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INSIDE

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Coffee: It's a GOOD thing!

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speaker's bureaus for Cephalon, Resmed, and Respironics.

Synopsis: *Women who drink little or no coffee appear to be at an increased risk of stroke compared with those who drink moderate amounts of coffee.*

Source: Larsson SC, et al. Coffee consumption and risk of stroke in women. DOI: 10.1161/STROKEAHA.110.603787. Published online March 10, 2011.

This report results from a secondary analysis of the Swedish Mammography Cohort, which is a population-based prospective study of Swedish women born between 1914 and 1948. The findings are based on two questionnaires completed by 39,227 women approximately 10 years apart. These questionnaires included items about diet and other lifestyle factors. Coffee consumption was assessed by asking respondents how many cups of coffee per day or per week they consumed during the past year. The questionnaire did not inquire about decaffeinated coffee because consumption of decaffeinated coffee in Sweden is very low. The investigators collected data about and controlled for smoking, education, body mass index, total physical activity, self-reported hypertension, diabetes, aspirin use, family history of myocardial infarction before age 60, daily caloric intake, alcohol consumption, and intake of red meat, fish, fruits, and vegetables. Stroke was classified as cerebral infarction, intracerebral hemorrhage, and unspecified stroke based on the International Classification of Diseases 10.

At baseline, the cohort was about 61 years old. The median coffee consumption was 3 cups/day. Compared with women with low coffee consumption, those with high consumption were less likely to have a university education, consumed fewer fruits and vegetables, and were more likely to be smokers. However, they were also less likely to have a history of diabetes or hypertension.

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Over about 10 years of follow-up, there were 1680 strokes in this group of women, including 1310 cerebral infarctions, 154 intracerebral hemorrhages, 79 subarachnoid hemorrhages, and 137 unspecified strokes. As expected, stroke risk was positively correlated with smoking, history of hypertension, obesity, and family history of coronary heart disease. Risk of stroke was inversely correlated with education. Aspirin use and exercise were not associated with overall or specific stroke risk.

Before adjustment for other lifestyle factors and their association with stroke, there was no statistically significant association between consumption of coffee and risk of stroke in the age-adjusted analysis. However, after adjustment for smoking (in particular) and other risk factors, women who consumed at least 1 cup of coffee per day had a statistically significant 22% to 25% lower risk of stroke compared with those who drank less than 1 cup of coffee per day. With regard to specific types of stroke, coffee consumption was associated with decreased risk of cerebral infarction (by far the most prevalent kind of stroke) and subarachnoid hemorrhage but not with risk of intracerebral hemorrhage. Increased coffee consumption was associated with reduced risk of cerebral infarction and subarachnoid hemorrhage, but not with overall risk of stroke.

■ COMMENTARY

This is not the first study to show that coffee consumption is associated with a reduced risk of stroke, but it is a large cohort that is carefully analyzed, so it is particularly noteworthy. In the Nurses' Health Study, women who drank at least 4 cups of coffee a day had a reduced risk of stroke,[1] so this paper confirms that finding, while suggesting that even 1 cup of coffee may confer some protection. There are also reports indicating that coffee consumption is associated with reduced risk of stroke in men,[2] but not all studies demonstrate a reduced risk of stroke among coffee drinkers.[3-5]

That coffee consumption could reduce the risk of stroke is biologically plausible. Coffee drinking has been associated with reduced inflammation,[6] reduction in oxidative stress,[7] and improved insulin sensitivity.[8] And that's not all! A systematic review suggests that coffee consumption may reduce the risk of Type 2 diabetes.[9]

In an era when counseling about lifestyle is increasingly important and time to do so is increasingly scarce, it's probably time to remove admonitions against coffee drinking from routine lifestyle recommendations. ■

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Effect of APCs and VPCs on the Risk of SCD

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

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Synopsis: *This study concluded that subjects without*

a known history of any cardiovascular disease who demonstrated ventricular premature complexes on a 2-minute rhythm strip are significantly more likely to die from sudden cardiac death and the effect appears to be additive when atrial premature complexes occur concurrently.

Source: Cheriyath P, et al. Relation of atrial and/or ventricular premature complexes on a two-minute rhythm strip to the risk of sudden cardiac death (the Atherosclerosis Risk in Communities (ARIC) Study). *Am J Cardiol* 2011;107:151-155.

