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Good News, Bad News—Sleep Apnea and Cardiovascular Risk

ABSTRACT & COMMENTARY

Synopsis: *Middle-aged men with sleep apnea have an increased risk of cardiovascular disease compared with controls, even when controlling for age, body mass index, and blood pressure. Effective treatment reduces that risk.*

Source: Peker Y, et al. *Am J Respir Crit Care Med.* 2002;166:159-165.

This study is a prospective, controlled look at development of cardiovascular disease (CVD) in 182 men whose average age was 46.8 years at enrollment. Sixty of these men had obstructive sleep apnea (OSA), with a mean oxygen desaturation index (ODI) of 16.5 events per hour of sleep. (ODI is roughly equivalent to Apnea plus Hypopnea Index [AHI], or respiratory disturbance index [RDI]. Alas, these terms are used interchangeably in the sleep literature.) The OSA patients were slightly heavier and older, had higher blood pressures, and desaturated more than did the 122 controls, though the controls smoked more. The OSA patients were relatively thin by US standards (mean BMI, 27.9 kg/m^2), and they were offered continuous positive airway pressure (CPAP), uvulopalatopharyngoplasty (UPPP), or an oral appliance. CPAP was titrated in-laboratory, and compliance was objectively assessed 3 and 12 months after initiation. Patients who received UPPP or oral appliances had follow-up studies to assess "efficiency." Efficiently treated patients were considered to be those who used CPAP at least 50% of sleep hours, or who had fewer than 30 oxygen desaturations of 4% (which was probably about an ODI or RDI of 5 events per hour of sleep or less) after UPPP or while using the oral appliance.

Of the 60 patients with sleep apnea, 14 chose CPAP, 22 chose UPPP, 4 chose an oral appliance, and 19 did not receive treatment (I know this only adds up to 59, but this is what the article says). The 19 who did not receive treatment were asymptomatic or had mild sleep-disordered breathing. Nine (64%) of those who received CPAP returned the machine, and 50% of those who had surgery still had an ODI over 15 at follow-up. Only 1 in 4 patients treated with an oral appliance was felt to be adequately treated.

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INSIDE

More than 50% of those with incompletely treated OSA had at least 1 cardiovascular diagnosis (hypertension, angina, atrial fibrillation, MI, cardiomyopathy, cardiac failure, or stroke) during the follow-up period. None of the patients with effectively treated OSA patients did. In a logistic regression analysis, controlling for age, BMI, smoking, and blood pressure, both age and OSA remained as significant predictors of the risk of CVD. A separate analysis revealed the ODI and the baseline minimum oxygen saturation to be significant predictors of CVD, without regard to treatment. Furthermore, those subjects who were felt not to have significant OSA, but who had 15-29 oxygen desaturations during the diagnostic test had a highly significant increase in incident CVD compared with those with lower levels of oxygen desaturation.

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Please call **Robin Mason,** Managing Editor, at (404) 262-5517 (e-mail: robin.mason@ahcpub.com) or **Neill Larmore**, Associate Managing Editor, at (404) 262-5480 (e-mail: neill.larmore@ahcpub.com) between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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Customer Service E-Mail: customerservice@ahcpub.com

Editorial E-Mail: neill.larmore@ahcpub.com

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COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

The bad news is that sleep apnea appears to be a definite risk factor for cardiovascular disease, even when controlling for blood pressure, obesity, age, BMI, and gender. The good news is that effective treatment appears to reduce that risk substantially. The Sleep Heart Health Study has already demonstrated a very strong relationship between sleep-disordered breathing and cardiovascular disease.[1] However, the current study is the first prospective, controlled study to look at sleep apnea, its treatment, and cardiovascular risk in a well-described cohort without CVD or hypertension at baseline.

We already know that OSA is a risk factor for hypertension,[2-5] and that CPAP treatment reduces blood pressure in sleep apnea patients.[6-8] What has been less clear is whether OSA is a risk factor for cardiovascular disease independent of the associated hypertension. This study suggests that it is, and that the severity of oxygen desaturation is the prime determinant of CVD risk.

One reservation I had about this study was the finding that CPAP and UPPP were each about 50% effective in this population. These Swedish subjects were much thinner than the typical American sleep apneic, and we know that obesity predicts poor outcome with surgical treatment of sleep-disordered breathing.[9,10] Further, the ODI for the surgically treated patient fell as a group to a statistically significant degree, and half were considered efficiently treated, but I don't think that an overall fall in ODI from 15 to 12 events/hour is clinically satisfactory, especially since Peker and colleagues point out that oxygen desaturation indices in the moderate range were a risk for the development of cardiovascular disease.

