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Hot Flash! More From the HERS Trial

ABSTRACT & COMMENTARY

Synopsis: *Postmenopausal women with cardiac histories who are still flushing do better with hormone replacement therapy.*

Source: Hlatky MA, et al. *JAMA.* 2002;287:591-597.

The heart and estrogen/progestin replacement study (HERS) trial enrolled postmenopausal women younger than 80 years who had coronary artery disease (CAD) into a randomized, double-blind, placebo-controlled trial. After randomization, the women were given 0.625 mg of conjugated equine estrogens and 2.5 mg of medroxprogesterone (Prempro®) or placebo and followed for up to 4 years. Hlatky and colleagues defined postmenopausal in 4 ways: age 55 years or older and no natural menses for at least 5 years; no natural menses for at least 1 year and a serum follicle-stimulating hormone (FSH) level greater than 40 mIU/mL; documented bilateral oophorectomy; or reported bilateral oophorectomy and FSH level greater than 40 mIU/mL and estradiol level less than 25 pc/mL. CAD was defined as previous myocardial infarction (MI), greater than 50% luminal narrowing on coronary angiography, or previous coronary revascularization. They excluded patients with MIs or revascularizations within the last 6 months, with hysterectomies, with contraindications to hormone replacement therapy (HRT), with use of HRT within the last 3 months, with life-threatening diseases, or who could not return for follow-up visits.

The 2763 women (1380 randomized to HRT) completed a quality-of-life questionnaire that included a physical function assessment, an energy/fatigue scale, a mental health inventory, and anxiety and depression scales at baseline, 4 months, 1 year, 2 years, 3 years, and 4 years. The data were analyzed for just the first 3 years. The analysis was by intention-to-treat.

At baseline, the 2 groups did not differ significantly. The average age was 66.6 years. They were predominantly white (89%). More than half of them had a smoking history, hypertension, prior MI, and prior revascularization. Despite this, 76% rated their health as good-to-excellent. Sixteen percent were still experiencing flushing at least

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INSIDE

some of the time. Their physical function assessment was consistent with a moderate amount of physical activity.

After 3 years of follow-up, the HRT group had a larger decline in physical activity and energy/fatigue compared to the control group. Both of these findings were statistically significant; the actual numerical scores dropped 17% vs. 12% and 8% vs. 5%, respectively. Both experimental and control groups showed minor declines in mental health that were not significantly significant. Patients assigned to HRT were less depressed at 3 years.

Hlatky et al looked at the data based on whether the patients were still flushing. As expected, the flushing patients were younger (63.0 vs 67.3 years) and had been postmenopausal for a shorter time (13.7 vs 18.7 years). The prevalence of flushing declined significantly among HRT patients, dropping from 16.7% to 5.8% after 3 years. Among the control group, the prevalence dropped from 14.7% to 11.2%. At baseline, physical activity, energy/fatigue, mental health, and depression scores were all significantly worse in the flushing patients than the nonflushing patients. Over the 3 years of the study, the decline in physical function and energy/fatigue among flushing patients was not significantly different between the HRT group and the control group, but HRT was associated with improvement in mental health and depression scores. On the other hand, women who were not flushing at baseline and who received HRT had significant declines in physical functioning and energy/fatigue, but no significant change in mental health or depression.

Subgroup analysis yielded these findings. Chest pain and lower level of education lowered quality-of-life scores. Older patients had lower physical activity scores, but better mental health and depression scores than younger patients. Heart failure, diabetes, and hypertension all lowered physical activity and energy/fatigue scores but had less effect on mental health and depression. Having a revascularization procedure did not affect quality-of-life. Having had an MI had no effect on physical activity or energy/fatigue but was associated with better mental health scores and less depression.

COMMENT BY ALLAN WILKE, MD

In 1998, the main results of HERS were published. Briefly, postmenopausal women with cardiac disease do not do well in the first 3 years after receiving HRT; they have more thromboembolic events and gallbladder disease and, at least in the first year, more cardiac events. The primary outcomes of the study were cardiovascular. This study looks at secondary end points and attempts to answer the question, "Do they feel better?" Measuring "feeling better" involves choosing outcomes and trying to determine "quality-of-life." The outcomes Hlatky et al chose are relevant, but they could have chosen to measure other things. For instance, in some studies, estrogen use has been associated with less Alzheimer's disease. One could reasonably suggest that Alzheimer's disease has an adverse effect on quality-of-life and that the investigators could have measured the Mini-Mental Status scores.

