polyethylene glycol because of the lower volume and better tolerability. Oral phosphate solutions however have been associated with hypokalemia, hypophosphatemia, hypernatremia, and hypocalcemia. Although these are generally transient, acute phosphate nephropathy has also been described with OSPS. Based on the findings, caution should be exercised using phosphorus preps especially in those patients who are risk for renal failure (*Arch Int Med.* 2008; 168:565-567).

FDA Actions

The FDA has issued in early communication about an ongoing safety review of tiotropium (Spiriva), Boehringer Ingelheim's inhaler for bronchospasm associated with COPD. Ongoing safety monitoring has identified a possible increased risk of stroke associated with use of Spiriva. Based on data from 29 placebo-controlled studies the risk of stroke was 8 patients per 1000 treated for one year with Spiriva vs 6 patients per 1000 treated with placebo. The FDA has not confirmed this analysis and recommends the patient should not stop taking Spiriva before talking to their doctor.

The FDA has approved desvenlafaxine for the treatment of depression. The drug is a metabolite of venlafaxine (Effexor) which has recently gone generic in some formulations. Desvenlafaxine is a serotonin-norepinephrine inhibitor which may have less drug-drug interactions than venlafaxine. The drug will be marketed by Wyeth as "Pristiq." ■