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INSIDE

Financial Disclosure:
Internal Medicine Alert's editor, Stephen Brunton, MD, serves on the advisory board for Abbott, Amarin, Boehringer Ingelheim, Duchesnay, Janssen, Lilly, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

In Loco Parentis

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

Synopsis: *Primary care physicians have a great opportunity to improve their discussions with their patients about cancer screening and the treatment of common chronic diseases.*

Source: Fowler FJ, et al. How patient centered are medical decisions? Results of a National Survey. *JAMA Intern Med* 2013;173:1215-1221.

HOW DO WE INVOLVE PATIENTS IN DECISIONS ABOUT THEIR HEALTH CARE? This study from the Informed Medical Decisions Foundation attempts to answer the question using the results of a survey conducted between 2010 and 2011 with a probability sample from across the United States. The subjects were all older than 40 years, and indicated that in the previous 2 years they were screened for cancer (colorectal, breast, or prostate); were treated for a chronic illness (hypertension, hypercholesterolemia, or depression); had surgery (for knee or hip replacement, cataract removal, or low back pain); or had discussed any of these conditions with a health care provider.

The survey asked four questions. The blanks were filled in by the condition that the patient had previously identified.

1. How much did you and the health care provider(s) discuss the reasons you might want ____?

2. How much did you and the health care provider(s) discuss the reasons you might not want ____?

3. Did the health care provider(s) explain to you that you could choose whether or not to have ____?

4. Did the health care provider(s) ask you whether or not you wanted to have ____?

The answers for #1 and #2 were limited to "a lot," "some," "a little," and "not at all" and questions #3 and #4 to " yes" or "no."

VOLUME 35 • NUMBER 14 • JULY 29, 2013 • PAGES 105-112

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A total of 2718 subjects completed the survey. If a subject had identified more than one decision, only two were considered. About one-fourth made only one decision. The demographics varied by problem, as might be expected (e.g., gender differences for prostate and breast cancer and age differences for patients contemplating cataract surgery). There were some interesting differences: Women were more likely to have discussions about depression medications, college graduates were more likely to discuss cancer screening, and whites were more likely to discuss cataract surgery. Younger women had more discussions about mammography and depression medication than older women.

In general, across all 10 conditions, there were more discussions about the "pros" than the "cons" of a medication or a procedure. For example, almost 80% of patients reported that there was "a lot" or "some" discussion of the advantages of antihypertensive medications, and less than 30% remembered "a lot" or "some" discussion of the drawbacks. The ratios of "pro" to "con" discussions were most dramatic for breast (7.6:1) and prostate cancer screening (5.7:1) with colon cancer screening (5:1) not far behind (no pun intended). The most "fair and balanced" discussions were around low back surgery (1.2:1). Taken as a group, surgeons performed better than primary care physicians.

■ COMMENTARY

Are there any primary care physicians in the United States who aren't preparing their practices for Patient-Centered Medical Home (PCMH) certification? It's right up there with motherhood, the flag, and apple pie. Part of the foundation of the PCMH is shared decision making (SDM),[1] so it was very disappointing to see how poorly we did in that area, especially compared to our surgical colleagues. Maybe all the years of getting surgical informed consent has given them an edge, or maybe having to deal with "failed back" patients has given them incentive to emphasize the risks up front. It is possible that the patients just didn't remember our conversations or that it was a different physician who ordered the medications and the screening tests, and they're to blame, not us, but I don't think so. In particular, it was surprising to see how infrequently our patients remembered a discussion of the downsides of breast and prostate cancer screening, especially since there is controversy surrounding both, and the debates have reached the media. I suspect that it wasn't the patients' memories that suffered. It is time consuming for physicians to lay out all the complex variables and decision pathways, but it really isn't an informed decision if we don't.

This study raises questions that will have to wait for future investigations. Are men uncomfortable discussing depression? Do doctors know how to initiate that discussion with men? What role do class, socioeconomic status, education, and age play in SDM? Why do physicians downplay the risks of medicine? Is it because their source of drug information is people who want them to prescribe their company's products, or do they think that patients' knowledge of the risks will make them more likely to refuse the therapy?

