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INSIDE

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Long-Term Cognitive Decline and Coronary Artery Bypass Surgery (CABG)

ABSTRACT & COMMENTARY

By John J. Caronna, MD

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Dr. Caronna reports no financial relationships relevant to this field of study.

This abstract originally appeared in the July 2008 issue of Neurology Alert.

Synopsis: *CABG does not increase the risk of long-term cognitive decline.*

Source: Selnes OA, Grega MA, Bailey MM, et al. Cognition 6 years after surgical or medical therapy for coronary artery disease. *Ann Neurol* 2008;63:581-590.

ENTHUSIASM FOR CORONARY ARTERY BYPASS GRAFTING (CABG) AS an intervention for cardiovascular disease has been tempered by concerns about postoperative cognitive decline. At one month after surgery, up to two-thirds of patients have cognitive decline.[1] Those with subtle neurological injury improve to baseline over the first few months after CABG.[2] The occurrence of late cognitive decline at 5 or more years after CABG has been reported but without appropriate control subjects.[3]

Selnes and colleagues conducted a 5-year observational study of patients with coronary artery disease who were treated at Johns Hopkins University Medical Center. Subjects included 152 CABG and 92 nonsurgical control patients treated medically or with percutaneous stents. Patients received baseline, 3-, 12-, 36-, and 72-month cognitive assessments with a comprehensive neuropsychological battery that included the Mini-Mental State Examination (MMSE)[3] at all time points.

At baseline, the CABG group had lower mean scores for several of the neuropsychological tests but there were no statistically significant differences between the CABG group and the nonsurgical patients in the unadjusted raw scores. *(See Table 1.)* Both groups showed improvement in cognitive performance from baseline to 12 months. Therefore, to evaluate the amount of decline in cognitive test performance over

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time for the two groups, the investigators examined change from baseline to 72 months. To address the question of the magnitude of late decline, they compared degree of change in cognitive performance from 12 to 72 months.

Mild late cognitive decline was observed in both study groups but there were no statistically significant differences between the CABG and control patients in the degree of change from 12 to 72 months for any cognitive domain. There also was no difference between groups in the degree of change from baseline to 72 months in the number of subjects with a MMSE score in the clinically impaired range. *(See Table 2.)*

The investigators, therefore, concluded that although late cognitive decline does occur in patients who have undergone CABG surgery, the degree of this decline does not differ from that observed in age-matched, nonsurgical patients with coronary artery disease. Their results indicate that there is no syndrome of late cognitive impairment that is specific to the use of cardiopulmonary bypass.

Table 1: Characteristics of Participants at Baseline

Characteristic	CABG n=152	Controls n=92
Mean age ± SD, yr.	64±9	66±9
Men, n (%)	115 (76)	71 (77)
White, n (%)	137 (90)	86 (93)
Mean MMSE score ± SD	28±2	28±2
MMSE score < 24*, n (%)	7 (5)	6 (6)
Any APO-E-4 Genotype, n (%)	38 (25)	29 (32)

* Indicative of dementia

Source: Selnes OA, Grega MA, Bailey MM, et al. Cognition 6 years after surgical or medical therapy for coronary artery disease. *Ann Neurol* 2008;63:581-590.

Table 2: Characteristics of The Study Population at 72 Months

Variable	CABG n=126 (survivors)	Controls n=73 (survivors)
Completed cognitive Testing, n (%)	96 (76)	61 (84)
Mean MMSE score ± SD	27±3	28±3
MMSE score <24, n (%)	7 (7)	5 (8)

Source: Selnes OA, Grega MA, Bailey MM, et al. Cognition 6 years after surgical or medical therapy for coronary artery disease. *Ann Neurol* 2008;63:581-590.