Because Peker et al used the ODI as their primary measure of severity of OSA, they have strengthened the relationship between oximetry findings and sequelae of OSA. While purists (and those who own sleep labs) will continue to insist that in-lab sleep testing is the only way to make a diagnosis of OSA, this study and others like it lend support to the notion that a good clinician with an oximeter can predict the likelihood of OSA with some degree of confidence. Since CPAP is a benign, effective, relatively inexpensive treatment, and since OSA affects about 3% of us and is growing more prevalent (as we get fatter), it is likely that insurance companies will soon permit good clinicians to do just that! ■

References

1. Shahar E, et al. *Am J Respir Crit Care Med.* 2001;163: 19-25.

2. Lavie P, et al. *BMJ.* 2000;320:479-482.
3. Nieto FJ, et al. *JAMA.* 2000;283:1829-1836.
4. Grote L, et al. *Am J Respir Crit Care Med.* 1999;160: 1875-1882.
5. Peppard PE, et al. *N Engl J Med.* 2000;342:1378-1384.
6. Pepperell JCT, et al. *Lancet.* 2002;359:204-214.
7. Dimsdale JE, et al. *Hypertension.* 2000;35:144-147.
8. Faccenda JF, et al. *Am J Respir Crit Care Med.* 2001; 163:344-348.
9. Sher AE, et al. *Sleep.* 1996;19:156-177.
10. Larsson LH, et al. *Laryngoscope.* 1994;104:1362-1368.

Heart Rate Predicts Elderly Fractures and Mortality

ABSTRACT & COMMENTARY

Synopsis: *Older women with resting heart rates of 80 beats/min and above had increased rates of osteoporotic fractures and both cardiovascular mortality and all-cause mortality.*

Source: Kado DM, et al. *J Am Geriatr Soc.* 2002;50:455-460.

As part of a large multicenter study on osteoporotic fractures in women aged 65 and older, nearly 10,000 women had measurements of supine pulse rate after resting 5 minutes in a quiet room. They were extensively screened for multiple other health problems and medication use. Bone mineral densities were measured and patients were monitored for any occurrence of fractures over a 2-year period, and mortality data collected for 99% of the subjects. Black women and men were excluded from the study due to their lower risk of osteoporotic fractures.

Women in this group (mean age, 72 years) had an average resting heart rate of 69 ± 10 beats/min. Only 1.3% had a pulse of 50 or below, and 15.5% had a rate 80 and above. Women with higher pulse rates were more likely to be heavier, less active, to smoke, and to report diabetes, hypertension, and have low bone mineral density.

Even after adjusting for potential confounders such as age, weight, physical activity, hyperthyroidism, and current smoking, women with a resting pulse of 80 beats/min and above had a 1.6-fold increased risk of hip, pelvis and rib fractures, and a 1.9-fold increased risk of vertebral fractures. Comparing the adjusted subjects in groups sorted by resting pulse rates starting at 60 beats/min, each increase of 10 beats/min resulted in a 1.2-fold increase in fracture risk for hip and vertebral fractures. Fractures in other sites did not necessarily demonstrate the increasing risk, but this was thought to reflect low numbers in those groups.

Mortality risk for all causes and for cardiovascular diseases also demonstrated the association with resting pulse rates 80 and above, which was not present for mortality from cancer or stroke. Excluding women who took estrogens, beta blockers or calcium channel blockers did not affect the association.

COMMENT BY MARY ELINA FERRIS, MD

Despite our ever-growing technological means to detect disease and predict risk, this study suggests that the simple measurement of a resting pulse rate can provide useful information about our patients' health. The association with increased risk of death and certain osteoporotic fractures in older women was linear in nature, similar to risks associated with increased blood pressure for both sexes.

Previous studies have suggested a similar association in older men with higher resting pulse rates as a risk predictor for cardiovascular mortality and all-cause mortality.[1] It is not difficult to imagine that rapid resting heart rate may reflect general poor health, or at least poor physical fitness. However, this study did not find that the rapid rates correlated with the subjects' self-reported health or activity levels, nor with objective measures such as decreased grip strength or the inability to rise from a chair without using one's arms.

Kado and colleagues suggest that rapid heart rate may reflect "long-standing cumulative stress" which has some literature support in association with cardiovascular disease and osteoporotic fractures, possibly by increased sympathetic nerve activity, which results in the production of interleukin-6.[2] They argue that clinicians should use a cutoff of 80 beats/min rather than 100 as the definition of tachycardia and its associated risks.