What are some other barriers to SDM? One is that our patients and we operate under a "doctor knows best" paradigm. In the same issue of *JAMA Internal Medicine*, Tak and colleagues reported that "96.3% of patients expressed a desire to receive information about their illnesses and treatment options," but "71.1% of patients preferred to leave medical decision making to their physician."[2] While it is mostly true that we have a better knowledge of medicine than our patients (they do access the Internet), medical knowledge is only one part of SDM. Sometimes, even being a doctor is not enough, as Dr. Lisa Rosenbaum describes in her article "How Should Doctors Share Impossible Decisions with Their Patients?"[3] If you've never heard of the "affect heuristic" or understand the roles that risk aversion and disgust play in decision making, I recommend you give it a read.

I think another major barrier is trying to apply studies done on populations to the patient sitting in front of you. Yes, atorvastatin can reduce the risk of heart disease by 16.5% in the elderly with heart disease,[4] but how do you respond to the 45-year-old woman with no heart disease and a sky-high cholesterol when she remarks that she saw a commercial for Lipitor® and wonders if it's the drug for

Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, a division of Thompson Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie Coplin.
MANAGING EDITOR: Neill L. Kimball.
INTERIM EDITORIAL DIRECTOR: Lee Landenberger.

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $21.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

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Questions & Comments
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her? What do you tell the 85-year-old man with a blood pressure of 160/90 who loves potato chips and has poor bladder control, when he says, "Give it to me straight, Doc. How much time do I have? Will this diuretic really improve my life?" I hope your answer is, "Bet you can't eat just one!" ■

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Will We be Giving Melatonin to Prevent and Treat Type 2 Diabetes?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

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

Synopsis: *A case-control study of women in the Nurses' Health Study Cohort showed that lower melatonin secretion is independently associated with a higher risk of developing type 2 diabetes. There is a physiologic basis for this finding since melatonin has a role in glucose metabolism and lack of melatonin is associated with increased insulin resistance.*

Source: McMullan CJ, et al. Melatonin secretion and the incidence of type 2 diabetes. *JAMA* 2013;309:1388-1396.

A study group at Harvard used the Nurses' Health Study Cohort and identified 370 women who developed type 2 diabetes between 2000 and 2012, and matched them with 370 controls. These women provided first morning blood and urine samples between 1999 and 2000 so metabolites of melatonin could be measured. It was found that women in the lowest category of melatonin secretion had more than twice the likelihood of developing diabetes (9.27 cases/1000 person-years) compared with those in the highest category of melatonin secretion (4.27 cases/1000 person-years).

Melatonin is secreted by the pineal gland in the brain and is controlled by the "biologic clock" in the hypothalamus that is regulated by light exposure. The secretion of melatonin follows a diurnal pattern and peaks about 3-5 hours after sleep onset and in darkness. A deficiency of melatonin, common in the elderly, is a cause of much insomnia, particularly early awakening.[1]

The role of melatonin in glucose metabolism is less well known, but has been studied extensively.[2] Melatonin receptors are found throughout the body, including the islet cells of the pancreas. Melatonin is felt to play an important role in energy metabolism and the regulation of body weight.[2]

Giving melatonin had a protective effect against the onset of diabetes in rats prone to diabetes, and improvements were also seen in the animals' cholesterol and triglyceride levels.[3,4] Studies in humans have been done — but are small in scale — and do show a protective effect of melatonin in diabetes development.[5]

Short sleep duration and snoring frequency are associated with decreased melatonin secretion and type 2 diabetes development. The authors postulate there is a causal role for reduced melatonin secretion and diabetes risk with a call for larger studies.

■ COMMENTARY

Physicians trained in the 1970s before CT scans and MRIs relied on a calcified pineal gland to look for a shift in the brain with head trauma and stroke. Elderly pineal glands calcify and are less likely to secrete melatonin over time. This explains in part the declining hours of sleep as we age. I regularly give melatonin to patients who have short sleep duration insomnia and use it myself when I know my regular sleep will be disrupted such as with long-distance travel.

The fact that people who sleep less gain more weight does not simply reflect that they eat more. Something else seems to be going on and the melatonin hypothesis may help explain that. If melatonin plays a role in the development of type 2 diabetes, that is a huge breakthrough. Think of it, an inexpensive over-the-counter medication is available to both prevent and treat type 2 diabetes!