COMMENTARY

The subject of cognitive impairment following CABG surgery received media attention recently following an article in *Vanity Fair* that suggested Bill Clinton had suffered a personality change since his CABG operation in 2004. Friends were quoted as saying that he was not the same person after surgery. The findings of Selnes and associates should put to rest the worries of Bill Clinton's family and friends, as well as reassuring patients and physicians that there is no increased risk of dementia from CABG surgery. The study is important because it is one of the few to include a control or comparison group of nonsurgical patents. Nevertheless, as pointed out by Yaffe and Covinsky[4] in their editorial comments, there was a high "lost-to-followup" rate of about 35% in both groups.

Although, for statistical analysis, one can assume that the lost-to-followup subjects are missing at random, it may be that these patients had more severe underlying disease, lower functional status, and a greater risk for poor cognitive outcome.

It also is disappointing that the study lacked brain MRI studies before surgery in CABG subjects and at baseline and 72 months in both groups. Perhaps additional studies involving neuroradiologists and in larger, more diverse cohorts may identify subgroups at greater risk for late cognitive decline and, therefore, in need of intervention in the form of more aggressive risk factor modification. ■

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Meta-analysis: Sequential Therapy Appears Superior to Standard Therapy for *Helicobacter pylori* Infection in Patients Naïve to Treatment

ABSTRACT & COMMENTARY

By Malcolm Robinson MD, FACP, FACG

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

Synopsis: *With minor reservations, 10 days of sequential therapy seems superior to standard triple therapy for the eradication of* H. pylori *infection.*

Source: Nadim F Jafri, et al. *Ann Intern Med.* 148:12:923-931.

Standard eradication therapy for *H. pylori* in the U.S. has involved use of a proton pump inhibitor (PPI) plus clarithromycin and either amoxicillin or an imidazole (metronidazole). Ranitidine bismuth citrate is often substituted for a PPI in this regimen outside of the U.S. In North America, most triple therapy regimens involve treatment durations of 7-10 days. In Europe, 7 day therapy is more commonly utilized. Unfortunately, probably due to antibiotic resistance, *H. pylori* eradication rates have been declining. This results in therapeutic failure in 25% (or even higher percentages) of patients treated traditionally for *H. pylori*. Some reports have suggested that sequential therapy may have better results than conventional triple therapy. The authors of this study have performed a very careful meta-analysis of randomized controlled trials comparing traditional triple therapy lasting either 7 or 10 days with sequential *H. pylori* eradication therapy. The latter approach usually begins with 5 days of a PPI plus an antibiotic (usually amoxicillin) and continues with another 5 days of a PPI plus 2 antibiotics (usually clarithromycin and an imidazole). None of these patients in the meta-analysis had undergone any previous *H. pylori* eradication regimen. Various tests were utilized to diagnose *H. pylori* infection: fecal antigen, biopsy urease, histology, or urea breath testing. Study populations included were evaluated for heterogeneity in terms of diagnosis (eg, duodenal ulcer vs gastric ulcer vs nonulcer dyspepsia), patient age, study quality, and documentation of resistance to clarithromycin and/or imidazoles. Results indicated that sequential therapy was superior to traditional triple therapy in all subgroup analyses. Studies were almost exclusively performed in Italy, and the possibility of publication bias was raised (funnel plot testing and other statistical maneuvers). There were differences in methodology among the studies selected for this meta-analysis. However, these authors' results mirrored two previous reviews. Outside the U.S., rates of eradication therapy failure have been as high as 40 to 50%. Most U.S. studies now report 25% failure rates. Jafri et al comments that there are no comparisons of sequential therapy in significant numbers of U.S. patients nor has this approach been compared to quadruple therapy (PPI, bismuth salt, tetracycline, imidazole) or with 14 days of traditional triple therapy.