One can't help but be struck by this research validation of a diagnostic maneuver used for centuries in Chinese medicine and other alternative approaches: the simple palpation of peripheral pulse rate as an indication of disease. Although we may not fully understand the underlying mechanisms, it provides support for the persistent value of our clinical skills in assessing the patient with our human touch. ■

References

1. Palatini P, et al. *Arch Intern Med.* 1999;159:585-592.
2. Papanicolaou DA, et al. *Ann Intern Med.* 1998;128: 127-137.

Dyspnea is a Better Predictor of 5-year Survival than Airway Obstruction in COPD

ABSTRACT & COMMENTARY

Synopsis: *In this prospective study of 183 patients, this study found that categorizing COPD patients on the basis of level of dyspnea correlated better with 5-year survival than categorizing on the basis of percentage of predicted FEV_1. The study also found no statistically significant difference in dyspnea grade among patients graded by FEV_1 criteria.*

Source: Nishimura K, et al. *Chest.* 2002;121:1434-1440.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is characterized by slowly progressive airway obstruction and is a major cause of mortality in developed countries. FEV_1 is the measure used to assess disease severity for staging and is reported to be the best single correlate of mortality. However, there is evidence that FEV_1 may not be the best single parameter and that other measures may be more helpful. Dyspnea is believed by some to be more discriminating with respect to health-related quality of life. The purpose of this study was to compare level of dyspnea vs. disease severity, as defined by FEV_1, as predictors of 5-year mortality in patients with COPD.

This was a prospective, observational, multicenter study in Japan following 183 COPD patients (90% male, 10% female) for 5 years. To be eligible, the patients had to have a clinical diagnosis of COPD or the presence of emphysema. Patients with respiratory diseases other than COPD or any severe systemic diseases that could affect prognosis were excluded. On each patient, initial clinical, physiologic, and radiographic features were examined in the stable state. The severity of obstruction was assessed based on American Thoracic Society guidelines. The level of dyspnea was recorded on a scale of I (breathlessness only on strenuous exertion) to V (too breathless to leave the house or breathlessness after undressing). Five years after entry, the patients were followed up with regard to their clinical course including any objective data and cause of death.

At the end of the 5-year period, 134 of 183 patients (73%) were alive. Of the 49 nonsurvivors 22 (45%) died of COPD and 10 (20%) died of malignancy. Between the group of survivors and nonsurvivors, there were significant differences in age (67 yr vs 71 yr, respectively; $P < 0.001$); dyspnea (grade 2.6 vs 3.3; $P < 0.001$); vital capacity (2.81 L vs 2.34 L; $P < 0.001$); FEV_1 (1.09 L vs 0.83 L; $P < 0.001$); DLCO/VA (2.66 mL/min/L/mm Hg vs 1.94 mL/min/L/mm Hg; $P = 0.004$); RV/TLC (51.6% vs 60.5%; $P < 0.001$); PaO_2 (75.2 mm Hg vs 67.6 mm Hg; $P < 0.001$); and $PaCO_2$ (41.2 mm Hg vs 43.9 mm Hg; $P = 0.017$). There were no significant differences in smoking history, presence of symptoms of chronic bronchitis and FEV_1/FVC%.

The staging of disease severity based on ATS guidelines did not significantly correlate with 5-year survival (stage I 5-year survival = 86%, stage II = 75%, stage III = 66%; $P = 0.08$). When the researchers applied British Thoracic Society and European Respiratory Society guidelines, no significant correlation was found (data not shown). When looking at patients classified according to dyspnea grade, there was a significant correlation with 5-year survival (grade II 5-year survival = 90%, grade III = 76%, grade IV = 35%, grade V = 0%; $P < 0.001$). A Cox proportional hazards model analysis revealed categorization by the level of dyspnea (with grade II as reference: grade III relative risk = 2.21, grade IV = 8.31, grade V = 61.3 [$P < 0.001$]) was more significantly related to survival than classification based on FEV_1 (with stage I as reference: stage II relative risk = 2.09, stage III = 2.51; $P = 0.20$). Comparing the backgrounds of groups delineated on the basis of ATS staging and dyspnea score, there was no significant difference in dyspnea among patients graded by ATS stage (dyspnea score stage I = 2.6, stage II = 2.7, stage III = 3.0; $P = 0.051$).

