INTERNAL MEDICINE ALERT

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INSIDE

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Which Acute Headaches Do Not Require Investigation?

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD, MA

Chair, Department of Integrative Medicine, Ross University School of Medicine, Commonwealth of Dominica

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

Synopsis: *Easily obtained clinical variables can identify patients at very low risk for subarachnoid hemorrhage.*

Source: Perry JJ, et al. High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: Prospective cohort study. *BMJ* 2010 Oct 28;341:c5204; doi: 10.1136/bmj.c5204.

These investigators from Canada designed a study to identify clinical characteristics that predict subarachnoid hemorrhage (SAH). Their second goal was to take these variables and develop a clinical decision rule. This prospective cohort study was conducted at six tertiary care, university teaching hospitals from 2000 to 2005. The inclusion criteria were: age ≥ 16 years; presentation to an emergency department complaining of a non-traumatic headache, which peaked in intensity within 1 hour of onset or syncope associated with a headache; and a Glasgow Coma Scale score ≥ 15. They excluded patients who had three or more similar headaches over the previous 6 months, patients referred from another facility with a confirmed diagnosis of SAH, patients who returned for reassessment of the same headache and who had already had a head computed tomography (CT) or lumbar puncture (LP) or both, and patients with papilledema, new focal neurologic deficit, history of cerebral aneurysm or SAH, brain neoplasm, or hydrocephalus. Each patient's data were collected on a standardized form.

Of 1999 enrolled patients, 130 (6.5%) had SAH. The remaining 1869 patients were actively followed for 6 months. Twenty (26) were lost to follow-up. The investigators were able to confirm that none of

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these patients had died in the 6 months after onset. The patients averaged 43 years (age range, 16-93 years) and were predominately female (60%). The headaches had their onset during exertion in 11.5%. Nineteen percent (19%) arrived by ambulance. The average time from the onset of the headache to its peak was 8.8 minutes. More than three-quarters described the headache as "the worst of my life." In 3% of cases there was witnessed loss of consciousness. More than a quarter experienced vomiting. Only 7% had neck stiffness with flexion and extension, although more than a third complained of neck stiffness or pain. The average blood pressure (BP) was 143/81 mm Hg. Most patients (83%) had head CT and/or LP. Twelve (12) patients died. Nine (9) cases of SAH were missed by the radiologists, but were picked up by positive results in cerebrospinal fluid. Head CT also picked up 48 (2.4%) other serious illnesses (e.g., transient ischemic attack, acute ischemic stroke, another type of hemorrhagic stroke, bacterial meningitis, hypertensive emergency, cerebral neoplasm). Most (81%) of the headaches were benign.

The researchers identified 26 possible predictor variables and, in univariate analysis, determined the strength of the association between them and SAH. They then developed multivariate models to predict SAH. They selected variables with good interobserver reliability, statistical significance, and clinical validity. The clinical rules were developed with the goal of 100% sensitivity. They used a sequential stepwise analysis, going from the most predictive variable to the least, until a low-risk group without any cases of SAH remained. In that way, a patient with any one of the variables would remain in the high-risk group and would need to be investigated. This resulted in three rules, each with four criteria:

Rule #1: Age > 40 years, complaint of neck pain or stiffness, witnessed loss of consciousness, and onset with exertion.

Rule #2: Arrival by ambulance, age > 45 years, vomiting at least once, and diastolic BP > 100 mm Hg.

Rule #3: Arrival by ambulance, systolic BP > 160 mm Hg, complaint of neck pain or stiffness, and age 45-55.

The authors excluded "arrival by ambulance" in the first rule specifically to address geographic areas where calling for an ambulance may be problematic. All three rules had 100% sensitivity. The specificity ranged from 28% to 39%. The investigation rates (those patients who received head CT, LP, or both) ranged from 64% to 74%.

■ COMMENTARY

A patient walks into your office complaining of the worst headache of her life. It started just a couple hours ago. This is a high stakes office visit. Many physicians, including me, would immediately send her for a head CT. Many physician educators, including me, have taught that a new onset headache in an adult is an indication for CT. This study says otherwise. I chose to review it because I am concerned that we are teaching our students and residents to ignore their clinical investigations and rely unnecessarily on technology.