■ COMMENTARY

In an accompanying editorial, Australian Nobel Laureate Barry Marshall (*Ann Intern Med.* 148:12:962-963) states that sequential therapy is both rational and practical. He asserts that the cost of sequential therapy should be comparable to traditional triple therapy, adherence should be good, and the effects of the sequential regimen on *H. pylori*'s microenvironment should favor improved eradication by major inhibition (8-10 log reduction) of most *H. pylori* during the first 5 days of therapy and elimination of the far fewer remaining deep-seated organisms during the final 5 day period. This reviewer (MR) agrees that *H. pylori* infection remains a source of major morbidity and mortality in many parts of the world. Fortunately for us, the situation in most of North America is far different. *H. pylori* infection is declining here, and its virulence also appears to be decreasing. Nevertheless patients with peptic ulcer disease or MALT lymphoma found to have *H. pylori* infection clearly continue to require eradication of this organism. The situation is far less clear for other indications such as nonulcer dyspepsia or the incidental discovery of the organism. If therapy is to be undertaken, there appears to be some fairly compelling initial evidence that sequential therapy may be the best available option. Further studies are awaited, preferably focused on North American populations and comparing sequential therapy to 14-day triple therapy and/or quadruple therapy. ■

Value of Homocysteine-lowering Folic-Acid/ vitamin B Therapy in Cardiovascular Prevention—Have We Been Wrong Again?

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.

Source: Albert CM , et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease. *JAMA.* 2008; 299:2027-2036.

Synopsis: *After 7.3 years of treatment and follow-up, a combination pill of folic acid, vitamin B6 and vitamin B12 did not reduce a combined endpoint of total cardiovascular events among high-risk women despite significant homocysteine lowering.*

ALMOST 40 YEARS AGO IT WAS FIRST SUGGESTED that homocysteine, an amino acid produced during catabolism of methionine, could cause arterial and venous atherothrombotic disease[1] by promoting oxidative stress, endothelial cell damage, endothelial dysfunction, inflammation, thrombosis, and cell proliferation.[2] Although epidemiological studies in general have demonstrated associations between elevated homocysteine levels and increased risk of coronary heart disease (CVD) and stroke,[6] new results from multiple recent clinical trials have not provided clear evidence of any beneficial effects of vitamin B and/or folic acid supplementation in CVD risk reduction.[3,4,5,7]

Women had been under-represented in observational studies and in randomized trials of homocysteine lowering despite the fact that observational studies have suggested that women may benefit from homocysteine lowering to a greater extent than men.[6] Albert and his colleagues conducted the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS) which tested whether a combination of 2.5 mg of Folic acid, 50 mg of vitamin B6 and 1.0 mg of Vitamin B12 would reduce total cardiovascular events among women at high risk for the development of CVD over 7.3 years of follow-up.[8] A total of 8171 female health professionals were randomized in a carefully controlled 2 x 2 x 2 factorial designed trial. After 7.3 years of treatment and follow-up, the combination pill of folic acid, vitamin B6 and vitamin B12 did not reduce the combined endpoint of total cardiovascular events among high-risk women despite significant homocysteine lowering.

■ COMMENTARY

The WAFACS trial[8] had several unique strengths in that it was focused on women (who were under-represented in the other homocysteine-lowering trials), follow-up was substantially longer (ie, 7.3 years) than was the case in previous trials and as many as 33% of the women studied had no prior vascular events thereby providing some limited data regarding high risk primary prevention. However, it should also be noted that there were some limitations in the trial, the most important being that the trial was conducted after the introduction of federal policies that mandated the addition of folic acid to white flour, cereal grains and related products in the United States which resulted in lower homocysteine concentrations in the US population. Therefore administration of folic acid and vitamin B6 lowered the homocysteine concentrations in the trial subjects to a lesser extent than had been anticipated at the time of its design and may have therefore affected its ability to adequately test the study hypotheses. Also, homocysteine levels were measured in only 5% of study participants and therefore detailed analysis of potential benefits in subsets of patients with high pretreatment homocysteine levels could not be performed and finally, it should be recognized that the trial evaluated a highly selective population of female health care professionals with relatively low CVD event rates. Despite these limitations the results obtained in the WAFACS trial were consistent with the results obtained in prior randomized trials performed primarily among men with established vascular disease[7] and do not support the use of folic acid and/or vitamin supplements as preventative interventions for CVD even in high-risk populations.