I hope randomized, controlled trials will be done with melatonin for the prevention and treatment of type 2 diabetes. I am not ready to give it to all my prediabetic and

diabetic patients, but for those with sleep problems, I do give it and will begin watching their blood sugars and HbA1c. This could be a very exciting development. ■

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Aspirin and Melanoma Prevention: Data from the Women's Health Initiative

ABSTRACT & COMMENTARY

By William B. Ershler, MD

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Dr. Ershler reports no financial relationships relevant to this field of study. The article originally appeared in the May 2013 issue of Clinical Oncology Alert.

Synopsis: *In a large population of Caucasian women participating in the Women's Health Initiative Observational Study, those who used aspirin had a significantly lower risk of melanoma and increased duration of use was associated with incrementally greater protection.*

Source: Gamba CA, et al. Aspirin is associated with lower melanoma risk among postmenopausal Caucasian women: The Women's Health Initiative. *Cancer* 2013;119:1562-1569.

The incidence of melanoma has been rising[1] and in light of marginally effective treatments for advanced disease, early recognition and prevention strategies are increasingly important. Of these, there has been much recent attention for the role of aspirin in the prevention of a broad range of cancers including breast, colon, and gastric.[2-4] There is reason to expect aspirin might be beneficial in melanoma prevention as well, in that human melanoma cells over-express cyclooxygenase-2 (COX-2)[5] and high COX-2 levels are associated with melanoma progression.[6] Indeed, case-control analyses have indicated a protective effect of non-steroidal anti-inflammatory drugs (NSAIDs),[7,8] but the results from other analyses have been negative. A randomized trial of alternate-day, low-dose (100 mg) aspirin[9] and two additional cohort studies[10,11] have failed to demonstrate melanoma prevention for those treated with NSAIDs.

Capitalizing on the well-characterized population participating in the Women's Health Initiative (WHI) Observational Study, Gamba and colleagues evaluated the association between NSAID use (including aspirin) and cutaneous melanoma risk.

At study entry, use of aspirin and non-aspirin NSAIDs was assessed among 59,806 postmenopausal Caucasian women ages 50-79 years. Cox proportional hazards models were constructed after adjusting for participant skin type, sun exposure history, and medical indications for NSAID use among other confounders.

During a median follow-up of 12 years, 548 incident melanomas were confirmed by medical review. Women who used aspirin had a 21% lower risk of melanoma (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.63-0.98) relative to nonusers. Increased duration of aspirin use (< 1 year, 1-4 years, and ≥ 5 years) was associated with an 11% lower risk of melanoma for each categorical increase (P trend = 0.01), and women with ≥ 5 years of use had a 30% lower melanoma risk (HR, 0.70; 95% CI, 0.55-0.94). In contrast, use of non-aspirin NSAIDs and acetaminophen were not associated with melanoma risk.

■ COMMENTARY

Postmenopausal women who used aspirin had a significantly lower risk of melanoma, and longer duration of aspirin use was associated with greater protection. The observed benefit with aspirin but not NSAIDs is curious and suggests the mechanism of protection might be through pathways other than COX inhibition. However, as the authors point out, women who were using non-aspirin NSAIDS were more likely to have intermittent rather than continuous use. Indeed, the fact that the protective effect increased with duration of aspirin treatment suggests that such might be the case. Still, although large, carefully conducted and analyzed, the study was observational in design and relied on self-report of medication use and sun exposure.

The data, particularly with regard to duration of aspirin use, are reminiscent of what has been observed for aspirin prevention of colon cancer[12] and quite possibly other malignancies as well. Randomized, prospective trials are warranted, with a specific focus on those at high risk for melanoma in a manner analgous to those demonstrating colon cancer reduction in patients with Lynch syndrome.[12] ■

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Value of Yoga Training in Paroxysmal Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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Dr. DiMarco does research for St. Jude, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific. The article originally appeared in the May 2013 issue of Clinical Cardiology Alert.