This group of researchers had previously examined how Canadian emergency physicians managed patients with an acute headache.[1] Not surprisingly, the physicians were able to distinguish SAH from other causes of headache solely on clinical grounds, but were loath to do so. I imagine that the results with U.S. emergency physicians would be very similar, considering the litigious nature of our society. This is not a diagnosis any of us would want to miss. On the other hand, the economics of testing every patient with a head CT and/or a lumbar puncture is substantial and subjects the patient to radiation or an invasive procedure. They also demonstrated that a negative head CT and a negative LP rule out SAH.[2]

About one patient of 40 had a serious illness that wasn't SAH. It is not clear whether any of these patients would have been excluded from investigation by any of the three rules, but I suspect not. The authors state, "For these patients, it was apparent from the documentation that physicians were concerned about the possibility of other pathology before they obtained results of imaging or lumbar puncture."

LPs are frequently performed after a negative head CT. Eight hundred fifty-four (854) patients in this study had both head CT and LP. An article from the United Kingdom in 2006 showed that for low-risk patients who had a

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negative CT, more than 1000 LPs would have to be performed to diagnose one case of SAH.[3] In a study from Sweden published earlier this year, CT alone diagnosed 295 of 296 cases of SAH.[4] Two hundred three (203) patients had a negative CT and a negative LP. In other words, LP diagnosed only one patient out of 499. Put down the spinal needle and back away from the patient.

It is important to remember that this study was performed on alert adults who were neurologically intact. Before these decision rules can be adopted, they will have to be independently validated in larger trials. (This group is currently performing its own prospective study of the rules.) If the rules are validated, as many as one patient in five could avoid investigation (the difference between the current rate of investigation of 83% and the low end of 64%) and the resultant exposure to radiation and post-LP headache. In the meantime, if a patient presents with any one of the seven findings from the three rules, the prudent physician should seriously consider SAH and perform a thorough investigation. ■

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Most Prostate Cancer Does Not Need Initial Treatment

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

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

Synopsis: *A decision analysis shows that active surveillance is a good option for men age 65 and older with low-risk prostate cancer (Gleason score of 6 or less). Active surveillance results in the highest quality-of-life scores compared with different treatment options, and 61% of these men will go on to treatment after a median of 8.5 years, with a slight increased mortality risk. Only 10% of men currently receive active surveillance for low-risk prostate cancer.*

Source: Hayes JH, et al. Active surveillance compared with initial treatment for men with low risk prostate cancer: A decision analysis. *JAMA* 2010;304:2372-2380.

A STUDY TEAM FROM HARVARD AND THE UNIVERSITY OF California, San Diego, conducted a decision analysis of the current literature to compare active surveillance with three initial treatment options for men age 65 or older with low-risk localized prostate cancer by biopsy (Gleason score 6 or less). Active surveillance is defined as regular physical examinations, PSA measurement, and rebiopsy 1 year following diagnosis and every 3 years thereafter. Treatment is triggered by progression to a Gleason score of 7 or higher, other evidence of disease progression such as a rapid rise in PSA, or patient preference.

Active surveillance was compared with initial brachytherapy, intensity-modulated radiation therapy (IMRT), and radical prostatectomy. Probabilities of complications and mortality were calculated from previous studies. The relative risk of death from initial treatment compared with active surveillance was 0.83, or 9% compared with 11%. Complications of treatment include impotence, urinary incontinence, bowel problems, or a combination of these, and most men get at least one of these from treatment. Sixty-one percent of patients choosing active surveillance went on to treatment after a median of 8.5 years, and the quality adjusted life-years was better in this group by 6 months compared with brachytherapy, the most effective initial treatment.

Men choosing active surveillance do not have any evidence of increased anxiety over time compared with men undergoing treatment.

■ COMMENTARY

In 2009, 192,000 men in the United States were diagnosed with prostate cancer, and the death rate is about 22,000. Seventy percent of men diagnosed with cancer have localized low-risk disease (Gleason score of 6 or less). Currently more than 90% of these men undergo treatment after diagnosis, and the majority experience at least one adverse effect. This analysis based on the current literature suggests that up to 60% of these men could choose active surveillance with a higher quality of life and a small risk of not pursuing initial treatment. Only 10% of men currently choose this option.