In conclusion, Folic acid and B vitamin supplements cannot currently be recommended for prevention of CVD events with the possible exception of individuals afflicted with rare genetic disorders. Therefore, there is no role for routine screening for elevated homocysteine levels at this time. However, ongoing clinical research may yield new evidence of the overall importance of homocysteine as a CVD risk factor at which time the issue of Folic acid/vitamin B therapy will almost certainly have to be re-addressed. So.....don't throw these apparently valueless pills away just yet! ■

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Pharmacology Update

Duloxetine Delayed-Release Capsules (Cymbalta®)

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.

DULOXETINE IS THE FIRST SEROTONIN NOREPInephrine reuptake inhibitor (SNRI) to be approved for the treatment of fibromyalgia. It joins pregabalin as one of only two drugs approved for this indication. Duloxetine was originally approved in 2004 for major depressive disorder.

Indication

In addition to approval for the management of fibromyalgia, duloxetine is also approved for major depressive disorder, generalized anxiety disorder, and diabetic peripheral neuropathy.[1]

Dosage

The recommended dose for fibromyalgia is 60 mg once daily. Treatment should be initiated at 30 mg daily for one week before escalating to 60 mg daily.[1]

Duloxetine is supplied as 20 mg, 30 mg, and 60 mg delayed-release capsules.

Potential Advantages

Duloxetine appears to be effective in fibromyalgia with or without major depressive disorder.[2,3] It also shows an improvement in Hamilton Depression Rating Scale compared to placebo.

Potential Disadvantages

Most common adverse events include nausea, dry mouth, constipation, anorexia, diarrhea, sleepiness, nervousness, increased sweating, and agitation.[1] Duloxetine, as with other antidepressants, may increase the risk of suicidal thinking and behavior. Hepatic failure, sometimes fatal, and risk of bleeding events have been reported.[1]

Comments

In clinical trials, duloxetine, has shown efficacy in patients (predominately women) meeting American College of Rheumatology criteria for fibromyalgia. Primary efficacy was assessed as reduction of the Brief Pain Inventory. About 40% of patients achieved a 50% reduction compared to about 20% for placebo.[1,3] The degree of pain reduction may be greater in patients with major depressive disorder. However the improvement in pain is independent of the drug's effect on depression. Secondary endpoints such as sleep and quality of life were generally improved. There was no efficacy difference between 60 mg daily compared to 60 mg twice daily but more adverse events were associated with the higher dose. There are currently no comparative trials between duloxetine and pregabalin or other agents (eg, tricyclic antidepressants). In a similar study, about 30% of patients on pregabalin (450 mg/day) showed a 50% pain reduction compared to 13% for placebo.[5] While sleep and quality of life were improved, depression scores were not improved with pregabalin. Pregabalin has a different adverse event profile than with duloxetine with dizziness, somnolence, headache, dry mouth, and peripheral edema most common.

Clinical Implications

Fibromyalgia is a chronic condition characterized by pain, stiffness, sleep disturbance, and muscle fatigue. These patients appear to be more sensitive to peripheral stimuli (ie, hyperalgesia and allodynia).[4] It is also associated with anxiety, cognitive disturbance, and depression. The overall prevalence is about 2% and more common in women. Pharmacotherapy has included a variety of drugs from different pharmacological classes such antidepressants (eg, tricyclic antidepressants, SNRIs), anticonvulsants (eg, gabapentin, pregabalin),

dopamine receptor agonists (eg, pramipexole), and analgesics (eg, tramadol).[4,6] Duloxetine offers a new option for the treatment of fibromyalgia and accompanying depression. ■

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CME Questions

29. Which of the following represent the largest cognitively impaired group in the U.S. population over the age of 70 years?