Ventricular tachyarrhythmias are the most common causes of sudden cardiac death (SCD), which is an extremely important public health issue with an estimated global prevalence in the range of 4-5 million deaths per year.[1,2] Ventricular premature complexes (VPCs) and atrial premature complexes (APCs) are not uncommon in apparently healthy subjects on routine electrocardiograms. In fact, VPCs are present in more than 6% of the general population and APCs occur in approximately 10%-73% of younger patients and in 21%-100% of elderly patients.[3-5] Subjects with VPCs have been considered to be at significantly higher risk for development of ischemic heart disease and death; however, it is quite commonly believed that VPCs and APCs are probably not often associated with a dire outlook when observed to occur in patients without known coronary heart disease (CHD).

Cheriyah and colleagues investigated the prospective relationship between baseline ventricular and supraventricular ectopy and clinical cardiac events including SCD, myocardial infarction, and fatal CHD in a population-based sample of subjects without any history of cardiac disease or stroke. They used public-use data from the Atherosclerosis Risk in Communities (ARIC) study, an ongoing prospective study of the cause and natural history of atherosclerosis funded by the National Heart, Lung, and Blood Institute (NHLBI).[6] The study population consisted of 14,574 subjects who were free of CHD and stroke history. Participants who demonstrated the presence of VPCs on a 2-minute rhythm strip were twice as likely to have fatal CHD — including SCD — when compared to subjects without VPCs. APCs were not associated with a higher risk for SCD; however, the risk of SCD increased more than sixfold when VPCs and APCs occurred together. Therefore, the association of APCs appears to be somewhat additive to the effects of VPCs on SCD.

■ COMMENTARY

Although the relationship between ischemic heart disease and VPCs is well-documented,[7] current medical practice does not recommend treatment of VPCs in patients without known CHD because of concerns regarding adverse reactions associated with antiarrhythmic medications.[8,9] Despite the results of these previously published studies, Cheriyath et al concluded that the presence of any VPC on a 2-minute rhythm strip was associated with a significantly increased risk of SCD and fatal CHD even in middle-aged Americans who did not have a prior history of CHD or stroke. In addition, they noted that the presence of APCs resulted in a negative synergistic effect in patients with VPCs resulting in an increased rate of SCD. It must be recognized that the data from the ARIC report, which formed the basis for their conclusions, was derived from 2-minute rhythm strips in patients followed for only a relatively short period of time (i.e., 3 years). However, before leaping to firm conclusions regarding the danger of isolated VPCs, it must be carefully recognized that the ARIC study included only middle-aged (mean age 49 years) Caucasian men studied over a relatively short period of time and that the study did not adjust for multiple co-variables including potassium and magnesium levels, and/or medications that can affect arrhythmias in either a positive or negative way, and that the study also did not exclude participants with a history of stroke.

Before accepting the conclusions of Cheriyath and colleagues, it should be noted that other studies have not shown an adverse outcome for patients with VPCs.[10] Obviously, what is now needed is a large, randomized, carefully controlled trial before concluding that administering potentially harmful drugs to any and all patients who demonstrate a simple PVC on a routine office electrocardiogram is appropriate. ■

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When It Comes to Exercise, Maybe More is Better

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips serves on the speaker's bureaus for Cephalon, Resmed, and Respironics.

Synopsis: *In this meta-analysis, individuals who exercised or had sex episodically had an increased risk of acute cardiac events during those activities compared with those who had high levels of habitual physical activity.*

Source: Dahabreh IJ, Paulus JK. Association of episodic physical and sexual activity with triggering of acute cardiac events: Systematic review and meta-analysis. *JAMA* 2011;305: 1225-1233.

THIS STUDY RESULTED FROM A META-ANALYSIS THAT WAS DONE to investigate the association of episodic physical or sexual activity with acute coronary syndromes, including myocardial infarction (MI) and sudden cardiac death. The investigators used combinations of search terms related to exposure (exertion, exercise, physical activity, sexual activity) and to outcomes (MI, acute coronary syndrome, sudden [cardiac] death). They also searched the reference lists of eligible studies. To be included in this analysis, studies had to have a case-crossover design and had to examine the effect of episodic physical or sexual activity (exposures) on the risk of acute coronary syndromes (outcomes). Each study was independently reviewed by two reviewers who extracted data about activity and risk, and standardized activity to make it comparable between studies. Studies were also assessed for validity and heterogeneity. The authors used data from the Framingham Heart Study[1] and the U.S. vital statistics mortality data[2] to establish the absolute (baseline) event rate for sudden cardiac death and MI.

Although the investigators identified more than 5000 articles that were potentially of use for this systemic review, they were left with only 13 eligible papers to include in the analysis after elimination of duplicate articles, reviews, editorials, letters, those without case-crossover design, those without data about the relevant outcomes or exposures, those with experimental design, and those not originally published in English.