Synopsis: *This small proof-of-concept study suggests that yoga may be helpful in patients with highly symptomatic, long-standing paroxysmal atrial fibrillation.*

Source: Lakkireddy D, et al. Effect of yoga on arrhythmia burden, anxiety, depression, and quality of life in paroxysmal atrial fibrillation: The YOGA My Heart study. *J Am Coll Cardiol* 2013;61:1177-1182.

In this paper, the authors report the results of a study that examined the impact of yoga training on patients with paroxysmal atrial fibrillation (AF). The authors enrolled 101 patients with paroxysmal AF who were on a stable medical regimen. Patients served as their own controls in a single-center, prospective, pre-post cohort study. Clinical characteristics and quality of life, anxiety, and depression scores were assessed at baseline, at the end of a 90-day control period, and at the end of a 90-day yoga intervention period. During the yoga intervention period, patients underwent structured Iyengar yoga training at least twice weekly. The sessions were group sessions conducted by a certified yoga instructor and lasted for at least 60 minutes. Patients were also encouraged to practice yoga at home on their own on a daily basis. The primary outcomes included the burden of symptomatic true AF, asymptomatic non-AF, and asymptomatic AF episodes. Secondary outcomes included changes in the Short Form 36 (SF-36) quality of life score, the Zung self-assessment anxiety score (SAS), and the Zung self-assessment depression score (SDS). AF burden was estimated using symptom triggered event monitors. Routine daily ECG transmissions were also made for all patients.

The study cohort included approximately equal numbers of men and women with a mean age of 61 ± 11 years. The mean duration of AF since diagnosis was 5 years. Most patients had no or only mild left atrial enlargement and a normal left ventricular ejection fraction. Hypertension and hyperlipidemia were the most common comor-

bid conditions. Patients with significant heart failure were not included. During the yoga intervention period, the number of symptomatic AF episodes decreased from 3.8 ± 3 to 2.1 ± 2.6. Symptomatic episodes not due to AF also decreased from 2.9 ± 3.4 to 1.4 ± 2.0. Asymptomatic AF episodes also decreased from 0.12 ± 0.44 to 0.04 ± 0.2. There were 11 patients (22% of the entire group) who had no documented AF during the yoga intervention phase. There was no change in the SF-36, the SAS, or the SDS scores during the control period. However, after the yoga intervention phase, the self-reported depression scores and self-reported anxiety scores improved significantly and the SF-36 scores improved in several domains: physical functioning, general health, vitality, social functioning, and mental health. Also noted was a decrease in resting sinus heart rate and diastolic blood pressure.

The authors conclude that this small proof-of-concept study suggests that yoga may be helpful in patients with highly symptomatic, long-standing paroxysmal AF.

■ COMMENTARY

Unfortunately, both antiarrhythmic drug therapy and catheter ablation approaches are frequently unsuccessful at completely eliminating AF. Yoga has been shown to be an effective adjunct in other chronic conditions, and the preliminary data in this paper suggest that it may be an additional tool that can make recurrent AF more tolerable for patients. Yoga can produce changes in autonomic nervous system activity, and it is likely that these effects both directly decrease the frequency of AF episodes and also make episodes that do occur better tolerated.

Not all patients are likely to be candidates for yoga therapy for their AF. We also need better controlled data to demonstrate that it is effective in a typical group of AF patients. However, for patients willing to try yoga, it may be possible to decrease symptoms and make the disease more tolerable. ■

Pharmacology Update

Paroxetine Capsules (Brisdelle™)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved paroxetine for the treatment of hot flashes (vasomotor symptoms) in postmenopausal women — the first nonhormone product to be approved for this indication. Paroxetine is the same drug as the widely used serotonin reuptake inhibitor (SSRI) Paxil. It is dosed at 7.5 mg, which is lower than the initial dose for depression (20-25 mg). It will be marketed by Noven Therapeutics as Brisdelle.

Indications

Paroxetine (7.5 mg) is indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause (VMS).[1]

Dosage

The recommended dose is 7.5 mg taken at bedtime.[1] It is available as 7.5 mg capsules.

Potential Advantages

Paroxetine provides a different mechanism of action for VMS and is the only FDA-approved, nonhormone treatment for this indication. It does not carry the same risk factors associated with hormonal treatment (e.g., thromboembolic events, breast cancer).