a. impaired cognition with dementia
b. impaired cognition from Alzheimer's Disease
c. impaired cognition without dementia
d. impaired cognition from vascular disease

30. Italian studies demonstrate that sequential therapy (two 5-day regimens) *of Helicobacter pylori* is superior to traditional triple therapy (usually for 7 days) in which patient groups:

a. only patients found to have major *H. pylori* virulence factors present
b. only in groups diagnosed with gastric and duodenal ulcers
c. only in patients found to be resistant to clarithromycin and imidazoles
d. all patient groups evaluated in the subanalyses that were tested
e. in patients allergic to penicillins

31. After 7.3 years of treatment and follow-up, a combination pill of folic acid, vitamin B6 and vitamin B12:

a. did not significantly reduce homocysteine blood levels
b. significantly reduced combined endpoint of total cardiovascular events among high-risk women
c. did not significantly reduce combined endpoint of total cardiovascular events among high-risk women
d. proved to be a toxic pharmaceutical combination

Answers: 29 (c); 30 (d) 31 (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.

Oral Prednisolone for Acute Gout

THERE HAVE BEEN NO MAJOR therapeutic steps added for the management of acute gouty arthritis (AGA) for over 30 years. Although extensive experience with NSAIDs and colchicine attests to their efficacy, recent recognition of important toxicities with both has stimulated interest in alternative interventions.

Corticosteroids (CTS)—oral, parenteral, or intra-articular—have shown efficacy in AGA. However, the comparative efficacy of CTS vs NSAIDs or colchicines is unknown, and was the subject of investigation by Nanssens, et al.

In a randomized controlled trial, 120 AGA subjects (confirmed by identification of urate crystals) were assigned to either 5 days of naproxen 500 mg bid (NAP) or prednisolone 35 mg qd (PRED); to make blinding secure, a double-dummy design, wherein PRED recipients received a matching placebo to provide b.i.d. dosing for both groups, was employed.

Four days into treatment, the results for pain reduction were essentially equivalent for PRED and NAP. There were no major adverse effects reported by either treatment group. Prednisolone 35 mg/d may be a reasonable alternative therapy for gout, especially when concerns about NSAID or colchicine toxicity are present. ■

Janssens H, et al. Lancet. 2008;371:1854-1860.

Adding Aliskiren to Losartan for Diabetic Nephropathy

Treatment with angiotensin receptor blockers (ARBs) reduces levels of proteinuria in diabetics, and forestalls endstage renal disease. Unfortunately, despite full therapeutic doses of either ARB or angiotensin converting enzyme inhibitors (ACEi), not all patients enjoy equal success in reducing renal protein losses. Combination therapies for proteinuria, such as ACEi + ARB or ACEi + spironolactone, offer promise in this regard, but the combination of the direct renin inhibitor aliskiren (ALIS) with ARB has not been previously investigated.

A population of type 2 diabetics with nephropathy (24 hr urine protein > 300 mg) was randomized to stabilization on losartan 100 mg/d plus either aliskiren titrated to 300 mg/d or placebo. Patients with nephrotic syndrome or severe chronic kidney disease (GFR <30) were excluded.

At six months, ALIS treatment produced a 20% greater reduction in the urinary albumin-to-creatinine ratio than placebo. Although BP reduction is also associated with reduced renal protein loss, correction for the modest BP effect of adding ALIS to ARB (2/1 mm Hg) stil indicated a statistically significant, BP-independent impact. Adverse effects were similar in both treatment groups. Simultaneous modulation of the renin-angiotensin-aldosterone system by more than one mechanism provides additional benefit for reduction of proteinuria. ■

Parving HH, et al. N Engl J Med. 2008;358:2433-2446.