COMMENT BY DAVID OST, MD, & CHARLES SCOTT HALL, MD

Previous researchers have found FEV_1 to be the most accurate predictor of mortality in COPD.[1] However, some researchers feel there needs to be a more comprehensive staging system that would allow for better categorization of patients with COPD.[2] Hajiro et al found the level of dyspnea correlated with health-related quality of life better than staging according to ATS guidelines.[3] Nishimura and colleagues in this study focused on mortality and found the dyspnea score correlated better than the ATS staging. Despite the lack of standardization in the PFT readings among the multiple hospitals involved and the questionably high proportion of men vs. women, these results confirm that FEV_1 cannot be used as the sole prognostic

marker and that grade of dyspnea should be included in evaluating patients with COPD. ■

Dr. Hall is a Fellow in Pulmonary and Critical Care Medicine, North Shore University Hospital-NYU School of Medicine, Manhasset, NY.

References

1. Anthonisen NR, et al. *Am Rev Respir Dis.* 1986;133: 14-20.
2. Celli BR. *Chest.* 2000;117(2 Suppl):S15-S19.
3. Hajiro T, et al. *Chest.* 1999;116:1632-1637.

Don't Crack the Back? No Benefit of Chiropractic for Low Back Pain

BRIEF REPORT

Synopsis: *Evaluation of 4 different back pain interventions showed no differential benefit between them.*

Source: Hsieh CY, et al. *Spine.* 2002;27:1142-1148.

This randomized, assessor-blinded clinical trial was designed to investigate the effectiveness of 3 manual treatment regimens (joint manipulation, myofascial therapy, or a combination of these 2) vs. a back education program. Two hundred patients were assigned to 1 of the 4 groups, with assessments at baseline, every 3 weeks, and at 6 months after the completion of therapy. The primary outcome measures used visual analog scales and Roland-Morris activity scales.

■ **COMMENT BY BRIAN R. APATOFF, MD**

All 4 groups showed equal improvement in pain and activity scores after 3 weeks of treatment and had no further benefit at the 6-month follow-up assessment. There was no significant difference between outcomes using chiropractic treatments as compared to the back education school. Given that back pain is such a large issue in neurology, costing hundreds of millions for the health economy, it is hoped that such well-designed studies will provide evidence-based medicine to guide rational health care and eliminate unhelpful chiropractic methods. ■

Dr. Apatoff is Associate Professor of Neurology, New York Presbyterian Hospital-Cornell Campus, New York, NY.

Pharmacology Update

Tegaserod for Women with IBS

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

The FDA has approved the first treatment for women with constipation-predominant irritable bowel syndrome (IBS). Tegaserod is a partial 5-hydroxytryptamine-4 (5-HT4) (serotonin) receptor agonist that increases bowel motility. This approval comes on the heels of the reintroduction of alosetron, a 5-HT3 receptor antagonist, for diarrhea-predominant IBS in women. Tegaserod will be marketed by Novartis under the trade name "Zelnorm."

Indications

Tegaserod is indicated for the short-term treatment of women with IBS whose primary bowel symptom is constipation.[1]

Dosage

The recommended dosage is 6 mg taken twice daily before meals for 4-6 weeks. For those who respond, an additional course can be considered.[1] Dosage adjustment is not required for patients with mild-to-moderate renal impairment or mild hepatic impairment. Food reduces the bioavailability of tegaserod.[2]

Tegaserod is supplied as 2-mg and 6-mg tablets.

Potential Advantages

Tegaserod is currently the only FDA-approved drug for the treatment of constipation-predominate IBS. It has a low potential for drug interaction involving the cytochrome P450 isoenzyme system and P glycoprotein. No known significant drug-drug interactions have been identified.[1,2] In contrast to other prokinetic-like drugs (eg, cisapride) tegaserod does not cause QT prolongation.

Potential Disadvantages

The most common side effect of tegaserod is diarrhea with an incidence of 12% compared to 5% for patients who received placebo. In the majority of the patients diarrhea is limited to 1 episode lasting a median of 2 days, occurring within the first week of therapy. Diarrhea usually resolves with continuous therapy.[4] In clinical trials, a higher rate of abdominal surgeries was observed in tegaserod-treated patients compared to placebo (0.3% vs 0.2%). These were mainly cholecystectomies (0.17% vs 0.06%).[1]