Ten studies provided data on episodic physical activity, three on sexual activity, and one had data for both of these activities. Of the studies that assessed episodic physical activity, seven studies enrolled patients with MI, three enrolled patients with sudden cardiac death, and one enrolled patients with mixed diagnoses of acute coronary syndrome. All of the studies assessing sexual activity as the exposure of interest included only patients with MI. The individuals in the analyzed reports had a mean or median age of older than 60 years, and most were male. All 10 studies of episodic physical activity quantified the intensity of the exposure based on multiples of metabolic equivalents (METs). Moderate activity in all studies was fairly uniformly defined as exertion of at least 5 to 6 METs.

Overall, the studies suggested a strong association between episodic physical activity and MI (relative risk [RR] = 3.45, $P < 0.001$). Three studies assessed the potential of episodic physical activity to trigger sudden cardiac death. Overall there was evidence of an increase in the risk of sudden cardiac death triggered by episodic physical exertion (RR = 4.98, $P = 0.01$). Four studies (2960 patients) investigated the association between sexual activity and triggering of MI. Overall, sexual activity was associated with an acutely increased risk of infarction (RR = 2.70, $P = 0.001$)

Overall, subgroups of patients with higher habitual activity levels tended to be less susceptible to the triggering effect of causing a coronary event by episodic physical activity. In groups with the lowest habitual activity, the RR for the triggering effect of episodic physical activity ranged from 4.47 to 107 for MI, indicating a very substantial increase in risk during or immediately following exertion. The corresponding range in the highest habitual activity groups was 0.86 to 3.3, indicating much smaller increases in risk. Similar patterns were observed for the associations of episodic physical activity with sudden cardiac death and of sexual activity with MI, although the differences were less pronounced and fewer studies contributed data.

Based on estimates in these studies, the authors estimated that the RR of MI triggered by episodic physical activity was decreased by approximately 45% for each additional (unquantified) time per week a person was habitually exposed to physical activity. The relative risk of sudden cardiac death triggered by episodic physical activity was decreased by approximately 30% for each additional time per week a person was habitually exposed to physical activity. Unfortunately, the studies of sexual activity did not provide enough data to estimate the risk reduction afforded by the number of events of sexual activity per week. There was a dose-response relationship between episodic physical and

both MI and sudden cardiac death regardless of the boundaries used to define physical activity levels.

■ COMMENTARY

This study got a lot of attention in the lay press, and your patients may be asking about it. What to say? First of all, there is a well-established beneficial effect of regular physical activity on the risk of acute coronary events,[3] and regular physical exercise is clearly part of a healthy lifestyle. The current study shows that during the period of acute exposure to physical or sexual activity, an individual's risk of an event is increased compared with unexposed periods of time, but regular physical activity may reduce this risk by more than 30%. In this study, individuals with the lowest habitual levels of physical activity had the highest risk for all coronary events during exercise or sex. The authors of this study estimate that for each additional time an individual is exposed to physical activity per week, the relative risk of MI or sudden cardiac death associated with this exercise is reduced by approximately 45% and 30%, respectively.

There were a few things about this study that were not clear to me. First, what is "episodic" exercise? I believe that this is exercise less frequent than once a week, since most of the reviewed studies classified habitual exertion as weekly frequency based on the definitions used in the analyzed studies. And how much "exercise" or physical activity counts? In the reviewed studies, moderate physical activity was typically defined as exertion of at least 5 to 6 METs. Some activities that consume 5 to 6 METs are presented in the Table.

Table. METs Associated with Common Activities[4]

- Carry anything up a flight of 8 steps without stopping: 5.0 – 5.5 METs
- Have sexual intercourse without stopping: 5.0 – 5.5 METs
- Garden, rake, weed: 5.6 METs
- Roller skate, dance, foxtrot: 5 – 6 METs
- Walk at a 4 mile per hour rate on level ground: 5 – 6 METs
- Walk down a flight of steps without stopping: 4.5 – 5.2 METs
- Shower without stopping: 3.6 – 4.2 METs
- Strip and make a bed: 3.9 – 5.0 METs
- Walk 2.5 miles per hour: 3.0 – 3.5 METs
- Bowl: 3.0 – 4.4 METs
- Play golf with walking and carrying clubs: 4.5 METs
- Push power lawn mower: 4 METs

What this means to us clinically is that our advice about exercise needs to be tailored to each individual. Those who are sedentary should be counseled to increase the frequency and intensity of physical activity gradually. We can point out that exercising does not necessarily have to involve having a gym membership. House and garden work and walking are great forms of exercise that most people can work into their daily routines. And everybody needs to be counseled that regular exercise will reduce the risk of having an MI or of dying while exercising, or — worse — having sex. ■

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Pharmacology Update

Belimumab Injection (Benlysta™)

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 relationship to this field of study.