It appears that the only women in this study who benefited from HRT are those who were flushing. So how many postmenopausal, cardiac patients who are flushing would you have to treat to help one woman? This is the concept of "number needed to treat" (NNT). We can use the data to answer the question. Looking at the HRT group, we see that the "pharmaceutical" cure rate is 10.9% (16.7-5.8%). If we look at the controls, we see

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that the "natural" cure rate is 3.5% (14.7-11.2%). If we assume that 3.5% of women in the experimental group would have had a "natural" cure, then this leaves 6.4% of women whom HRT helped. The last piece of mathematics is to convert 6.4% into a fraction, 1/15. In other words, we would have to treat 15 women with flushing to provide relief to 1, at the risk of increased thromboembolism and gallbladder disease.

There are some nonintuitive results in this study. For instance, why would having an MI be associated with no effect on physical activity or energy/fatigue, but better mental health scores and less depression? In the main study, the women on HRT had more cardiac events in the first year than the control group. I can imagine that having an MI during the study period could have a negative effect on my quality-of-life. ❖

Dr. Wilke is Assistant Professor of Family Medicine, Medical College of Ohio, Toledo, Ohio.

Consume More Calcium and Cut Down on the Occurrence of Calcium Oxalate Stones!

ABSTRACTS & COMMENTARY

Synopsis: *Restricted intake of salt and protein in conjunction with a normal calcium intake provides greater protection from recurrent calcium oxalate stones than a low-calcium diet.*

Sources: Borghi L, et al. *N Engl J Med.* 2002;346:77-84; Bushinsky DA. *N Engl J Med.* 2002;346:124-125.

Borghi and colleagues point out that physicians usually prescribe a low-calcium diet for patients with idiopathic hypercalciuria and calcium oxalate stone formation. They note that there are no long-term studies on the efficacy of this approach.

Their study was a 5-year randomized trial comparing the effect of 2 diets in 120 men with recurrent calcium oxalate stones and hypercalciuria. Sixty men were assigned to a diet containing a normal amount of calcium (30 mmol/d) but reduced amounts of animal protein (52 g/d) and salt (50 mmol of sodium chloride/d); the other 60 men were assigned to the traditional low-calcium diet, which contained 10 mmol of calcium per day.

After 5 years, 12 of the 60 men on the normal-calcium, low-animal protein, low-salt diet and 23 of the 60 men on the low-calcium diet had had relapses, the unadjusted relative risk of a recurrence for the group on the first diet, as compared with the group on the second diet, was 0.49 ($P = 0.04$). During follow-up, urinary calcium levels dropped significantly in both groups by approximately 170 mg/d. However, urinary oxalate excretion increased in the men on the low-calcium diet, by average of 5.4 mg per day, but decreased in those on the normal calcium, low animal protein, low salt diet by an average of 7.2 mg per day.

In men with recurrent calcium oxalate stones and hypercalciuria, restricted intake of animal protein and salt, combined with a normal calcium intake, provides greater protection than the traditional low calcium diet.

COMMENT BY RALPH R. HALL, MD, FACP

It is surprising to read that there are still many physicians who recommend a low-calcium diet for this disorder.

The paper by Curhan and colleagues in 1993[1] with a convincing editorial by Lemann[2] contained enough data to convince most physicians that a low-calcium diet was potentially harmful. Low-calcium diets in a group of patients who had been losing excessive amounts of calcium for most of their lives was certainly exposing them to serious osteoporosis. Curhan et al also documented the need for increased fluid intake.

Bushinsky, the author of the excellent editorial commenting on the paper by Borghi et al, also presented evidence that low-calcium diets should not be used.[3] He reviews the evidence that kidney stones are a significant problem resulting in an estimated 1.32 million visits to physicians in 1995. In approximately 70% of the cases, the stones are composed of calcium oxalate. In his editorial, Bushinsky succinctly reviewed Lemann's data indicating a low-calcium diet may indeed increase the production of calcium oxalate stones.