Comments

Tegaserod is a selective 5-HT4 receptor partial agonist that stimulates gastrointestinal motility and normalize impaired motility. It increases colonic motility, orocecal transit, and esophageal clearance.[3,4] The efficacy of tegaserod was shown in 3 large phase III double-blind, placebo-controlled trials involving about 2500 patients. Tegaserod was shown in these 12-week studies to have a modest effect, compared to placebo, on constipation-predominate IBS. The proportion of responders at the 12 mg/d, ranged from 31-35% the first month and 39-44% the third month compared to 17-22% and 28-39% for placebo, respectively.[1] Responders were those who reported considerable or complete relief of symptoms for at least 2 of the 4 weeks of the assessment period. Relief included overall well being, abdominal pain/discomfort, and altered bowel habits. Response rates were statistically significant ($P < 0.05$) in 2 out of 3 studies.[4] Effect was seen as early as the first week and showing the greatest differential from placebo between weeks 4-6.[4,5] In addition, compared to placebo, tegaserod improved abdominal pain and discomfort based on a visual analog scale (29.9% vs 22.6%; $P = 0.044$).[5] The drug is well tolerated with less than 2% of patients discontinuing tegaserod due to diarrhea.[1,4]

Women respond better than men, and currently the drug is only approved for women. The average wholesale cost for a 30-day supply of either strength is about $150.

Clinical Implications

IBS, as defined by the Rome criteria, is the presence of at least 12 weeks in the preceding 12 months of abdominal discomfort or pain not explained by structural or biochemical abnormalities. The predominate symptoms can be divided into 4 categories, abdominal pain, diarrhea, constipation, or constipation alternating with diarrhea.[6] This syndrome is believed to affect 15-20% of the population and affecting 2-3 times more women than men. Current treatment of constipation-predominate IBS includes diet change and laxatives. Tegaserod provides an alternative with modest efficacy. ■

References

1. Zelnorm Product Information. Novartis Pharmaceutical Corporation. July 2002.
2. Baker DE. *Rev Gastroenterol Disord.* 2001;1(4): 187-198.
3. Lacy BE, Yu S. *J Clin Gastroenterol.* 2002;34(1):27-33.
4. Camilleri M. *Aliment Pharmacol Ther.* 2001;15: 277-289.
5. Muller-Lissner SA, et al. *Aliment Pharmacol Ther.* 2001;15:1655-1666.
6. Horwitz B, et al. *N Engl J Med.* 2001;344:1846-1850.

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We look forward to hearing from you. ■

CME Questions

13. Which one of the following statements about sleep apnea and cardiovascular risk is most true?

a. Sleep apnea is a risk factor for hypertension and incident cardiovascular disease, and CPAP treatment reduces that risk.
b. Sleep apnea is a risk factor for hypertension but not for incident cardiovascular disease. CPAP treatment reduces blood pressure in hypertensive patients.
c. Sleep apnea is a risk factor incident cardiovascular disease, and CPAP treatment reduces that risk. Sleep apnea is not a risk factor for hypertension.
d. Sleep apnea is a risk factor for hypertension and incident cardiovascular disease, but CPAP treatment does not affect that risk.

14. Which one of the following has an association with resting pulse rates of 80/min and above in women aged 65 years and older?

a. Current smoking
b. Cancer mortality
c. Increased osteoporotic fractures
d. Depression
e. Visual impairments

15. Which of the following parameters best correlated with 5-year survival in COPD patients in the study by Nishimura et al?

a. ATS Staging system
b. Grade of dyspnea
c. Smoking history
d. ERS Staging system

16. Which one of the following is *not* true about tegaserod?

a. It is approved for diarrhea-predominant IBS.
b. It is only approved for use in women.
c. It is not likely to cause drug-drug interactions.
d. It is a serotonin receptor partial agonist.

By Louis Kuritzky, MD

Injection of Botulinum Toxin for Wrist and Finger Spasticity after a Stroke

POST-STROKE SPASTICITY IN THE hands and wrists is potentially particularly disabling in that it may complicate basic essential daily activities like dressing, washing, and eating. There is a paucity of information about the role of botulinum toxin (BOT) on functional outcome in post-stroke spastic disorders.

Brashear and colleagues studied patients (n = 126) with post-stroke spasticity of the upper extremity. In addition to an overall global assessment, functional disability outcomes measured were hygiene, dressing, limb position, and pain. Each patient selected one of these 4 end points as their personal "principal target," though all parameters were measured for all subjects. Most patients selected "dressing" as the principle target, but more than one quarter chose limb position. Patients received a single set of 4-5 injections in wrist and finger muscles, or placebo. Outcomes were measured at 4, 6, 8, and 12 weeks.