THE FDA HAS APPROVED THE FIRST NEW TREATMENT FOR systemic lupus erythematosus (SLE) since 1955 when hydroxychloroquine and corticosteroids were approved. Belimumab is a recombinant human IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS).[1] It is marketed by Human Genome Sciences and GlaxoSmithKline as Benlysta.

Indications

Belimumab is indicated for the treatment of adult patients with active, autoantibody-positive, SLE who are receiving standard therapy.[1]

Dosage

The recommended dose is 10 mg/kg at 2-week intervals for the first three doses and every 4 weeks thereafter.[1]

Pre-medication for prophylaxis against infusion reactions and hypersensitivity reactions should be considered.[1]

Belimumab is supplied as 120 mg and 400 mg single-use vials.

Potential Advantages

Patients treated with belimumab and standard therapy experienced less disease activity than those treated with standard therapy alone.[1-3]

Potential Disadvantages

African American patients and patients of African heritage do not appear to respond to belimumab.[1] The response rates were less than that for placebo.

Comments

Belimumab is a human monoclonal antibody specific for BLyS. This cytokine plays an essential physiologic role in the homeostatis and survival of B-cells. BLyS is overexpressed in patients with lupus erythematosus.[4] The efficacy and safety of belimumab was studied in three randomized, double-blind, placebo-controlled studies in patients with SLE according to the American College of Rheumatology criteria for systemic disease (score ≥ 6 on the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index [SELENA-SLEDAI]). Patients were on a stable standard of care treatment (e.g., corticosteroids, antimalarials, NSAIDs, or immunosuppressives alone or in combination). Biologics and intravenous cyclophosphamide were not permitted. Study 1 (n = 449) was a dose evaluation study while studies 2 and 3 (n = 1684) evaluated 1 mg/kg or 10 mg/kg of belimumab compared to placebo.[1-3] Study 2 (BLISS-76) was 76 weeks and Study 3 (BLISS-52), 52 weeks. The primary endpoint was improvement in the Systemic Lupus Erythematosus Responder Index (SRI) defined as a reduction of at least 4 points in the SELENA-SLEDAI score, no new British Isles Lupus Assessment Group (BILAG) A organ domain score, no more than 1 new BILAG B organ domain score, and no worsening in Physician Global Assessment score. The clinical response rates (SRI) for the FDA recommended dose of 10 mg/kg were 43% for Study 1 and 58% for study 2 compared to 34% and 44%, respectively, for placebo. The combined efficacy of belimumab at week 52 was 50.6% (n = 562) vs. 38.8% (n = 563) for placebo.[3] Subgroup analyses of African American patients (n = 148) showed that these patients had a lower response rate than placebo, 36% for belimumab, 10 mg/kg compared to 44% for placebo. Common adverse events (compared to placebo) include nausea (15% vs. 12%), diarrhea (12% vs. 9%), and pyrexia (10% vs. 8%). Mortality (0.9% vs. 0.4%), serious infections (6% vs. 5.2%), and depression (16% vs. 12%) were reported more frequently with belimumab compared to placebo.

Clinical Implication

SLE is a serious autoimmune disease that affects approximately 300,000 to 1.5 million Americans.[5] African American women have a three times higher incidence than Caucasian women. Belimumab is the first biologic approved for the treatment of SLE and the first drug to be approved for this disease in more than a half century. While the efficacy of belimumab is encouraging, it appears to be less effective in African Americans. ■

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CME Questions

20. Regarding physical and sexual activity and the risk of acute coronary syndromes, which of the following is true?

a. The risk of acute coronary syndrome is acutely increased during periods of physical or sexual activity.
b. Regular physical exercise reduces the risk of acute coronary syndromes overall, but not during exercise itself.
c. Extreme amounts of exercise (e.g., at least an hour of at least 7-8 METs) are required to reduce the risk of acute coronary syndromes.
d. Regular physical activity reduces the risk of acute coronary syndromes during exercise, but not during sex.

21. Coffee consumption is associated with:

a. reduced likelihood smoking.
b. reduced risk of stroke.
c. increased risk of diabetes.
d. increased inflammatory mediators.

Answers: 20. a, 21. b

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.

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

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

Long-Term CV Effects of Intensive Glucose Lowering: The ACCORD Study

Source: Gerstein HC, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 2011;364:818-828.