This study has reframed my approach to low-risk localized prostate cancer, particularly in men 65 and older.

It is important to remember that there are two general types of prostate cancer. Younger men, age 40-60, who get prostate cancer often have a very aggressive disease that commonly defies treatment and has high mortality. Older men more often have a more benign type of cancer. Most of us already consider prostate cancer in men age 80 and older as something that most likely the patient will not suffer from or die of. Cancer in men age 65 is a different matter.

I have already summarized this study with patients in this situation, and found them very open to active surveillance when they realize that it is not a foolish decision. Many men do not seek treatment to an area involved with their sex life and with urination. What I like about the term and definition of active surveillance is that it does not imply "forget about it and take your chances." Close attention is given to the cancer and more than half of the men will eventually undergo treatment.

This study is a simulation model using the current research evidence. Obviously, this will change with more research. I hope this study gives us many more men who choose active surveillance so that we will have a large cohort of real men on which to base our evidence in guiding patients. ■

Predictors of Mortality in Parkinson's Disease

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

Assistant Professor, Neurology and Neuroscience, Weill Cornell Medical College

Dr. Nirenberg reports that she has consulted for Biovail.

This article originally appeared in the December issue of Neurology Alert. *At that time it was peer reviewed by M. Flint Beal, MD, Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center, New York, NY. Dr. Beal reports no financial relationship to this field of study.*

Synopsis: *Clinical predictors of mortality in Parkinson's disease include age at onset, chronological age, male sex, motor severity, psychosis, and dementia.*

Source: Forsaa EB, et al. What predicts mortality in Parkinson disease? A prospective, population-based long-term study. *Arch Neurology* 2010;75:1270-1276.

PARKINSON'S DISEASE (PD) IS A CLINICALLY AND GENETICALLY heterogeneous disorder, with striking variability in its presentation and rate of progression. Factors such as young age of onset and tremor predominance have been associated with an overall favorable prognosis. In contrast, features such as later age of onset, dementia, and prominent postural instability-gait disturbance features tend to predict a more malignant disease course. Given this clinical heterogeneity, it is not surprising that there is also tremendous variability of life expectancy in PD. For this reason, it is of considerable clinical interest to determine factors associated with increased mortality in PD.

In this study, the authors examined clinical and demographic predictors of increased mortality in PD. The study population was a large (n = 230), prospective, community-based cohort in Norway. Subjects underwent serial motor and non-motor assessments between 1993 and 2005. The vital status of all study subjects was obtained from a national registry in 2009; this included the date of death for subjects who were deceased. Kaplan-Meier analysis was used to examine unadjusted survival after motor onset. Cox proportional hazards models were used to determine the independent predictors of mortality in the cohort.

Within the study period, 211 subjects (92%) died. Survival times ranged from 2.2 to 36.6 years, with a mean survival of 15.8 years from motor onset. The mean age of death was 81.1 ± 6.3 years (79.8 ± 6.1 for men vs 82.4 ± 6.3 for women). Independent predictors of mortality included older age at onset, higher chronological age, male sex, higher Unified Parkinson's Disease Rating Scale (UPDRS) motor scores (indicative of greater motor impairment), the presence of psychotic symptoms, and the presence of dementia. The use of atypical antipsychotics, however, was not an independent predictor of mortality.

The authors conclude that treatments that prevent motor progression, dementia, and psychosis might potentially reduce mortality in PD.

■ COMMENTARY

Physicians who treat patients with Parkinson's disease are frequently asked to provide patients with an estimate of their life expectancy and overall prognosis. While several factors are known to portend a better or worse prognosis in PD, there is no way to predict the clinical course or life expectancy of an individual patient. This reality is reflected in the striking variability of survival times in this study — which ranged from 2.2 to 36.6 years after onset of motor symptoms.