Early Aggressive Therapy in Type 2 Diabetes Pays Off

USING CURRENT CRITERIA FOR THE diagnosis of type 2 diabetes (DM2), approximately 50% of beta-cell function has been lost at the time of initial diagnosis. DM2 has been characterized as a disease of progressive decline in beta cell function; the UKPDS trial showed that all treatment regimens (sulfonylurea, metformin, insulin) were associated with progressive decline in control of A1c.

Because pancreatic beta cells become dysfunctional when subjected to persistent supraphysiologic glucose levels (perhaps as low as 140 mg/dL, sustained), investigators have opined that prompt intensive control of glucose might rejuvenate dysfunctional beta cells; limited data supports this concept.

Weng, et al performed a clinical trial on DM2 patients (n=382) comparing intensive insulin regimens (IIR) to oral hypoglycemic agents. Intensive insulin was either multiple daily insulin injections (basal insulin plus thrice daily insulin analog injections) or continuous subcutaneous insulin infusion.

Most IIR patients achieved glycemic control within 6 days, compared to 9.3 days using oral agents. All regimens were continued for 2 weeks once control was attained, and then discontinued, after which subjects used diet and exercise to try and maintain control for 1 year.

At one year, remission rates for IIR groups (45-50%) were statistically greater than oral agent rates (27%). First phase insulin response was improved only by IIR. Early intensive treatment produces durable improvements in beta cell function. ■

Weng J, et al. Lancet. 2008;371:1753-1760.

A Scooped ST Tachycardia

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.