Potential Disadvantages

Paroxetine does not affect other problems associated with menopause such as vaginal atrophy and reduction in bone mineral density. It may actually increase the risk of fractures.[1] Paroxetine may be less effective than hormonal treatment and reduces the effectiveness of tamoxifen.[1] Paroxetine has a completely different safety profile compared to estrogens. It also carries the same boxed warning for suicide risk as the antidepressant form of the drug.

Comments

The safety and efficacy of paroxetine were evaluated in two randomized, double-blind, placebo-controlled studies. Subjects (n = 1174) with moderate-to-severe VMS (minimum of 7-8 per day at baseline, ≥ 50 per week, 30 days prior to treatment initiation) were randomized to paroxetine 7.5 mg at bedtime or placebo. One study was 12 weeks and the second was 24 weeks. The study population had an average age of 54-55 years, two-thirds to three-fourths were Caucasian, 81-82% were naturally menopausal, median VMS frequency was about 10 per day with a median severity of 2.5 (0-4 scale). The co-primary efficacy endpoints were the reduction from baseline in VMS frequency and severity at week 4 and 12. The persistence of benefit was assessed in the 24-week study. Analysis was by modified intent-to-treat requiring a valid baseline value and at least one dose taken. Paroxetine treatment showed a placebo-subtracted difference of -1.2

and -1.3 for median frequency reduction at week 4 and -0.9 and -1.7 at week 12. Severity was reduced by -0.05 and -0.03 at week 4 and -0.04 and -0.05 at week 12. This represents about an unadjusted 40% reduction in VMS and only a 12% reduction relative to placebo due to a high placebo effect (26-30% reduction). Reduction in severity is about 0.5 points on the severity scale. For subjects categorized as responders (≥ 50% reduction in frequency) at week 12, 48% of those randomized to paroxetine maintained this level of efficacy at week 24 compared to 36% for placebo. Common adverse reactions (compared to placebo) were headache (6.3% vs 4.8%), fatigue/malaise/lethargy (4.9% vs 2.8%), and nausea/vomiting (4.3% vs 2.3). There are currently no published comparative studies between paroxetine 7.5 mg vs hormonal treatment. The FDA only approved the 7.5 mg dose for VMS. Greater effectiveness has been previously reported with higher doses of paroxetine (12.5-25 mg); mean reduction of hot flash composite scores (frequency × severity) were 62.2% and 64.6% for the two doses of paroxetine, compared to 37.8% for placebo.[2] These doses likely would be associated with a higher frequency of side effects. Low-dose estrogen appears to be more effective. It has been reported to reduce the number of VMS episodes by 65% compared to 35-40% for placebo.[3]

Clinical Implications

Hot flashes significantly affect quality of life of menopausal women. A recent survey by the North American Menopause Society (NAMS) reported that 89% of respondents reported experiencing hot flashes and about 50% were moderate and 34% were severe.[4] Hormone therapy is still the most effective treatment.[5] However, this may not be an option for certain patients (e.g., intolerance, increased breast cancer risk). Interestingly, in the same NAMS survey, 85% felt traditional hormone treatment was unsafe, suggesting a desire for nonhormone options. Antidepressants such as venlafaxine and paroxetine have been widely studied as nonhormonal alternatives and appear to be the most consistent in effectiveness.[6,7] Paroxetine is the first to be approved and provides modest benefit in relieving VMS. ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

CME Questions

1. **In a survey of patient-centered decision-making, what was discovered?**
   a. Men were more likely to have discussions about depression medications.
   b. High school graduates were more likely to discuss cancer screening.
   c. There were more discussions about the "pros" of antihypertensive medications than the "cons."
   d. Primary care physicians performed better than surgeons.

2. **Which statement is true about the role melatonin may play in diabetes?**
   a. Giving melatonin is associated with an increased risk of type 2 diabetes.
   b. Melatonin blocks the effect of insulin and interferes with glucose metabolism.
   c. There are melatonin receptors on the islet cells of the pancreas and melatonin helps regulate glucose metabolism.
   d. Decreased melatonin secretion is associated with developing hypoglycemia at night in diabetic patients.