There is strong experimental evidence that animal protein and salt increase calcium excretion.[4] Borghi et al also advised their patients to avoid large amounts of oxalate-rich foods (eg, walnuts, spinach, rhubarb, parsley, and chocolate.)

As Bushinsky notes in his editorial, "It is not known whether these results are valid for women." Further, he suggests that future studies should address the independent role of these 3 dietary components. There is strong experimental evidence, but no long-term studies to verify the long-term results of treatment.

It also would be helpful to know how simply prescribing small doses of inexpensive thiazide diuretics might compare to these diets. Prospective, controlled clinical trials have demonstrated the effectiveness of low-dose treatment with thiazides.[5] This approach must

be associated with a restricted sodium intake and monitoring of the serum potassium. ❖

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MRI vs. Ultrasound for DVT

ABSTRACT & COMMENTARY

Synopsis: *The sensitivity and specificity of MRI were similar to venography and ultrasound.*

Source: Fraser DG, et al. *Ann Intern Med.* 2002;136:89-98.

THIS TRIAL EVALUATED THE EFFICACY OF MRI IN diagnosing DVT. The trial enrolled 338 consecutive patients suspected of having a DVT. Venography was successfully performed in 298 of these patients; this was used as the gold standard for the presence or absence of DVT. All patients with a positive venography (n = 58) and 48 patients with a negative venography were included in the study. By study protocol, every fourth patient with a negative venography was included in the study.

Selected patients then underwent MRI of both lower extremities. Two reviewers blinded to the venography results, an expert radiologist and a non-radiologist trained in MRI, interpreted the MRIs. The reviewers were asked to comment on the presence or absence of DVT, and the location of the DVT (isolated calf, femoropopliteal, and ileofemoral).

The overall sensitivity of MRI was 96% (95% CI, 89-99%) and the specificity was 90% (95% CI, 79-96%). The MRI was 100% sensitive and specific for ileofemoral DVTs, and 97% sensitive and 100% specific for femoropoliteal DVTs. The MRI was less sensitive (reviewer 1: 92%; reviewer 2: 83%) and specific (reviewer 1: 94%; reviewer 2: 96%) for isolated calf DVTs.

There was good intra-observer agreement (k = 0.94; 95% CI, 0.88-1.0)

COMMENT BY JEFF WIESE, MD

Venography, the gold standard for diagnosing DVT, has largely been replaced by noninvasive tests such as ultrasound or impedence plethysmography. Ultrasound is 89% sensitive and 97% specific for DVTs above the knee, but is limited in its ability to diagnose pelvic DVTs and DVT recurrence.[1] Other limitations of venography and ultrasound include its use in patients with full-length leg casts, patients suspected of having pelvic DVTs, or patients suspected of having DVT recurrence.

This study confirms that MRI is a viable option for diagnosing DVT. The positive and negative likelihood ratios for MRI are 9.6 and 0.04.[2] This study is limited by the high number (26%) of participants that dropped out after enrollment. It does not appear, however, that the loss of these patients from the protocol would have changed the results. The sensitivity and specificity of MRI were similar to venography and ultrasound.

The primary limitation of MRI is the cost and access to the test. The MRI protocol in this study used a standard clinical magnet with no special patient preparation or use of contrast. The cost of the MRI depends on the scanning time. On average, a 40-minute scanning time costs $1000. The average scanning time in this study was 12 minutes, making the estimated cost of MRI of $300 comparable to ultrasound ($300) and venography ($450). The scanning time depends on the experience of the technician, the skill of the radiologist, and the access to the MRI scanner. All of these parameters will vary from hospital to hospital; clinicians should make the decision as to the use of MRI in diagnosing DVT based on their access to MRI scanning, the facilities of their individual hospital, and the scanning time used in their hospital.

