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INSIDE

Protecting the Oldest of Old Bones

ABSTRACT & COMMENTARY

Synopsis: *Use of risedronate in women 80 years and older reduced the incidence of vertebral fractures and was well tolerated.*

Source: Boonen S, et al. *J Am Geriatr Soc*. 2004;52:1832-1839.

RISEDRONATE (ACTONEL®) IS A PYRIDINYL BISPHOSPHONATE, prescribed to treat low bone density. Its mechanism of action is inhibition of bone resorption, which it accomplishes by binding to the mineral surface of bone and reducing osteoclast activity. It decreases the incidence of vertebral and hip fractures in postmenopausal women. Boonen et al sought to answer the question, "Is risedronate safe and effective in women aged 80 years and older?"

By combining data from 3 studies of risedronate (the Vertebral Efficacy with Risedronate Therapy North America, the Vertebral Efficacy with Risedronate Therapy Multinational, and the Hip Intervention Program), Boonen and colleagues were able to amass 1392 women (688 in the placebo group, 702 in the risedronate group) who were 80 years or older (average age 83.0 years). The 2 groups were comparable at baseline. The 3 studies were randomized, double-blind, placebo-controlled conducted between 1993 and 1998. In all of the studies, patients were randomized to risedronate 5 mg daily or placebo. They also received calcium 1000 mg daily. Sixteen percent of patients received vitamin D 500 IU daily because their serum 25-hydroxy-vitamin D levels were low. They weren't allowed to continue any other medication they were receiving, except for other osteoporosis medications. After baseline assessment, the end points were any new vertebral fracture, any new nonvertebral fracture, bone turnover markers, bone mineral density (BMD), and adverse events.

After 1 year, the incidence of new vertebral fractures was 2.5% in the risedronate group and 10.9% in the placebo group, a statistically significant difference (number needed to treat [NNT] 12). At 3 years the rates were 18.2% and 24.6%, respectively, (NNT 16), again statistically significant. Similarly, the changes from baseline of bone turnover markers and

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BMD favored the risedronate group. The adverse event rate did not differ significantly between the 2 groups, including incidences of esophagitis and gastric and duodenal ulcer, even in patients who had preexisting gastrointestinal comorbidities or who were taking GI-active medications. At 3 years, there was no significant difference in the rate of new non-vertebral fractures (14% vs 16.2%).

COMMENT BY ALLAN J. WILKE, MD

This is very good news for our oldest old female patients, who comprise the most rapidly growing portion of the population. Women 80 years and older have a greatly increased prevalence of vertebral fractures, when compared to women in their 50s. Vertebral fractures carry with them pain, deformity, decreased lung function, and decreased mobility. It should be a no-brainer then, to treat them with risedronate (or probably, other bisphosphonates) because it is safe and effective. However, in the immortal words of Pogo, "We have met the enemy and he is us!" As previously reported by Andrade and reviewed in *Internal Medicine Alert*,[3] we do a particularly lousy job of treating women with osteoporosis, even after they suffer fractures. I am afraid that the therapeutic nihilism that we extend to the elderly will only make matters worse and result in many women going without treatment.

There are 2 findings from this paper that merit more attention. The first is that risedronate had an effect on fracture rate reduction during the first year. The second is that there was no improvement in non-vertebral fractures. Boonen and colleagues speculate that this may be because non-vertebral fractures in this group have less to do with BMD and more with increased rates of falls.

There are a few questions that this study does not answer. Is this a class effect? Do the results apply to alendronate (Fosamax®) and other bisphosphonates? Boonen and colleagues say, "We're not sure, but maybe not", but their caution may be related to the support the study received from the manufacturer of Actonel. What happens after 3 years? After all, a woman who is 80 today has a life expectancy of almost 10 years. Are there any long-term benefits or risks? Assuming for the moment that bisphosphonates share characteristics, we can look to a report about alendronate. Bone (how apropos is that?) and colleagues presented data on women whom they had followed for 10 years. They found that alendronate remains safe and effective even if taken for the entire follow-up period and that its bone-protective effects attenuate after discontinuation.

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VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

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Anticoagulating the Elderly With Atrial Fib: How Low Should You Go?

ABSTRACT & COMMENTARY

Synopsis: *Maintaining INRs (International normalized ratios) between 2 and 3 is safer than INRs below 2, as suggested by some guidelines.*

Source: Fang MC, et al. *Ann Intern Med.* 2004;141:745-752.