More than twice as many persons who received BOT than those who received placebo achieved improvement in their primary target. For functional disability, BOT recipients' improvements (at least 1 point on an 8-point scale) were again superior to placebo (83% vs 53%). The physician's global assessment score was significantly higher for BOT at all follow-up visits. No serious adverse events were seen in either group.

Statistically significant and clinically meaningful improvements in upper extremity function are seen as early as 1 week after BOT injections and are maintained for at least 12 weeks. ■

Brashear A, et al. N Engl J Med. 2002;346:395-400.

Prescribed Exercise in People with Fibromyalgia

THE TREATMENT OFFERED FOR fibromyalgia (FMG)—typically consisting of analgesics, NSAIDs, and antidepressants, alone or in combination—often provides suboptimal efficacy. Although some trials of exercise have suggested a favorable effect on FMG, their widespread applicability to the ambulatory setting has been limited by underpowered study groups and provision of specialized exercise plans administered in hospitals by health professionals with special expertise in this field.

Richards and Scott investigated the effect of aerobic exercise (treadmill walking or exercise bicycles) or stretching/relaxation activities. Twice-weekly classes of aerobic activities began with two 6-minute sessions and were advanced as tolerated to 2 25-minute sessions over a 12-week observation period. The primary outcome was self-rated global impression, rated on a 7-point scale, with 1 being "very much worse" and 7 being "very much better." Only persons with a score of 6 or greater were considered responders.

The 108 participants were highly disabled at baseline, with a mean SF-36 score greater than 3 SD below normal, and two thirds were receiving disability benefits.

At 3 months, a statistically significantly greater portion of exercise subjects were responders than relaxation subjects (35% vs 18%). This beneficial effect was still measurable at 12 months. A substantial number of individuals were noncompliant: specifically, only 53% of subjects attended at least one third of the exercise classes. Accordingly, the authors do suggest that future investigation should evaluate methods to enhance compliance with exercise, given the favorable effects demonstrated in this trial. ■

Richards SCM, Scott DL. BMJ. 2002; 325:185-187.

Risk of Diabetes Among Patients with Schizophrenia

THE ADVENT OF NEWER ANTIpsychotic agents for schizophrenia has broadened the clinician's therapeutic palette, with the additional benefit of fewer extrapyramidal adverse effects. Nonetheless, this pharmacotherapeutic evolution has introduced a different panel of adverse effects, such as weight gain, dyslipidemia, glucose perturbations, and cardiac toxicities. This study draws upon a very large database from 400 British general practice sites, including 3.5 million patients. The primary outcome was the quantification of risk of new onset diabetes in schizophrenic subjects who received newer antipsychotics, ie, olanzapine and risperidone.

Cases were defined as having been newly diagnosed with the diabetes at least 3 months after the beginning of the study period. Comparators were controls that did not have a diagnosis of diabetes. Study subjects were further classified as those receiving "conventional" antipsychotics or "newer" antipsychotics (olanzapine, risperidone).

Among 19,637 persons with schizophrenia from the study population, 451 cases of incident diabetes were discerned. Compared with matched controls, the odds ratio for diabetes among users of olanzapine was increased almost 6-fold, and was more than 4-fold greater than patients who had received "conventional" agents. There was no significant increase in risk for persons who took risperidone. Koro and colleagues conclude that the metabolic consequences of antipsychotics merit consideration by clinicians. ■

Koro CE, et al. BMJ. 2002;325:243.