Understanding the physiology of MRI is important to selecting patient subgroups that may benefit from MRI. Methemoglobin production increases once blood clots, and this shortens the T1 magnetic resonance. The result is an increased density seen within the vein on MRI. The production of methemoglobin declines over time, enabling MRI to distinguish acute (high density) from chronic (low density) DVTs.[3] Unlike ultrasound or venography, MRI does not depend on venous occlusion of flow for diagnosis. This makes MRI less likely to be falsely negative in patients with venous underfilling due to poor circulation or dehydration.

Patients that may particularly benefit from MRI include pregnant patients (due to MRI's ability to diagnose pelvic DVTs), patients with full-length leg casts, and those with a history of chronic DVTs being evaluated for DVT recurrence.[4]

Measurement of ELISA d-dimer levels was not performed in the study, and the addition of this test to diagnostic protocols may improve the specificity of the diagnostic protocol. ❖

Which SSRI for Treatment of Depression?

ABSTRACTS & COMMENTARY

Synopsis: *A prospective study comparing the 3 most commonly used SSRIs for initial treatment of depressed primary care outpatients found no difference in their effectiveness for depressive symptoms, adverse effects, or discontinuation rates.*

Sources: Kroenke K, et al. *JAMA.* 2001;286:2947-2955; Simon G. *JAMA.* 2001;286:3003-3004.

To evaluate the effectiveness of paroxetine, fluoxetine, and sertraline in actual primary care offices, 2 non-profit volunteer primary care research networks, involving 8600 physicians across the country and an academic clinical organization of 150 physicians, were organized to enroll patients over an 8-month period and follow them for 9 months. In order to duplicate "real-world practice" as much as possible, the decision to initiate antidepressant treatment was based strictly on the physician's judgment rather than any research scale. Choice of medications was not blinded, and physicians and patients were allowed to change doses, switch medications, or discontinue them as they would in a typical clinical setting.

Six hundred patients were eventually randomized from 63 sites to begin treatment with 1 of the 3 SSRI antidepressants (paroxetine 20 mg, fluoxetine 20 mg, or sertraline 50 mg). Computer-assisted telephone interviews were conducted at baseline and 1, 3, 6, and 9 months later. Study patients received a small stipend in compensation, and interviews were successfully completed in 94% of patients at 1 month, down to 79% at 9 months. Depression was assessed with several measures, including the SF-36 Medical Outcomes Study Mental Component Summary and other psychological outcome measurement scales. Social and work function and other health-related quality-of-life measures were also recorded along with actual medication use. Patients with other medical problems or substance abuse were excluded.

All of the SSRI groups had marked improvement in measures of depression and other health-related symptoms; patients who met criteria for major depression by interview dropped from 74% at baseline to 26% at 9 months, and reports of anxiety attacks declined from 35% to 14%. There was no difference in outcome among the 3 medication groups; recovery was present at 9 months for 81% in the paroxetine group, 77% in the fluoxetine group, and 84% in the sertraline group. These were not substantially different whether patients continued with the same initial antidepressant throughout the study or were switched or dropped out. Statistical analyses did not reveal any differences in patient characteristics or other biases. More than 80% of patients were satisfied with their treatment and their physician's interest, and this did not differ among the 3 medication groups.

The proportion who stopped or switched to another antidepressant were 13% at 1 month, 32% at 6 months, and 40% at 9 months, and did not differ by drug group. Adverse effects such as GI complaints or insomnia were the most common reason, and also did not differ by choice of medication. Specific questions on 4 areas of sexual function did not reveal any significant concerns or differences among the medications, and in fact showed a slight improvement under treatment rather than worsening.

COMMENT BY MARY ELINA FERRIS, MD

Despite the claims of drug manufacturers that one SSRI is preferable to another, this groundbreaking study conducted in real primary care offices fails to demonstrate any clear difference in effectiveness among the 3 most commonly prescribed antidepressants. They also failed to find any other patient characteristics that would predict which of the 3 antidepressants would work better in particular situations; no conclusion could be drawn that a specific drug was better for any patient factor.