The action to control cardiovascular risk in diabetes (ACCORD) study is really three studies in one, providing information about blood pressure, glucose, and triglyceride treatment in high-risk diabetic patients. Probably the most unsettling component of ACCORD was the early termination of the comparison of tight glucose control (attainment of an A1c < 6) with standard control (A1c 7-7.9) due to an unanticipated INCREASE in mortality associated with tight control. The glucose control arm of ACCORD was designed to go on for 5 years, but intensive glucose control was stopped at 3.5 years. Though various explanations for these results have been offered, none is wholly satisfying.

Once the increased mortality of tight control was appreciated, ALL study subjects were switched to the standard control regimen and followed to the 5-year mark. This most recent publication details outcomes of persons who originally were treated with tight control, and then were switched to standard control for the next 17 months.

Just as had been seen in the initial results of ACCORD, the group that had been assigned to tight control (even though now they had been receiving more relaxed control, and their A1c had risen 7.2%) continued to experience a statistically significant 19% greater risk for death. During Phase 2 of ACCORD, the frequency of hypoglycemia was the same between the standard control group and the group that had changed from tight to standard control; hence, although the greater frequency of hypoglycemia seen in tight control had received some focus as a culprit in inducing greater mortality, this follow-up suggests that is not the case. Why tight control is associated with increased mortality remains unknown. ■

Cysteine as a Biomarker for Sleep Apnea

Source: Cintra F, et al. Cysteine: A potential biomarker for obstructive sleep apnea. *Chest* 2011;139:246-252.

Obstructive sleep apnea (OSA) is consistently associated with cardiovascular misadventure: An increased risk for hypertension, tachycardia, cardiac arrhythmia, myocardial infarction, and stroke has been noted. OSA seems to reset the sympathetic nervous system to a higher level of activity, thus explaining some of these adversities. Tools to identify OSA are somewhat cumbersome and expensive. Were biomarkers available to identify OSA, clinicians could better reserve expensive confirmatory testing for persons with higher pre-test likelihood of disease.

Animal studies have found that sleep deprivation and hypoxia produce elevations in cysteine (CYS). Cintra et al measured CYS levels in subjects undergoing sleep studies (n = 75) and a group of matched controls (n = 75). A non-obese OSA subgroup was included to ascertain whether obesity has an impact on CYS.

CYS levels were significantly higher (15%-17%) in OSA subjects than controls ($P < 0.01$), whether obese or lean. A 6-month period of CPAP treatment resulted in a reduction of CYS levels. No pathogenetic role of CYS is known, but if further studies confirm the relationship between CYS and OSA, it may serve as a reasonable screening tool for selecting those who might benefit from sleep studies. ■

Steroid or Steroid Plus Long-Acting Beta Agonist for Mild Persistent Asthma

Source: Postma DS, et al. Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control. *Chest* 2011;139:311-318.

The largest body of asthmatics is classified as mild persistent asthma, defined as daytime symptoms more than once weekly but not daily, nocturnal symptoms less than once weekly, and essentially normal lung function between exacerbations. At this stage, long-term controller medications — inhaled corticosteroids (ICS) or leukotriene inhibitors (LKT) — are suggested, reserving combination inhaled corticosteroid/long-acting beta agonist (ICS/LABA) for refractory cases or patients who progress to moderate persistent asthma and beyond. LABA monotherapy is no longer considered appropriate for asthma patients at any stage of disease.

Ciclesonide (CIC) is a novel ICS with at least two favorable attributes: once daily dosing, and minimal hypothalamic pituitary axis perturbation at typical clinical doses. This clinical trial compared low-dose CIC with low-dose fluticasone/salmeterol in patients with mild persistent asthma (n = 657). The two co-primary endpoints were time to first severe asthma exacerbation and number of poorly controlled asthma days.

CIC alone was not superior to placebo in time to first severe asthma exacerbation, but ICS/LABA was. Other aspects of asthma control were comparable between the two regimens. Although ICS alone is advocated as appropriate initial treatment for mild persistent asthma, this comparison trial suggests that ICS/LABA provides at least one aspect of superiority. ■

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, Travel Medicine Advisor.*

Apixaban and Rivaroxaban Near Approval for Nonvalvular AF

In this issue: Apixaban and rivaroxaban near approval for nonvalvular atrial fibrillation; fidaxomicin for *C. difficile* infections; guideline for intensive insulin therapy; and FDA Actions.