ECG Review

A Code From a Cause

By Ken Grauer, MD

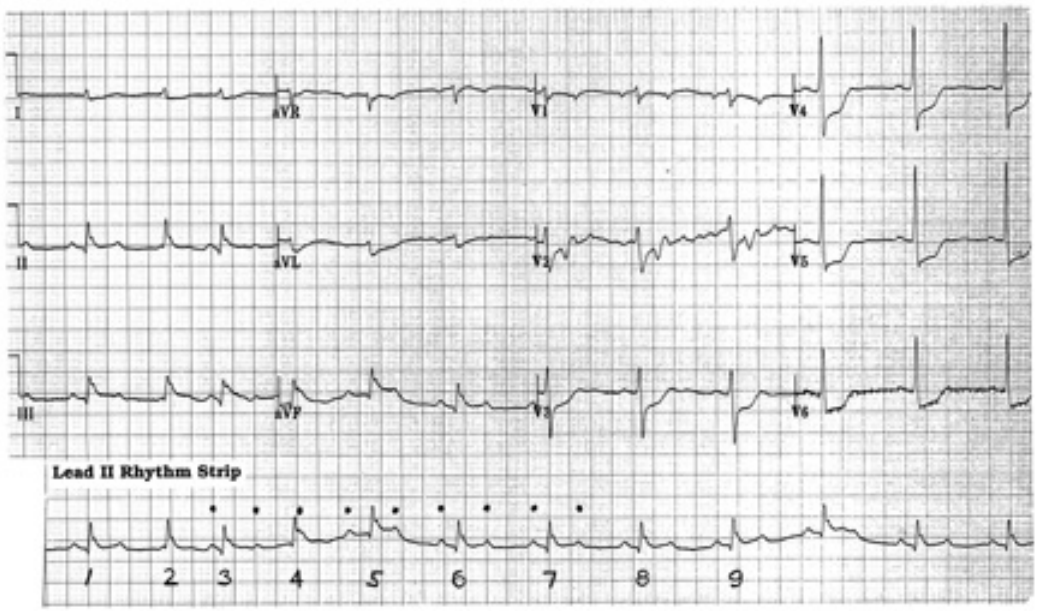

Figure. 12-lead ECG and lead II rhythm strip obtained from a 62-year-old woman shortly before her cardiac arrest.

Clinical Scenario: The ECG in the Figure was obtained from a 62-year-old woman who was admitted for chest pain. She was doing poorly from a clinical standpoint at the time this tracing was obtained, and suffered a cardiac arrest shortly thereafter. How would you interpret her precode ECG that is shown in the Figure?

Interpretation: This is a complex tracing. Dots in the lead II rhythm strip suggest that after some initial irregularity, 2:1 AV conduction becomes established. We suspect that the rhythm is 2° AV block, mostly Type I (Wenckebach) with atrial tachycardia at a rate of 140/min. It is difficult to be certain if beats #2 and #4 represent junctional escape or Wenckebach conduction with a long preceding PR interval—but the presence of normal QRS width and the suggestion of acute inferior infarction (subtle but real ST segment elevation in leads II, IIII, and aVF) are most consistent with a Mobitz I etiology for the 2:1 AV block. Marked ST segment depression in virtually all other leads on the tracing suggest extensive evolving acute infarction that probably also involves the posterior wall. The combination of acute infero-postero wall infarction with extensive reciprocal ST segment depression in conjunction with atrial tachycardia and 2:1 AV block explain why the patient soon suffered a cardiac arrest. ■

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Internal Medicine Alert*. Send your questions to: Neill Larmore, *Internal Medicine Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Internal Medicine Alert* via the internet by sending e-mail to neill.larmore@ahcpub.com. We look forward to hearing from you. ■

In Future Issues:

Did You Remember to Take Your Ginkgo?

PHARMACOLOGY WATCH

WHI Trial Arm Stopped Due to Increase in Breast Cancer

Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women" is the stunning conclusion from the Women's Health Initiative published in the July 17 *Journal of the American Medical Association*. The trial, which randomized 16,608 healthy postmenopausal women to conjugated equine estrogen/medroxy-progesterone or placebo, was stopped just 5.2 years into the 8.5 year study when the risk for invasive breast cancer exceeded the stopping boundary. Excess coronary heart disease (CHD), stroke, and pulmonary embolism (PE) were also noted; however, the combination reduced the risk of colorectal cancer, endometrial cancer, and hip fracture. The findings were front-page news coast-to-coast as well as the subject of cover stories in *Time* and *Newsweek*. Important aspects of the study include:

Although there is a higher risk of adverse events with the combination of conjugated estrogen and medroxyprogesterone, the absolute risk is low. The hazard ratios were: CHD 1.29, breast cancer 1.26, stroke 1.41, PE 2.13, colorectal cancer 0.63, endometrial cancer 0.83, hip fracture 0.66, and death due to other causes 0.92. Per 10,000 person-years, estrogen/progestin resulted in 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, but 6 fewer colorectal cancers and 5 fewer hip fractures. All-cause mortality was no different between the 2 groups.

This study, which enrolled healthy women with an intact uterus, was designed as a primary prevention trial of CHD. When combined with the results from HERS II published just one week earlier (*JAMA*. 2002;288:49-57) (a secondary prevention trial in women with known CHD), the notion of estrogen/progestin being cardioprotective is essentially eliminated.

Another wing of WHI is looking at nearly 11,000 women who have had hysterectomies and are on estrogen alone. So far, that study has not shown an increase in the rate of breast cancer, and the study will continue. The WHI group also admits that other estrogen/progestin combinations may result in different outcomes.