Although individual life expectancy is highly variable in PD, this study identified a number of clear clinical predictors of mortality on a population basis. Male sex and higher chronological age, both major predictors of mortality in the general population, were not surprisingly also

associated with increased mortality in PD. In addition, the authors identified several disease-specific factors associated with mortality in PD. These included older age of PD onset, greater UPDRS motor impairment, the presence of psychotic symptoms, and the presence of dementia. The use of antipsychotics was not independently associated with increased mortality, suggesting that studies associating antipsychotic use with increased morbidity in elderly patients with Alzheimer's disease may not be applicable to those with PD.

Strengths of the study include the large sample size, prospective study design, low dropout rate (for reasons other than death), and availability of complete and accurate mortality data. Limitations include the ethnic and geographical homogeneity of the population that was studied, and the observational nature of the study.

In summary, mortality in PD is associated not only with factors that increase risk in the general population (advanced age, male sex), but also with disease-specific factors such as age at PD onset, severity of motor impairment, and specific non-motor symptoms (dementia and psychosis). These findings may be helpful to physicians in identifying patients at increased risk of mortality. ■

Pharmacology Update

Drospirone/Ethinyl Estradiol/Levomefolate Calcium Tablets (Beyaz™)

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 FIRST ORAL CONTRACEPTIVE COMBINED WITH A FOLATE has been approved by the FDA. The new product is the same contraceptive combination found in Bayer's popular oral contraceptive Yaz®, along with levomefolate calcium, a metabolite of folic acid. The combination is marketed by Bayer HealthCare Pharmaceuticals as Beyaz™.

Indications

DRO/EE/FOL is indicated for the prevention of pregnancy. It is also indicated for the treatment of the symptoms of premenstrual dysphoric disorder, moderate acne, as well as to raise folate levels in oral contraceptive users.[1]

Dosage

The recommended dose is one tablet daily at the same time of day. Drospirenone 3 mg and ethinyl estradiol 2 mg is taken for 24 days and levomefolate calcium 0.451 mg is taken for 28 days.

Potential Advantages

Beyaz provides folate supplementation for women who may choose to become pregnant after discontinuation of the oral contraceptive.

Potential Disadvantages

The activity of folate may be reduced by certain drugs such as methotrexate, sulfasalazine, bile-sequestering agents, and certain epileptics (e.g., carbamazepine, phenytoin, phenobarbital, primidone, and valproic acid).[1] Drospirenone may increase serum potassium.

Comments

The efficacy of drospirenone and ethinyl estradiol has been established with the combination product, Yaz. The combination of Yaz and levomefolate calcium produced higher plasma and red blood cell folate levels than Yaz plus folate-fortified food. Mean increases in value were approximately 35%.

Clinical Implications

The Centers for Disease Control and Prevention and the U.S. Preventive Services Task Force recommend that women of childbearing age take at least 0.4 mg of folic acid daily to reduce the risk of neural tube defect in the infant. Despite these recommendations and mandated folate fortification of enriched cereal gain products, a recent analysis of data from the National Health and Nutritional Examination Survey indicated that only 24% of nonpregnant U.S. women aged 15-44 years consumed the recommenced amount of folic acid.[2]

In addition, women ages 18-24 years, who account for approximately one-third of all births, had the least awareness regarding folic acid consumption and the lowest reported daily use of supplements containing folic acid compared to other age groups.[3] Beyaz is combination oral contraceptive that is "fortified" with levomefolate. It offers another option for women who wish to use a contraceptive as well as to raise their folate levels without taking folic acid supplement. Other than the convenience, there is no advantage over taking an oral contraceptive without a folic acid supplement. ■

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CME Questions

62. Which patient who complains of the worst headache of her life would *not* need an investigation for subarachnoid hemorrhage? Use one of the three rules to decide.

a. A 40-year-old who drove herself to the emergency department complaining of nausea and who had a blood pressure of 160/100 mm Hg.
b. A 40-year-old complaining of neck pain who reported loss of consciousness after a headache that had its onset with exertion.
c. A 54-year-old who arrived by ambulance complaining of neck stiffness and who had a blood pressure of 156/110 mm Hg.
d. A 60-year-old who drove herself to the emergency department, reported vomiting three times, and had a blood pressure of 170/110 mm Hg.
e. A 35-year-old who arrived by ambulance, complaining of neck pain and who had a blood pressure of 210/100.