3. **In the Women's Health Initiative Observational Study, the risk of developing melanoma in women taking aspirin daily compared to non-users was approximately:**
   a. 10%.
   b. 20%.
   c. 40%.
   d. 60%.

4. **Yoga training in patients with paroxysmal atrial fibrillation can reduce:**
   a. symptomatic episodes.
   b. asymptomatic episodes.
   c. symptoms not due to atrial fibrillation.
   d. All of the above

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Diabetes and Cognitive Function

Source: Spauwen PJ, et al. Effects of type 2 diabetes on 12-year cognitive change: Results from the Maastricht Aging Study. *Diabetes Care* 2013;36: 1554-1561.

The relationship between vascular disease and type 2 diabetes is consistent: Risk for microvascular events (retinopathy, neuropathy, and nephropathy) and macrovascular events (stroke and MI) is increased compared to non-diabetics. Additionally, when diabetics suffer macrovascular events, the consequences are typically more severe than similar events in non-diabetics.

The etiology of cognitive impairment is often multifactorial, including vascular insufficiency. Diabetics have a higher prevalence of cognitive impairment than non-diabetics, but the rate of cognitive decline in diabetics has not been studied.

The Maastricht Aging Study is comprised of 10,396 adults residing in the province of Limburg, the Netherlands. A sample from this population (n = 1290) underwent extensive neuropsychological testing at baseline, 6 years, and 12 years. At baseline, approximately 5% of the population had type 2 diabetes, with an incidence of an additional 5% over subsequent 6-year intervals.

When compared with controls, diabetics had a significant rate of cognitive decline over 6 and 12 years. Even when adjusted for variables that are more commonly comorbid in diabetics (hypertension, dyslipidemia, obesity), the acceleration in cognitive decline was greater in diabetics. As might be intuitive, diabetics with baseline cognitive impairment progressed at a more rapid rate than those without. Whether any specific intervention among diabetics (e.g., better control of glucose, lipids, blood pressure) might ameliorate the exaggerated rate of cognitive decline remains to be determined. ■

Low Creatinine Excretion Associated with Mortality in Type 2 Diabetes

Source: Sinkeler SJ, et al. Creatinine excretion rate and mortality in type 2 diabetes and nephropathy. *Diabetes Care* 2013;36:1489-1494.

Creatinine excretion (CER), as measured by the 24-hour urinary excretion of creatinine, has recently been noted to be associated with increased mortality, both in persons with underlying renal disease and the general population. CER reflects overall lean muscle mass, so that declines in CER may simply reflect deconditioning, loss of muscle mass, cachexia, malnutrition, etc., each of which may have a negative impact on mortality.

Sinkeler et al report on data accrued from two previously completed trials of angiotensin receptor blockers in diabetic nephropathy: Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan trial and the Irbesartan Diabetic Nephropathy trial. Twenty-four hour urinary CER was measured at baseline for the majority (n = 2360) of participants. Since mortality data from both trials are available, the relationship between CER and mortality can be evaluated.

Across the population studied, each halving decrement of CER was associated with a doubling of mortality risk. Since the primary association of CER is with muscle mass, the authors pose the interesting question of whether efforts expended to improve muscle mass, such as enhanced exercise and nutrition, might favorably effect mortality in this population. ■

Benefits of Screening for Lung Cancer with Low-Dose CT

Source: The National Lung Screening Trial Research Team. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med* 2013;368:1980-1991.

Lung cancer (LCA) is responsible for more deaths than any other cancer worldwide. The burgeoning growth of smoking in developing countries suggests that this dismaying fact is unlikely to diminish in the foreseeable future. Clinical trials of screening for LCA through chest x-ray (CXR) did not show improved outcomes, likely because of its relatively poor discriminative ability in early disease.

The National Lung Screening Trial enrolled smokers and ex-smokers with at least a 30 pack-year history. Participants were randomized to an annual low-dose CT × 3 (n = 26,714) or standard chest x-ray (n = 26,035).

A positive radiographic finding on at least screening was seen in three times as many CT screenees as chest x-ray (27.3% vs 9.2%). LCA was diagnosed in 1.1% of the CT group vs 0.7% in the CXR group.