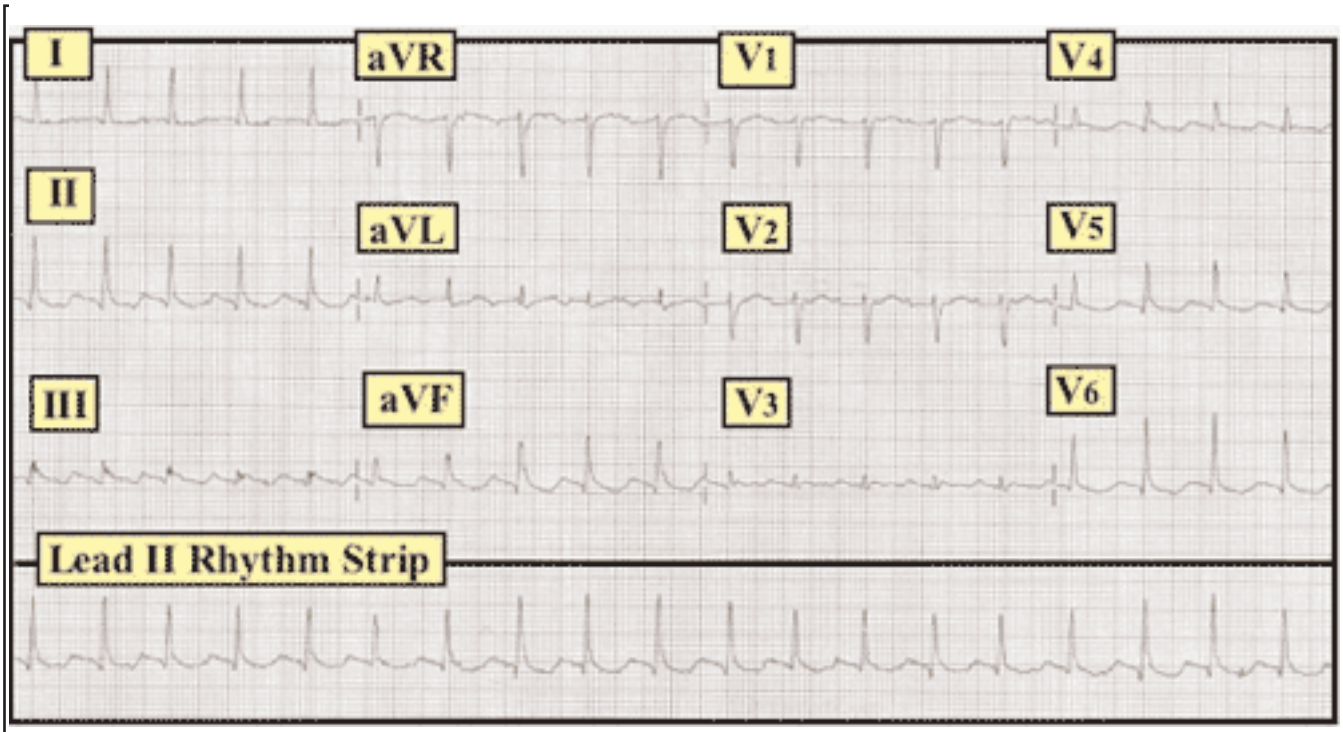

Figure: 12-lead ECG and lead II rhythm strip obtained from a 83-year-old woman with "rapid heart rate."

Clinical Scenario:

The 12-lead ECG and lead II rhythm strip in the Figure were obtained from a 83-year old woman who presented with rapid heart rate. She was on no antiarrhythmic medications. How would you interpret her ECG?

Interpretation/Answer:

There is minor irregularity in this supraventricular tachycardia that occurs at a rate of between 120-130/minute. At first glance in lead II, the rhythm looks like sinus tachycardia with a scooped ST segment. This is *not* what is occurring.

The key to interpreting this rhythm lies in lead III, which is best viewed by stepping back a little bit from the tracing. Doing so reveals the suggestion of a *saw-tooth* pattern that is really not evident in any other lead. Application of a vagal maneuver confirmed atrial flutter as the diagnosis. Although the atrial rate of *untreated* flutter is usually between 250-350/minute (most often very close to 300/minute) — this tracing illustrates how atrial flutter can occasionally occur at a slightly *slower* rate despite no treatment with antiarrhythmic drugs. ■

In Future Issues:

Fatigue — Can it Be Due to Cardiac Malfunction?

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.

CDC Adds Shingles Vaccine to List for Adults 60 Plus

In This Issue: Shingles vaccine added to CDC list of vaccines for adults 60 and older; CDC recommends Tdap for postpartum women; new study suggests sequential therapy with antibiotics for *H. pylori* may be more effective than standard therapy; FDA Actions.

The Centers for Disease Control and Prevention (CDC) have added shingles vaccine to the list of routine vaccines recommended for adults. Shingles vaccine (Zostavax) is recommended for adults 60 years of age or older even if they have a history of having shingles. The recommendation is based on data showing that the vaccine reduces the occurrence of shingles by 50% in those over the age 60. For the group age 60 to 69, the vaccine reduces the occurrence by 64%. Over 95% of adults have been infected by varicella-zoster virus during their lifetime, most developing chickenpox during childhood. After the acute infection the virus lies dormant in a nerve ganglion until it reactivates as shingles. Most children now receive varicella vaccine as part MMRV or individually with the chickenpox vaccine (Varivax). Shingles becomes more common over the age of 50 with as many as one third of the population developing shingles during their lifetime and one third of those may develop complications such as postherpetic neuralgia (PHN). The vaccine is also effective at preventing PHN (66% reduction). If the vaccine is given to older adults, it is more likely the virus will attenuate the severity of shingles rather than preventing shingles itself. In those older than 80, efficacy of preventing shingles was only 18%; however, there was still efficacy at preventing PHN (39% reduction). A comprehensive of review of this topic may be found at MMWR web site www.cdc.gov/mmwr.