63. For men with low-risk localized prostate cancer, what option results in a higher quality of life over more than 8 years of follow-up?

a. Brachytherapy
b. Intensity-modulated radiation therapy
c. Radical prostatectomy
d. Active surveillance

64. All of the following are predictors of mortality in Parkinson's disease *except*:

a. dementia.
b. psychosis.
c. female sex.
d. older age at onset.

Answers: 62. a, 63. d, 64. c.

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 a consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Daiichi, Sankyo, Forest Pharmaceuticals, Lilly, Novo Nordisk, Takeda.

Have people with HTN reduced salt intake?

Source: Ayala C, et al. Actions taken to reduce sodium intake among adults with self-reported hypertension. *J Clin Hypertens* 2010;12:793-799.

The most recent advice from the U.S. Department of Agriculture (2005) recommends that the general population of adults not consume > 2300 mg/day of sodium, and that persons with hypertension (HTN) consume ≤ 1500 mg/day. In contrast to these recommendations, NHANES data from 2005-2006 indicate that U.S. adults consume essentially 1.5 times the recommended ceiling. One would hope that with all the health information available to consumers that persons with HTN would be particularly attuned to restricting their sodium intake, especially as awareness and treatment of HTN have increased over the last two decades.

The HealthStyles survey is sent annually to thousands of randomly selected homes in the United States by an international research organization. Surveys in 2005 (n = 6168) and 2008 (n = 7000) from non-pregnant adults who self-identified as hypertensive and also as having received advice from their clinician to reduce salt intake were analyzed for responses to questions about their sodium habits.

Over the 3-year interval, the percentage of adults who reported reading food labels increased from 49.1% to 53.0%; persons who reduced the amount of sodium in their diet increased from 48.3% to 56.6%. Overall, women more often read food labels than men, and blacks more often than Hispanics or whites.

Lifestyle intervention can have a meaningful impact on an individual- or population-wide basis. Although it is encouraging to note that a majority of adults with hypertension currently do read food labels for sodium content, and have reduced their sodium intake, there remains much room for more widespread adoption of such potentially healthful habits. ■

The P450 system and CV outcomes with clopidogrel

Source: Pare G, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *N Engl J Med* 2010;363:1704-1714.

A great deal of controversy has surrounded the clinical relevance of the P450 system and efficacy of clopidogrel. The basic story line is as follows: To reduce CV events in persons with atrial fibrillation or post-ACS, clopidogrel must reduce platelet aggregation. This inhibition of platelet aggregation (IPA) is dependent not upon clopidogrel itself, but on a metabolite of clopidogrel, which is generated through the CYP2C19 pathway. In vitro, it is clear that genetic variations in CYP2C19 activity can impact IPA: Loss-of-function genetic alleles have been shown to produce reduced IPA in vitro. Similarly, things that block activity of the CYP2C19 system also reduce IPA in vitro. End of story? Not so fast.

Initial retrospective studies reported a concerning increase in events in persons on clopidogrel who were concomitantly receiving CYP2C19-inhibiting proton pump inhibitors. Two subsequent prospective analyses, however, failed to demonstrate reduced efficacy when clopidogrel and PPI were used concomitantly.

This study compared CV outcomes in post-ACS or atrial fibrillation subjects (total n = 5059) who had undergone genetic testing and been found to have a variety of genetic CYP2C19 loss-of-function variants. No meaningful impact of CYP2C19 genotype upon CV outcomes (or bleeding risk) was found.

For the time being, use of CYP2C19 genotyping does not seem to help us decide how to better provide IPA for our patients. Whether this reflects inaccuracy of currently available testing methods, recognition that other forces are at play beyond simple aggregation of platelets, or other as-yet undefined issues remains to be determined. ■

Risk assessment for bleeding during warfarin therapy

Source: Pisters R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation. *Chest* 2010;138:1093-1100.