Dabigatran for stroke in patients with nonvalvular atrial fibrillation

Dabigatran, a direct thrombin inhibitor, recently was approved for prevention of stroke in patients with nonvalvular atrial fibrillation. The evidence for its benefit is strong enough that the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society recently upgraded their atrial fibrillation guidelines to include dabigatran (*Circulation* published online February 14, 2011). Meanwhile, the direct factor Xa inhibitor rivaroxaban is working its way through the FDA approval process for the same indication, with approval expected later this year. The latest player in the field is apixaban, also a direct factor Xa inhibitor. Apixaban was studied in a double-blind Phase 3 study of 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable. Patients were randomized to receive apixaban 5 mg twice daily or aspirin 81-324 mg per day with a mean follow-up of 1.1 years. The primary outcome was occurrence of stroke or systemic embolism. The study was terminated early because of a clear benefit in favor of apixaban. There were 51 events (1.6 % per year) in the apixaban group vs 113 events (3.7% per year) in the aspirin group (hazard ratio with apixaban 0.45, 95% confidence interval 0.32-0.62; P < 0.001). The death rate was 3.5% in the apixaban group vs 4.4% in the aspirin group (P = 0.07). The rates of major bleeding or intracranial hemorrhage were similar; however, the risk of first hospitalization for cardiovascular causes was significantly lower with apixaban. The authors suggest that apixaban is more effective than aspirin. In indirect comparisons, apixaban is more effective than aspirin plus clopidogrel and at least as effective as warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation (*N Engl J Med* published online February 10, 2011). Apixaban is currently being studied head-to-head with warfarin in the ARISTOTLE trial. If the data from that trial looks favorable, it is likely that both apixaban and rivaroxaban also will be approved for this indication in the not-too-distant future. Dabigatran and apixaban are both dosed bid while rivaroxaban is a once-a-day drug. The extent to which these drugs gain general usage at the expense of warfarin in large part will be due to patient preference and cost. ■

Fidaxomicin for *C. difficile* infections

A new option may soon be availiable for treating *Clostridia difficile* infections. Fidaxomicin (not yet approved in this country) is a non-systemic (poorly absorbed) narrow spectrum macrolide antibiotic that is bacteriocidal against *C. difficile* infections. It recently was compared to vancomycin in a head-to-head Phase 3 noninferiority study of 629 adults. Patients with a positive stool toxin test to *C. difficile* were randomized to

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fidaxomicin 200 mg twice a day or vancomycin 125 mg four times a day. The primary endpoint was clinical cure and the secondary endpoint was recurrence within 4 weeks and global cure (no recurrence). Fidaxomicin was noninferior to vancomycin in both the intention-to-treat (88.2% cure rate with fidaxomicin vs 85.8% with vancomycin) and per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients had recurrence with fidaxomicin in both groups (15.4% vs 25.3%, $P = 0.005$ intention-to-treat, and 13.3% vs 24.0%, $P = 0.004$ per protocol) although the lower rate of recurrence was in the less virulent strains. For the more virulent strains, the recurrence rate was about 25% for both drugs. Fidaxomicin was associated with a higher rate of hyperuricemia and elevated transaminases (*N Engl J Med* 2011;364:422-431). An accompanying editorial points out that the incidence and virulence of *C. difficile* infections is increasing at an alarming rate in this country. Fidaxomicin inhibits vegetative forms of *C. difficile* while preseving intestinal flora, a combination that holds promise, and if borne out "this new agent could become a recommended therapy for *C. difficile* infection" (*N Engl J Med* 2011;364:473-475). ■

Guideline for intensive insulin therapy

A guideline from the American College of Physicians (ACP) recommends against aggressively controlling blood glucose in hospitalized patients. Intensive insulin therapy (IIT) is no longer recommended for patients in intensive care units, regardless of whether they have diabetes. Specifically, the ACP recommends not using IIT to strictly control blood glucose or even normalized blood sugar in surgical ICU or medical ICU patients, and recommends a target blood glucose level of 140-200 mg/dL if insulin therapy is used. The recommendation is based on multiple studies that show no reduction in mortality with a blood glucose target of 80-180 mg/dL compared with higher targets using a variety of intensive insulin regimens. This includes treatment of patients with myocardial infarction, stroke, acute brain injury, or those under perioperative care. The guideline further recommends that avoiding targets less than 140 mg/dL should be a priority because harm is likely with lower blood glucose targets (*Ann Intern Med* 2011;154:260-267).

FDA actions

The FDA is warning against the use of terbutaline for prevention or prolonged treatment of preterm labor in pregnant women. The drug, which is approved for treatment of asthma, has been used off label for treatment of preterm labor and uterine hyperstimulation; however, the agency has received postmarketing reports of serious adverse reactions, including heart problems, and even maternal deaths, associated with the drug. The FDA has added a Boxed Warning and Contraindication to the labeling of the drug warning against these uses. This extends to both the IV and oral forms of terbutaline.