What to do with women on HRT who are doing well? The authors and editorialists of WHI suggest that there is no urgency, but that all women should be moved away from HRT as a strategy for preserving health and preventing disease. New patients should look for alternatives, and women currently on HRT should reevaluate the reason the drugs are being used and consider other options (*JAMA*. 2002;288:321-333; *JAMA*. 2002;288:366-367).

Side Effects Overrated in Beta Blockers

The side effects of beta blockers may be overrated by most physicians according to a new study. This leads to underuse of these important drugs, especially in cardiac patients. The authors performed a quantitative review of 15 trials, which included more than 35,000 patients. Beta

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. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. 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.

blockers were not associated with an increased risk of depression, and only a small risk of fatigue (18/1000 patients 95% CI, 5-30) or sexual dysfunction (5/1000 95% CI, 2-8). There was no difference in these side effects with the lipid solubility of the various drugs; however, late-generation beta blockers were associated with less fatigue than the older drugs (*JAMA*. 2002;288[3]:351-357).

Aranesp Approved in Cancer Treatment

Aranesp (darbepoetin alpha), Amgen's long-acting erythropoietin, has been approved for use in cancer patients undergoing chemotherapy. The drug was initially approved for treatment of anemia associated with renal failure and dialysis. Aranesp maintains blood levels about 3 times longer than previous available erythropoietin (Procrit), allowing for dosing every 2-3 weeks as compared to weekly dosing for Procrit.

Zelnorm to Provide IBS Relief

The FDA has approved tegaserod maleate (Zelnorm—Novartis) for the treatment of women with irritable bowel syndrome (IBS) whose primary symptom is constipation. The drug is a serotonin-4 receptor agonist that is been shown to reduce constipation, bloating, and abdominal discomfort.

The approval was based on results of 3 randomized, double-blind, placebo-controlled trials each lasting 12 weeks. The efficacy of tegaserod was greater at 1 month than at 3 months, suggesting a decrease in efficacy over time. The drug is approved for short-term treatment, as long-term efficacy as well as safety is not established. The efficacy in men with constipation-predominant IBS has also not been established. Not surprisingly, the primary side effects of tegaserod are diarrhea. The approval has already come under criticism by the consumer watchdog group Public Citizen calling the approval "reckless." The group contends that users of tegaserod were more likely to need surgery in clinical trials and were also more likely to develop ovarian cysts. Public Citizen has also been critical of the FDA for reapproving alosetron (Lotronex) for the treatment of women with diarrhea predominant IBS.

FluMist Delayed for Second Time

The FDA approval of FluMist has been delayed for a second time. The intranasal, live attenuated influenza vaccine was first delayed 1 year ago when the agency requested more safety data. The current delay is due to the FDA's need for additional information regarding the manufacturer's biologics license application. FluMist may someday provide an alternative to injection based flu vaccines.

Elderly Patients: Keep Taking Your Statins!

Elderly patients frequently discontinue statin therapy on their own according to 2 new studies in *JAMA*. A large group of elderly patients enrolled in a New Jersey Medicaid and pharmaceutical assistance program were followed to assess their compliance with statin therapy over time. Based on the quantity of drugs dispensed, only 60% of patients were adhering to therapy at 3 months and only 32% at 120 months. Factors predicting poorer adherence with therapy included nonwhite race, low income, older age, less cardiovascular morbidity at the start of therapy, depression, dementia, and coronary events after starting treatment. Patients who started therapy more recently were more likely to continue therapy compared with those who started the statin therapy in 1990. In the second study, researchers in Canada looked at patients age 66 and older who were on statin therapy and fell into 1 of 3 groups: those with recent acute coronary syndrome, those with chronic coronary artery disease, and those without coronary disease who were taking statins for primary prevention. Patients older than the age of 66 had 2-year adherence rates of 40.1% for patients with recent acute coronary syndromes, 36.1% among patients with chronic CAD, and only 25.4% among those taking statins for primary prevention. As pointed out in an accompanying editorial, both studies are based on pharmacy databases, which are only a surrogate for compliance; however, the sheer size of the studies and the magnitude and consistency of the trends noted make the findings likely be correct. In light of the recent National Cholesterol Education Program recommendations, which dramatically increases the number of elderly patients eligible for statin therapy, compliance programs in this population are needed (*JAMA*. 2002;288:455-461; 462-467; 495-497). ■