Pertussis, Tetanus, and Diphtheria Vaccines for Pregnant Women

The CDC through their Advisory Committee on Immunization Practices has also issued new recommendations for the pertussis, tetanus, and diphtheria vaccine for women during and after pregnancy. Mothers are an identified source of pertussis infections in infants where the rates for complications and fatalities are the highest. Women who have not received the tetanus, reduced diphtheria, and acellular pertussis (Tdap[Adacel]) vaccine previously should be vaccinated postpartum before they leave the hospital or soon as possible after discharge. They may receive it as soon as two years after their most recent diphtheria and tetanus (Td) vaccination. They can also receive diphtheria tetanus vaccination during pregnancy if needed or defer it to receive the Tdap

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.

immediately postpartum. Currently the Tdap vaccine is not recommended during pregnancy although health-care providers "should weigh the theoretical risks and benefits before choosing to administer Tdap vaccine to pregnant women." The full text of the CDC's recommendations can also be found online at www.cdc.gov/mmwr.

Standard therapy for eradicating *H. pylori* infections fails in up to one quarter of patients. A new study published online as an early release article in *The Annals of Internal Medicine* suggests that sequential therapy with antibiotics may be more effective than standard therapy which generally consists of triple drug regimens including a proton pump inhibitor and clarithromycin with either amoxicillin or a imidazole for 7 to 14 days. In a meta-analysis of 10 randomized controlled trials involving 2747 patients, eradication rates were 93.4% for sequential therapy (95% CI, 91.3%-95.5%) and 76.9% for standard triple therapy (CI, 71.0%-82.8%). Sequential therapy is more complicated for the patient, involving five days of a proton pump inhibitor with an antibiotic followed by five days of a proton pump inhibitor with two other antibiotics. The median rates of adherence were 97.4% for sequential therapy and 96.8% for standard therapy. Both treatments had similar side effect profiles. The authors state that most of the studies were conducted in Italy and there was evidence of publication bias. Despite this they conclude that 10-day sequential therapy appears superior to standard triple therapy for eradication of *H. pylori* infection (published early release *Ann Int Med.* 20th May 2008, print 17 June 2008).

FDA actions

The FDA has proposed broad new labeling requirements for prescription drugs regarding their use during pregnancy and breast-feeding. This labeling information is directed at physicians and other health-care professionals. The new labeling would eliminate the letter categories from the pregnancy section of prescription labeling. The new format would include sections called "Fetal Risk Summary" which would describe what is known about the effects of the drug on the fetus and the strength of the data. This section would be required to include "risk conclusions" for the possibility of fetal harm based on available data. Another section, called "Clinical Considerations" would include information about the effects of the drug if it is taken prior to pregnancy as well as information on the risk of the disease being treated to the mother and baby. The third section under the heading "Data" would describe details regarding data on use of the drug in humans and animals that were used to develop the Fetal Risk Summary. The section on lactation is similar in format as that for pregnancy. Newly approved drugs will need to follow this format while previously approved drugs will be phased in over time.

The FDA has approved lubiprostone for the treatment of the irritable bowel syndrome with constipation (IBS-C) in adult women aged 18 over. The drug was previously approved in 2006 for chronic idiopathic constipation. There is currently no prescription drug therapy available in this country for IBS-C after the withdrawal of Novartis' tegaserod (Zelnorm) last year. The safety and efficacy of lubiprostone was demonstrated in two studies involving 1154 patients of which 92% were women. The drug is not approved for use in men due to lack of data demonstrating efficacy. The dose is 8 µg twice a day orally with food and water. Lubiprostone is manufactured by Sucampo pharmaceuticals and will be jointly marketed Takeda Pharmaceuticals under the trade name "Amitiza."

The FDA is reminding health-care professionals and patients that HFA propelled albuterol inhalers will no longer be available in the United States after December 31, 2008. These inhalers contain chlorofluorocarbon (CFC)-propelled inhalants which are thought to harm the Earth's ozone layer. New inhalers use hydrofluroalkane (HFA) as a propellant, and three have already been approved by the FDA including ProAir HFA, Proventil HFA, and Ventolin HFA. In addition levalbuterol is available in an HFA formulation (Xopenex HFA). Some patients have complained about the HFA propellant, noting the spray has a softer feel. Patients must also prime and clean HFA-propelled albuterol inhalers to avoid build- up of medication in the device. ■