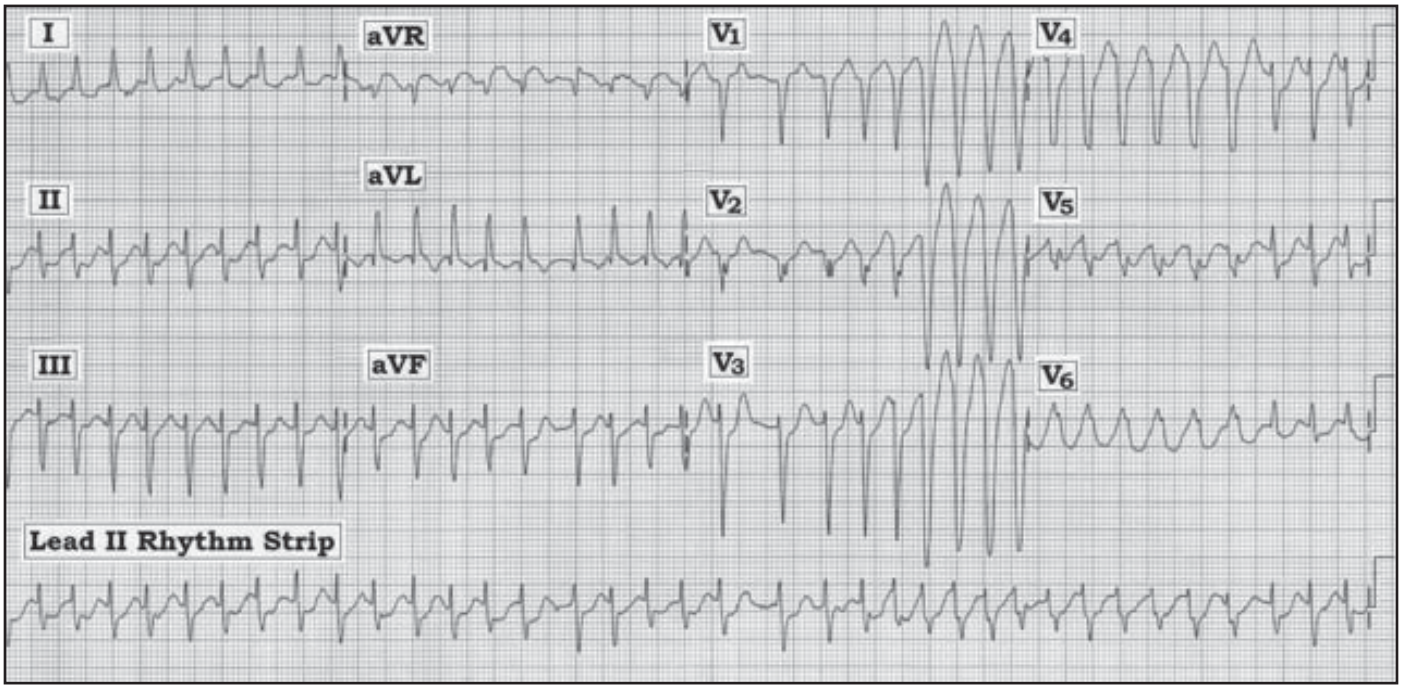
The CHADS2 score has proven to be very useful in stratifying risk of stroke for patients with atrial fibrillation (AF). The risk reduction for stroke provided by warfarin anticoagulation in AF is about 66%. Yet, at lower baseline risks (e.g., CHADS2 score 0-1), the risk of bleeding starts to counterbalance stroke risk reduction. To date, there has been no comparably simple tool to predict risk of bleeding while on warfarin.

HAS-BLED incorporates seven readily available risk factors to predict bleeding risk from warfarin in persons with AF with the following number of points: hypertension (1 point), abnormal renal/hepatic function (1 point each), stroke (1 point), bleeding history/diathesis (1 point), labile INR (1 point), elderly > 65 (1 point), and drugs/alcohol use (1 point each). Whenever the HAS-BLED score is greater than the CHADS score, bleeding risk may outweigh clinical benefit. Clinicians may want to consider refining their bleeding risk prediction for patients with potential indications for warfarin based upon the HAS-BLED stratification tool. ■

A Burst of VT?

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*

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



Scenario: The ECG shown above was obtained from an older man with palpitations. He was hemodynamically stable with a systolic BP of 140 mm Hg at the time this tracing was recorded. How do you interpret the rhythm? What are your initial priorities?