Screening for LCA was found to reduce LCA-related mortality by 20% and all-cause mortality by 7%.

Most of the abnormalities detected by low-dose CT screening were benign, so that the positive-predictive value for a positive CT was only 3.8% (i.e., about 4% of study subjects with any positive suspicious finding on CT turned out to have LCA). Reassuringly, repeatedly negative low-dose CT had a negative predictive value of 99.9% (i.e., essentially no one who had negative sequential CT screening was diagnosed with LCA during the screening and follow-up period). ■

In Future Issues:

Validation of the Male Osteoporosis Risk Estimation Score (MORES) in a Primary Care Setting

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Is Naproxen the Safest NSAID for the Heart?

In this issue: NSAIDs and cardiovascular risk; new antithrombotic guidelines; warfarin during surgery; Pfizer selling Viagra online; azithromycin and cardiovascular risk; and FDA actions.

NSAIDs associated with less vascular risk

Naproxen may be the safest anti-inflammatory — at least when it comes to cardiovascular risk — according to a new study. Researchers from the United Kingdom undertook a meta-analysis of 280 trials of non-steroidal anti-inflammatory drugs (NSAIDs) vs placebo and 474 trials of one NSAID vs another. Main outcomes were major vascular events, major coronary events, stroke, mortality, heart failure, and upper gastrointestinal (GI) complications including bleeding. All NSAIDs and COX-2 inhibitors (coxibs) increased major vascular events except for naproxen (rate ratio [RR], coxibs 1.37 [95% confidence interval (CI), 1.14-1.66; $P = 0.0009$] and diclofenac 1.41 [95% CI, 1.12-1.78; $P = 0.0036$] mostly due to an increase in major coronary events). Ibuprofen also significantly increased the risk of major coronary events (RR 2.22, 95% CI, 1.10-4.48; $P = 0.0253$), but not major vascular events. Naproxen did not significantly increase the risk of major vascular events. Coxibs and diclofenac also significantly increased risk of vascular death, and there was a nonsignificant increase with ibuprofen, while there was no increase with naproxen. Heart failure risk was roughly doubled by all NSAIDs. The risk of upper GI complications was lowest with coxibs and highest with naproxen (coxibs 1.81, 95% CI, 1.17-2.81; $P = 0.0070$; diclofenac 1.89, 95% CI, 1.16-3.09; $P = 0.0106$; ibuprofen 3.97, 95% CI, 2.22-7.10; $P < 0.0001$, and naproxen 4.22, 95% CI, 2.71-6.56; $P < 0.0001$). The authors conclude that the vascular risks of diclofenac and possibly ibuprofen are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk (but higher GI risk) than other NSAIDs (*Lancet* published online May 30, 2013). The authors speculate that high-dose naproxen has fewer cardiovascular effects because it is the strongest inhibitor of COX-1, resulting in near complete suppression of platelet thromboxane biosynthesis (thus blocking platelet aggregation) throughout the 12-hour dosing interval. ■

New antithrombotic guidelines

A new guideline from the American Academy of Neurology gives primary care doctors guidance on periprocedural management of antithrombotic medications in patients with a history of stroke. Among the recommendations is that stroke patients undergoing dental procedures should routinely continue aspirin. Aspirin should also be considered for continuation in stroke patients undergoing invasive ocular anesthesia, cataract surgery, dermatologic procedures, transrectal ultrasound-guided prostate biopsy, spinal/epidural procedures, and carpal tunnel surgery. Aspirin should possibly be continued during other procedures such as virtroretinal surgery, EMG, transbronchial lung biopsy, colonoscopic polypectomy, upper endoscopy and biopsy/sphincterotomy, and abdominal ultrasound-guided biopsies. For stroke patients on warfarin, the guideline recommends continuation of the drug

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during dental procedures and probably during most dermatologic procedures. Other more invasive procedures should warrant discussion. The guideline states there is insufficient evidence to support or refute periprocedural heparin-bridging therapy to reduce thromboembolic events in chronically anticoagulated patients. Bridging therapy is probably associated with increased bleeding risk as compared with warfarin cessation, but the risk difference compared with continuing warfarin is unknown (*Neurology* 2013;22:2065-2069). ■