The FDA has approved hydroxyprogesterone caporate injection to reduce the risk of preterm delivery before 37 weeks of pregnancy in a pregnant woman with a history of at least one spontaneous preterm birth. The drug is not intended for use in women with a multiple pregnancy, such as a twin pregnancy, or other risk factors for preterm birth. The drug was approved under the FDA's accelerated approval regulations, and, as such, additional studies will be required after approval to show that the drug does indeed have clinical benefit. Hydroxyprogesterone caproate is given once a week by injection into the hip beginning at week 16 and no later than week 21. The drug is marketed by Hologic Inc. as Makena.

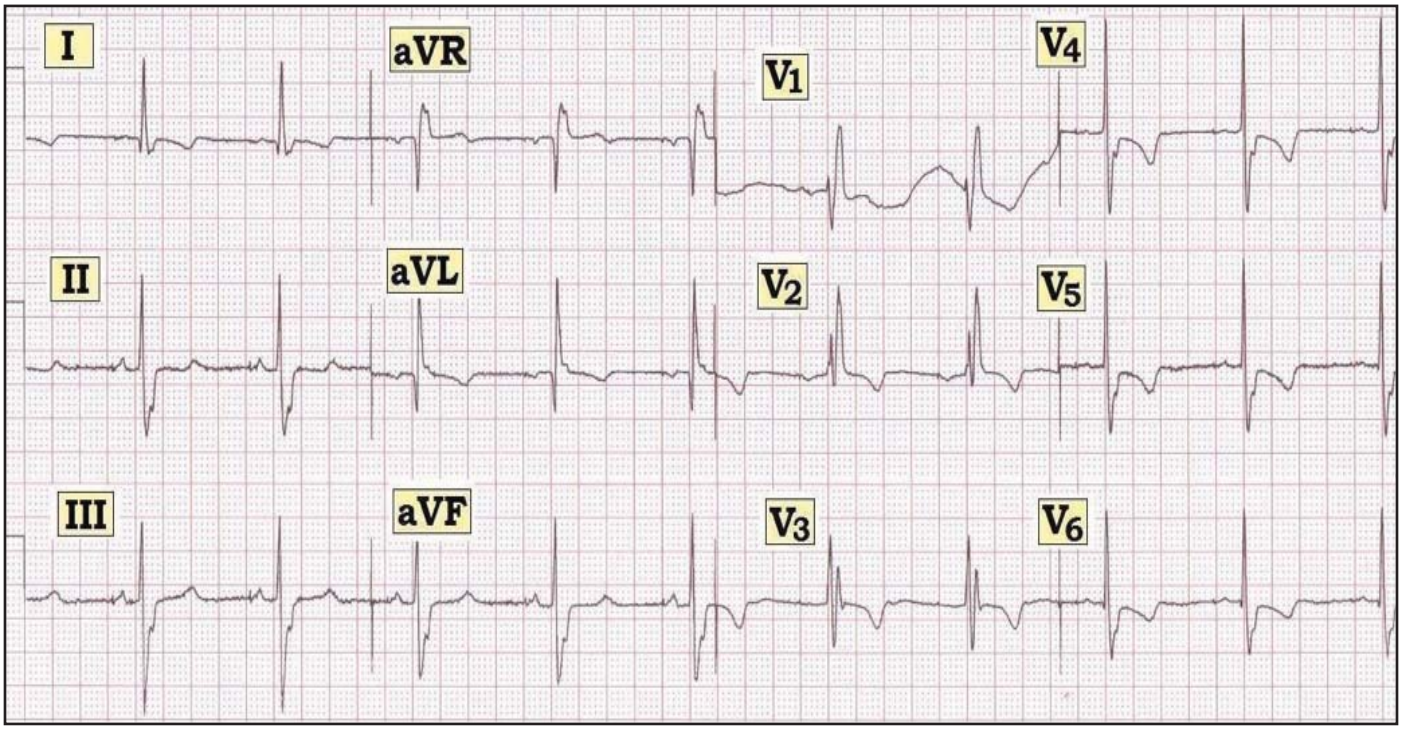
The FDA has issued a drug safety alert regarding the risk of serious liver injury with dronedarone (Multaq). The drug — which is approved for prevention of atrial fibrillation/flutter — has been associated with multiple cases of severe liver injury, including two cases that required liver transplantation. Dronedarone previously was found to double the risk of death in patients with severe heart failure and was approved with a REMS designed to prevent its use in that patient population. Physicians are reminded to advise patients to contact a health care professional immediately with any signs of hepatic injury or toxicity. All patients on dronedarone should get periodic hepatic serum enzymes especially during the first 6 months of therapy.