Interpretation: The first priority in evaluation and management of any tachycardia has already been accomplished — namely, ensuring that the patient is hemodynamically stable. If the patient were unstable (i.e., hypotensive, unresponsive, with severe chest pain or shortness of breath), then synchronized cardioversion would be immediately indicated. This is not the case here. Even patients in sustained ventricular tachycardia (VT) may sometimes remain in this rhythm for hours or longer.

The key to interpreting this tracing lies with the lead II rhythm strip above. Careful observation reveals that in addition to being extremely rapid, the rhythm is irregular. Lack of atrial activity confirms the rhythm to be atrial fibrillation with a very rapid ventricular response. Of note is a 10-11 beat run of a wide tachycardia (encompassing the last 4-5 beats in leads V_1,V_2,V_3 — and the first 6 beats in V_4,V_5,V_6. As per the title of this ECG Review, the question is whether this represents a burst of VT. Our answer is probably not. Instead, we suspect that the underlying rhythm of atrial fibrillation continues throughout with the period of QRS widening being due to LBBB aberration. Factors in favor of this include: 1) the rhythm during the run maintains the same irregularity as the underlying atrial fibrillation; 2) the wide tachycardia starts and stops without disturbing the underlying rhythm (VT often manifests a post-ectopic pause); and 3) the QRS morphology in the three key leads (I,V_1,V_6) is consistent with LBBB.

We acknowledge that we cannot be sure this is not VT. That said, the key to management is to slow the rate. Regardless of the true etiology, the wide tachycardia will probably resolve once the heart rate slows. ■

In Future Issues:

Body Mass Index and Mortality

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.*

Tiotropium for Uncontrolled Asthma

In this issue: Tiotropium for uncontrolled asthma, sibutramine pulled from market, incidence and mortality data from WHI, FDA Actions.

Tiotropium for uncontrolled asthma

Tiotropium, a long-acting anticholinergic inhaler, is approved for treatment of chronic obstructive pulmonary disease. A new study suggests that it may also be effective for patients with asthma.

In a study of 210 adults with asthma with inadequate control with inhaled glucocorticoids, tiotropium was compared to doubling the dose of glucocorticoids, and was also compared to the addition of salmeterol, a long-acting beta agonist (LABA). Tiotropium was superior to doubling the dose of inhaled glucocorticoid as assessed by measuring the morning peak expiratory flow (PEF) ($P < 0.001$). It also improved evening PEF, asthma control days, and FEV1, as well as daily symptom scores. The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and was superior to salmeterol in measures of prebronchodilator FEV1 ($P = 0.003$).

The authors conclude that tiotropium is superior to doubling the dose of glucocorticoid in patients with inadequately controlled asthma, and is equivalent to the addition of salmeterol in the same patient group (published online *N Engl J Med* Sept. 19, 2010). This study is important because it may result in options for patients with poorly controlled asthma beyond adding a LABA. Recently, asthma experts and the FDA have questioned the safety of LABA therapy (FDA Drug Safety Communication June 2, 2010), and a recent meta-analysis suggests that use of LABAs without concomitant inhaled corticosteroids increase the risk for intubation or death (*Am J Med* 2010;123:322-328). ■

Sibutramine pulled from market

Abbott Laboratories announced in October that it is withdrawing the weight-loss drug sibutramine (Meridia®) from the market. The move comes a month after the FDA finished a review of the drug and found that patients with cardiovascular disease or diabetes given sibutramine had a significantly higher rate of serious cardiovascular events compared to placebo. The drug was originally approved in 1997. In a news release, the FDA states "physicians are advised to stop prescribing Meridia to their patients and patients should stop taking this medication." *The Wall Street Journal* reports that while Meridia may be off the market, sibutramine is still available illegally in many weight-loss nutritional supplements, most of which are available via the Internet from oversee suppliers. The supplements are marketed as "all-natural" and their labels list only herbal ingredients. The FDA recently advised consumers that Slimming Beauty Bitter Orange Slimming Capsules contains sibutramine, and last year published a list of more than 50 other supplements containing the banned drug. For complete list of supplements containing sibutramine go to: www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm136187.htm. ■

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Incidence and mortality data from WHI

In 2002, the Women's Health Initiative (WHI) study was stopped early after 5.6 years when data showed that combination estrogen and progesterone therapy increased the risk of breast cancer. Mortality data had never been reported from WHI, however, and other studies have suggested that hormone therapy-associated breast cancers might have a more favorable prognosis than other breast cancers. A new analysis of WHI data dispels that notion.