However, this does not invalidate the clinical necessity to change dosage and switch medications to obtain the best outcome. Nearly 20% of patients in this study switched medications 1 or more times, and in the end two thirds of the patients who began treatment had recovered at the 9-month follow-up, which had been demonstrated in previous academic studies.[1]

An accompanying editorial in the same issue makes the important point that "equal on average does not mean equal for everyone." Patients who do not respond to the initial SSRI antidepressant will frequently benefit from another in the same class, and side effects may also necessitate a medication change to ensure compliance. New research is suggesting individual genetic variability in liver enzyme metabolism and serotonin transporter proteins, which may enable a more scientifically based approach to drug selection in the future.

In the meantime, there is no evidence-based approach to predict effectiveness in the initial choice of SSRIs, but there is a need to frequently use the other SSRIs when adjusting treatment. The editorial points out that restrictive managed care formularies may be justified indicating a low-cost initial SSRI, but that the

other SSRIs clearly need to be available for the predictable frequent medication changes needed for maximal patient benefit. ❖

Reference

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ID Alerts

Influenza 2002/2003

Source: PHLS. Press Release, Feb. 6, 2002; ProMED-mail post, Feb. 7, 2002. www.promedmail.org.

INFLUENZA EXPERTS, WHO MEET ANNUALLY TO DEtermine the composition of the following year's influenza vaccine, are focused on a new strain of Influenza A virus (H1N2), which has been identified as causing human infection in Israel, England, and Egypt. This new subtype appears to contains a little bit of each of 2 influenza viruses that have been circulating in the human population for years, H1N1 and H3N2. Both the H1 hemagglutinin and the N2 neuraminidase of the new strain appear very similar to the corresponding parts of the existing subtypes. A similar reassortment occurred in China during the 1988/1989 flu season, although it did not spread farther at that time, and has also been found in swine for more than 10 years. This information provides an even more compelling reason to strive for maximal vaccine coverage of the elderly and high-risk patients next year. **—CAROL A. KEMPER, MD**

Anthrax Vaccine Program Bombs

Source: ProMED mail post, Jan. 9, 2002. www.promedmail.org.

THE FEDERALLY SPONSORED EFFORT TO PROVIDE POSTexposure anthrax vaccine to more than 5100 individuals potentially exposed to the deadly organism last fall has met with significant resistance and disinterest. Lacking union support, postal workers uniformly eschewed vaccination, including those workers at the New Jersey facility that experienced 2 deaths and 2 nonfatal cases of infection. Only 152 people, many of whom are congressional staffers, agreed to participate in the program. The controversial program was intended to thwart concerns regarding the possible risk of "reactivation" of anthrax despite receipt of prophylactic antimicrobials. In addition, adherence to the prophylactic regimen was amazingly poor. Reports suggest that half of those receiving prophylaxis did not complete their course of therapy. **—CAROL A. KEMPER, MD**

Dr. Kemper is Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center, Redwood City, Calif.

Pharmacology Update

Pimecrolimus Cream 1% (Elidel—Novartis)

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

NOVARTIS PHARMACEUTICALS IS READY TO MARKET pimecrolimus cream for the treatment of atopic dermatitis. The drug is an immune modulator similar to tacrolimus topical (Protopic), which was also recently approved for this indication. Both of these agents are calcineurin inhibitors and are believed to have the same mechanisms of action. Pimecrolimus cream will be marketed by Novartis under the trade name "Elidel."

Indications

Pimecrolimus is indicated for the short-term and intermittent long-term therapy of mild-to-moderate atopic dermatitis in nonimmunocompromised patients 2 years of age and older. It is recommended for patients in whom alternative, conventional therapies were not effective or not appropriate due to intolerance or potential risk.[1]

Dosage

A thin layer should be applied to the affected skin twice daily and should be rubbed in gently and completely. Pimecrolimus can be applied to all skin surfaces. After symptoms have resolved, therapy should be discontinued and may be resumed at the first sign of recurrence. If symptomatic improvement does not occur within 6 weeks, the condition should be re-evaluated. Patients should be advised to minimize exposure to ultraviolet A or B light either natural or artificial.[1]