The FDA has approved a new treatment for head lice. Spinosad is an insecticide originally derived from a naturally occurring soil bacterium. The 0.9% topical suspension was shown to be effective in two Phase 3 active-control, randomized studies in which 86% of patients treated with the active drug were lice free after 14 days compared to 44% of controls. The product should not be used in children under 6 months of age because it contains benzyl alcohol. Spinosad is applied as a single 10-minute application which may be repeated in one week if lice are seen. It will be marketed by ParaPro LLC as Natroba. ■

A Woman with Heart Problems

By Ken Grauer, MD, *Professor Emeritus in Family Medicine, College of Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.



Scenario: The ECG above was obtained in the office from a 47-year-old woman who said she had "heart problems" that resulted in hospitalization the month before. She has had no symptoms over the past few weeks. How would you interpret her ECG? What kind of heart problems might she have had?

Interpretation: This is an extremely interesting tracing. The rhythm is slow and regular, at a rate of about 60/minute. Although the rhythm appears to be sinus (with upright P waves in lead II) — a tiny, vertical spike precedes the P wave in this lead as well as in several other leads (best seen in leads II, III, and aVF). The patient has a DDD pacemaker, and is being atrial paced. The QRS is obviously wide, but not preceded by any pacing spike. Thus, there is atrial pacing at 60/minute with preservation of normal AV conduction. QRS morphology is consistent with complete right bundle branch block (RBBB) — with an rSR' complex in lead V1 and wide terminal S waves in leads I, V6. There are deeper-than-expected Q waves in leads I and, especially aVL, suggesting possible prior lateral infarction. Support for this possibility derives from the ST segment coving and shallow T wave inversion in lead aVL. ST segment coving and symmetric T wave inversion is also seen in lead I and across the precordial leads. Although normally there is ST-T wave depression in anterior precordial leads with RBBB — it should not be nearly as diffuse as is seen here.

We suspect this patient's heart problems are related to one or more episodes of marked bradycardia, necessitating placement of a permanent pacemaker. The fact that she is set to atrial pacing suggests that there was no significant AV block. Her RBBB, lateral Q waves, and diffuse ST-T wave changes probably reflect ischemia and/or recent infarction. ■

In Future Issues:

You're Overweight. There, I've Said It

INTERNAL MEDICINE ALERT

2011 Internal Medicine Alert Reader Survey

In an effort ensure *Internal Medicine Alert* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey. The results will be used to ensure you are getting the information.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write your answers to the open-ended questions in the space provided. Return the questionnaire in the enclosed postage-paid envelope by **July 1, 2011**.

In future issues of *Internal Medicine Alert*, would you like to see more or less coverage of the following topics?

	A. more coverage	B. less coverage	C. about the same
1. Endocrinology	O A	O B	O C
2. Pulmonology	O A	O B	O C
3. Cardiology	O A	O B	O C
4. Dermatology	O A	O B	O C
5. Neurology	O A	O B	O C
6. Gastroenterology	O A	O B	O C
7. Rheumatology	O A	O B	O C
8. Men's Health	O A	O B	O C
9. Women's Health	O A	O B	O C
10. Pediatrics	O A	O B	O C
11. Preventive Medicine	O A	O B	O C

12. What other topics would you like to see discussed in *Internal Medicine Alert*? _____

_____

13. Are the articles in *IMA* written about issues of importance and concern to you?

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

14 Are the articles in *Internal Medicine Alert*

O A. Too short O B. Too long O C. About right

15. What type of information not currently provided in *Internal Medicine Alert* would you like to see added? _____

_____

Please rate your level of satisfaction with the the items listed: Please mark your answers in the following manner:

	A. excellent	B. good	C. fair	D. poor
16. quality of newsletter	O A	O B	O C	O D
17. article selections	O A	O B	O C	O D
18. timeliness	O A	O B	O C	O D
19. quality of commentary	O A	O B	O C	O D
20. clearness of abstracts	O A	O B	O C	O D
21. overall value	O A	O B	O C	O D
22. customer service	O A	O B	O C	O D

23. To what other publications or information sources about internal medicine do you subscribe?

_____

_____

24. Including *IMA*, which publication or information source do you find most useful, and why?

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25. Please describe your work place:

O A. private practice O B. hospital O C. government institution O D. research

O E. Other_____

26. In the future, how do you plan to obtain your CME and CNE credits?

O A. travel to live conferences O B. subscription-based newsletters/journals O C. outside-sponsored teleconferences

O D. Internet-based activities O E. Other (please specify)_____

27. *Internal Medicine Alert* is currently accredited for a maximum of 24 hours of Prescribed credit by the American Academy of Family Physicians. If you participate in this CME activity for credits, how many hours do you spend in the activity each year?_____

28. List the top three challenges you face in your job today:

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