The current study is a follow-up study of more than 16,000 women enrolled in WHI who were randomized to conjugated equine estrogen 0.65 mg per day plus medroxyprogesterone 2.5 mg per day (Prempro®) or placebo. Participants were followed for an average of 11 years with the main outcome measure being breast cancer incidence and breast cancer mortality. Women on hormone therapy had a higher rate of breast cancer compared to women on placebo (0.42% vs 0.34% per year; hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.07-1.46; $P = 0.004$) and breast cancers in the hormone group were more likely to be node-positive (23.7% vs 16.2%; HR, 1.78; 95% CI, 1.23-2.58; $P = 0.03$). The death rate associated with breast cancer was higher in the hormone group (0.03% vs 0.01% per year; HR, 1.96; 95% CI, 1.00-4.04; $P = 0.049$), a finding that barely reached statistical significance because of the low number of cancers in either group.

The authors conclude that estrogen plus progesterone was associated with a higher breast cancer incidence, as well as cancers that were more commonly node-positive. Breast cancer mortality was also higher in the combined hormone group (*JAMA* 2010;304:1684-1692). An accompanying editorial points out that despite the borderline statistical significance of these findings it is likely that "the increase in breast cancer deaths due to hormone therapy has been underestimated in the current study." However, it is still unclear whether short courses of hormone therapy for relief of postmenopausal symptoms right after menopause may be safe and further research is needed "to determine whether lower doses or shorter durations of hormone therapy could alleviate menopausal symptoms without increasing cancer risk" (*JAMA* 2010;304:1719-1720). ■

FDA actions

The FDA has approved fingolimod, the first oral drug for the treatment of relapsing forms of multiple sclerosis. Fingolimod is a sphingosine 1-phosphate receptor modulator that is believed to reduce migration of lymphocytes into the central nervous system. Compared to interferon beta-1a, the annualized relapse rate was significantly lower with fingolimod. Patients need to be monitored for decreased heart rate and elevation of liver transaminases. Fingolimod is given as a once-daily 0.5 mg tablet. It is marketed by Novartis as Gilenya™.

As anticipated, the **FDA has approved dabigatran to prevent strokes and blood clots in patients with atrial fibrillation.** The drug is a direct thrombin inhibitor and is given orally twice a day. The approval was based on the RE-LY trial, which showed that dabigatran at 150 mg given twice a day was superior to warfarin for this indication. Unlike warfarin, dabigatran requires no monitoring. Dabigatran will be available in 75 mg and 150 mg capsules and will be marketed as Pradaxa® by Boehringer Ingelheim Pharmaceuticals.

The FDA has ordered a labeling change for bisphosphonates, warning of the risk of atypical femoral fractures. In March, the FDA announced an ongoing safety review of bisphosphonates and the occurrence of subtrochanteric and diaphyseal femoral fractures. The new warning is a result of that review and, while not acknowledging a direct link, the warning suggests that these fractures may be related to use of bisphosphonates for longer than 5 years. The agency further suggests that health care professionals consider periodic reevaluation of the need for continued bisphosphonate therapy in patients who have been on the drugs for more than 5 years. The labeling change will only affect bisphosphonates approved for osteoporosis, which include alendronate (Fosamax®), risedronate (Actonel®), ibandronate (Boniva®), and zoledronic acid (Reclast®).

The FDA has approved extended-release naltrexone to treat and prevent relapse of patients with opioid dependence who have undergone detoxification treatment. Extended-release naltrexone is administered by intramuscular injection once a month, and blocks opioid receptors in the brain. It was initially approved in 2006 to treat alcohol dependence. The drug is only approved for patients who have completed rehabilitation, otherwise it may trigger opioid withdrawal. The efficacy of naltrexone was shown in a 6-month placebo-controlled trial in which treated patients were more likely to stay in treatment and refrain from using illicit drugs. Extended-release naltrexone injection is marketed as Vivitrol® by Alkermes Inc. ■