Potential Advantages

In vitro data indicate that pimecrolimus has one-tenth the skin penetration of tacrolimus.[2] This may lead to lower systemic bioavailability. With twice-daily applica-

tion in 12 patients with extensive atopic dermatitis, 78% of 444 blood samples evaluated were below the limit of the assay (0.5 ng/mL).[3]

Potential Disadvantages

Pimecrolimus is indicated for mild-to-moderate atopic dermatitis while tacrolimus is indicated for moderate-to-severe disease. In patients with at least moderate disease, pimecrolimus was reported to be less effective than 0.1% betamethasone valerate cream at 3 weeks.[4] Similar to tacrolimus, pimecrolimus is associated with an increased risk of chicken pox, shingles, or eczema herpeticum. Lymphadenopathy has also been reported (0.9%). Application site reactions (eg, warmth or burning sensation) occur in 8-26% of patients.[1]

Comments

Pimecrolimus, an ascomycin derivative, is a topical immunomodulator. Its mechanisms of action appeared to include inhibiting the catalytic function of calcineurin and binding to macrophilin-12 resulting in suppressed T-cell activation.[1,8] In vitro data demonstrate a reduced production and release of proinflammatory cytokines from T cells and histamine from mast cells.[1,5,6] Pimecrolimus can be applied to any skin surface and does not appear to be atrophogenic.[1,4] The drug has been studied in vehicle controlled trials in mild-to-moderate atopic dermatitis. In 2 6-week studies (n = 403), 10% of patients were cleared of the disease compared to 4% for the vehicle, 35% vs. 18% clear or almost clear, and 67% vs. 40% clear to mild disease.[1] Fifty-nine percent had moderate disease, mean body surface involvement was 26%, and about 75% had disease affecting the face and/or neck region. Optimal effect was achieved in about 30 days. In a one-year study, pimecrolimus, when applied at the first sign of eczema, resulted in 50% of patients avoiding the progression of atopic dermatitis to flares.[7]

There are no published comparative studies between pimecrolimus and tacrolimus.

Pimecrolimus cream is priced about $34 for 30 g and $106 for 100 g.

Clinical Implications

Atopic dermatitis is a chronic relapsing inflammatory skin disease affecting up to 10-20% of children. It is characterized by erythematous scaling papules and plaques, and intensive itching.[8] Topical corticosteroids have been the mainstays of therapy. Pimecrolimus along with tacrolimus offer alternatives to topical corticosteroids. These agents are steroid sparing, are safe in children, can be used on the face and intertriginous areas, and do not appear to cause skin atrophy or systemic toxicity. ❖

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CME Questions

15. Which one of the following statements is *false*? In the HERS trial, women who took estrogen and progestin:

a. had a larger decline in physical activity.
b. had a larger decline in energy/fatigue.
c. were more depressed.
d. had less flushing.
e. had significant cardiac histories.

16. Which one of the following statements is true?

a. Increasing fluid intake does not reduce recurrent stone formation.
b. The normal calcium diet as well as the low calcium diet was accompanied by a recommendation to reduce oxalate intake.
c. There is little chance that a low calcium intake in patients with hypercalciuria in this group of patients will predispose to osteoporosis.

17. Which of the following is true for a 35-year-old woman presenting with symptoms of DVT?

a. Ultrasound is the best testing modality because of its better sensitivity and specificity.
b. Provided the patient is not pregnant and has not had a previous DVT, the choice for the diagnostic test depends on the cost of the MRI scan.
c. A previous DVT is equally likely to be diagnosed by ultrasound and MRI.
d. MRI offers no additional advantage over ultrasound in diagnosing pelvic DVTs.

18. Which of the following SSRI antidepressants have been shown to have a clear advantage in successful initial treatment?

a. Paroxetine
b. Fluoxetine
c. Sertraline
d. None of the above

19. Which one of the following is *not* true about pimecrolimus cream?

a. It can be applied to any skin surface.
b. It does not cause atrophy.
c. It is the first immune modulator approved for atopic dermatitis.
d. It can be used on children 2 years of age and older.