Continuing warfarin for surgery

In related news, a new study suggests that continuing warfarin for pacemaker or defibrillator surgery is safer than heparin bridging. Nearly 700 patients with an annual risk of thromboembolic events of ≥ 5% who required pacemaker or defibrillator surgery were randomized to continued-warfarin treatment or bridging therapy with heparin. The primary outcome was clinically significant device-pocket hematoma, which occurred in 12 of 343 patients (3.5%) in the continued-warfarin group as compared with 54 of 338 (16.0%) in the heparin-bridging group. There was one episode of cardiac tamponade and one myocardial infarction in the heparin-bridging group and one stroke and one TIA in the continued warfarin group. This study was stopped early after interim analysis found that the primary outcome occurred four times as often in the heparin-bridging group. These findings suggest that a strategy of continued warfarin therapy at the time of pacemaker or defibrillator surgery markedly reduced incidence of clinically significant device pocket hematoma as compared with heparin bridging (*N Engl J Med* 2013;368:2084-2093). ■

Pfizer launches own Viagra website

Pfizer is aggressively pursuing the online market for sildenafil (Viagra) by launching its own "Viagra home delivery" website. The drug will be available online directly from Pfizer but will still require a doctor's prescription. This move is also designed to counter online marketing of counterfeit Viagra, the most commonly counterfeited drug in the world. Pfizer plans to make Viagra available online at approximately $25 a pill. Meanwhile, the company has lost patent protection for its other version of sildenafil citrate marketed for pulmonary hypertension under the trade name Revatio. This version of the drug is only available in 20 mg strength, but is otherwise identical to Viagra, which is available in 25, 50, and 100 mg strengths. It is yet to be seen whether physicians will prescribe generic 20 mg sildenafil off label for erectile dysfunction. ■

Azithromycin and cardiovascular risk

Does azithromycin increase cardiovascular (CV) risk? A recent observational study showed that azithromycin was associated with a 2-3 times higher risk of death from CV disease in patients at high risk for CV disease (*N Engl J Med* 2012;366:1881-1890). A new study looks at the risk of the drug vs placebo and a comparator antibiotic (penicillin V) in Danish adults ages 18-64. As compared with no use of antibiotics, use of azithromycin was associated with a significantly increased risk of CV death (rate ratio 2.85; 95% CI, 1.13-7.24); however, when compared to penicillin V, there was no increased risk (crude rate CV death 1.1/1000 person years azithromycin vs 1.5/1000 penicillin V). With adjustment for CV risk, current azithromycin use was not associated with increased risk of CV death compared with penicillin V in a general population of young and middle-aged adults. (*N Engl J Med* 2013;368:1704-1712). This study is reassuring, suggesting that the increased risk of death is probably due to the illness rather than the drug, especially in low-risk populations. However, the risk of the macrolides still should be considered among patients with a high baseline risk of CV disease. ■

FDA actions

The FDA has approved a new once-daily combination inhaler for the treatment of chronic obstructive pulmonary disease (COPD). The product combines the long-acting beta-agonist (LABA) vilanterol with the steroid fluticasone furoate. Vilanterol is a new LABA and fluticasone furoate is reported to have longer lung retention time compared to the proprionate allowing for once-daily dosing. The product is a dry powder that is delivered via the Ellipta device. The new inhaler was evaluated in 7700 patients with COPD and showed improved lung function and reduced exacerbations compared to placebo. Vilanterol/fluticasone furoate is marketed by GlaxoSmithKline in collaboration with Theravance as Breo Ellipta.

The FDA has approved a new cholesterol combination drug, combining ezetimibe and atorvastatin. The drug is indicated for lowering cholesterol in patients with primary or mixed hyperlipidemia and in those with homozygous hypercholesterolemia. It is approved in four strengths, each containing 10 mg of ezetimibe with 10, 20, 40, or 80 mg of atorvastatin. The combination reduces LDL cholesterol levels up to 61% in clinical trials. Like the previously marketed simvastatin/ezetimibe, there is no evidence that the combination improves cardiovascular outcomes over a statin alone. The combination will be marketed by Merck as Liptruzet. ■