By Louis Kuritzky, MD

Alcohol Consumption and Risk of Dementia

Observational studies indicate salutary effects of moderate alcohol consumption (MAC) upon incidence of stroke and myocardial infarction. Since some portion of dementia is attributable to cerebral vascular ischemic changes, the idea that MAC might favorably affect cognitive impairment or dementia appears plausible. To study this relationship, Ruitenberg et al performed a prospective observational analysis examining participants in the Rotterdam study, a group of almost 8000 adults in The Netherlands, age 55 or older. At baseline (enrollment 1990-1993), all subjects were ostensibly free of dementia. The study was completed in 1999.

Over a mean follow-up of 6 years, 197 persons developed dementia, of which Alzheimer's disease was most frequent (74%), but vascular dementia was the next most common (15%).

Alcohol consumption was associated with a reduced risk of dementia. Persons who engaged in MAC had an 18-42% reduced likelihood of dementia when compared with heavy drinkers. Additionally, MAC persons had lower risk than non-drinkers. Both dementia (all forms combined) and vascular dementia alone showed comparable risk reduction patterns. No form of alcohol (beer, wine, liquor) showed a preferential effect. The fact that vascular dementia was reduced to a greater degree than Alzheimer's is consonant with recognized impact of MAC upon such cardiovascular risk factors as platelet aggregation and lipids. ❖

Ruitenberg A, et al. Lancet. 2002;359: 281-286.

Benefit of Atrial Pacing in Sleep Apnea Syndrome

Sleep apnea syndrome (SAS) has a diversity of immediate and distant consequences, including disrupted sleep, daytime fatigue resulting in traffic accidents, hypertension, increased cardiovascular morbidity, and increased mortality. Numerous therapies, none of which is wholly satisfactory for all patients, are available, including CPAP, theophylline, and surgical intervention. The serendipitous observation that persons who had received an atrial overdrive pacemaker noted improvement in SAS, combined with the knowledge that SAS is associated with both bradycardia and paroxysmal tacyharrhythmias, which might be favorably altered by atrial pacing, led to this current study.

Out of a population of 152 patients with dual-chamber pacemakers inserted at least one year previously, Garrigue and colleagues studied 15 patients with SAS confirmed by overnight sleep lab polysomnography. Subjects were assigned to be studied with and without overdrive pacing, set to provide a rate 15 beats per minute faster than the previously ascertained mean nocturnal heart rate in these individuals.

Overdrive atrial pacing produced a significant reduction in apnea, including a greater than 50% reduction in 13 of the 15 patients. Garrigue et al conclude that atrial overdrive pacing can effectively improve SAS in persons with pacemakers. Whether such an intervention might benefit other groups of patients, including those with no otherwise apparent indication for use of a pacemaker, remains an unanswered question. ❖

Garrigue S, et al. N Engl J Med. 2002; 346:404-412.

Metabolic Syndrome Among US Adults

The metabolic syndrome is defined as the presence of 3 or more of 5 potential measurements : 1) abdominal obesity (waist circumference > 102 in men, > 88 cm in women); 2) hypertriglyceridemia (>150 mg/dL); 3) low HDL < 40 in men, < 50 in women); 4) BP > 130/85; and 6) fasting glucose > 110 mg/dL. Metabolic syndrome has been recognized to be associated with increased cardiovascular risk, as well as increased risk of developing diabetes and increased total mortality. The most recent guidelines on lipid management by the National Cholesterol Education Program have affirmed a new prioritization for clinicians to address the metabolic syndrome, but the current prevalence of this syndrome in America has not been heretofore determined.

The National Health and Nutrition Examination Survey (NHANES) has been operative since the 1960s, and does periodic epidemiologic reporting on an ethically diverse adult population of men and women. Information to ascertain the prevalence of metabolic syndrome is available from this 1988-1994 data set (n = 8814).

Overall, more than 1 out of 5 Americans fits the criteria for the metabolic syndrome. The frequency of metabolic syndrome increases with age, so that in persons 60-69 years old, more than 40% had metabolic syndrome. Mexican-Americans had the highest overall frequency of metabolic syndrome. ❖

Ford ES, et al. JAMA. 2002;287: 356-359.

In Future Issues: **Is CT Necessary Before LP in Suspected Meningitis?**