Atrial fibrillation is a common event in the older population. Intracranial hemorrhage is the most dangerous complication of warfarin therapy because of its high risk for death and severe neurological complications. However, fear of hemorrhage may prevent some physicians from prescribing anticoagulation. Recent guidelines recommend using lower intensity anticoagulation for the prevention of stroke in patients older than 75 years of age who have atrial fibrillation.[1] These guidelines recommend INRs of 1.6 to 2.5.

The objective of this study was to examine the relationship of age, anticoagulation intensity, and the risk of intracranial hemorrhage. It was a case-controlled study involving 170 case-patients who developed intracranial hemorrhage during warfarin therapy and 1020 matched controls who did not: Both case-patients and controls were taking warfarin for atrial fibrillation.

Fang et al performed statistical analysis to determine the odds of intracranial hemorrhage with regard to age and INRs, controlling for comorbid conditions and aspirin use.

Case patients were older than controls (median age, 78 years vs 75 years : $P < 0.001$) and had significantly higher INRs (2.7 vs 2.3). The risk of intracranial hemorrhage increased at 85 years of age or older, (odds ratio 2.5), and at an INR range of 3.5 to 3.9, (odds ratio 4.6). The risk for intracranial hemorrhage at INRs of less than 2 did not differ from INRs of 2 to 3.

Conclusion: The risk of intracranial hemorrhage increases at age 85. INR ratios of less than 2 were not associated with lower risk for intracranial hemorrhage compared to INRs in the 2 to 3 range. Therefore, anticoagulation should focus on maintaining INRs in the 2 to 3 range, even in older patients with atrial fibrillation. Similarly, INRs of 3.5 or greater should be avoided.

COMMENT BY RALPH R HALL, MD, FACP

Fang and colleagues note the limitations of this study. The case-controlled design may have resulted in a selection bias and, in contrast to controls, many of the case-patients were not followed in the same clinic, and differences in patient characteristics, anticoagulation management, and monitoring may have biased some of the risk estimates. Further, the difficulties in controlling aspirin intake data are always a problem in that patients may not accurately report the frequency or dose of aspirin. In this study it was reported that approximately 20% of the patients in each group took aspirin. Nevertheless, this is a compelling study and offers new guidelines in the management of atrial fibrillation in older patients.

It is of note that the contrasting guidelines for the management of older patients with atrial fibrillation by other organizations referenced by Fang and colleagues, is from the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee on Practice Guidelines. These guidelines were published in 2001.[1] It is hoped that these organizations will review this study and other new data and republish their guidelines soon.

It goes without saying that one of the most important aspects of managing anticoagulation is the precise education and monitoring of the patients.

References

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Fecal DNA vs Fecal Occult Blood For Colorectal Cancer Screening in an Average Risk Population

ABSTRACT & COMMENTARY

Synopsis: *Most neoplastic lesions are not detected either by Hemoccult screening or by multitarget analysis of fecal DNA. Nevertheless, the fecal DNA analysis was significantly more efficient than Hemoccult testing.*

Source: Imperiale TF, et al. *N Engl J Med.* 2004; 351;26:2704-2714.

Colorectal cancer is a serious health problem, comprising the second leading cause of cancer death in adults, and over 55,000 deaths from colon cancer were anticipated in 2004. Despite strong recommendations, Imperiale et al state that less than 40% of the

population undergoes colorectal cancer screening. Guaiac-based detection of occult blood is known to be an effective screening modality that reduces cancer incidence and risk of death. Nevertheless, even annual fecal occult blood testing detects only 25-50% of colon cancers and less than 10% of colon adenomas (known precursors of most colon cancers). Frequent false positive occult blood results also occur. Recent advances in the understanding of the molecular genetics of colon cancer have led to the discovery of multiple DNA markers associated with colonic neoplasia. Since exfoliated epithelial cells from cancers and adenomas will be contained in feces, the concept of fecal DNA testing has great theoretical appeal. The current study involved 81 study sites. All these participating average risk subjects provided stool samples for DNA abnormalities (21 different targets) and also performed Hemoccult II™ tests prior to colonoscopy (done without knowledge of fecal DNA test results). Four thousand four hundred and four subjects were evaluable. Fecal DNA testing detected 16 of 31 invasive cancers vs 4 identified with Hemoccult testing (56% vs 12.9%). Thirteen cancers were found by DNA testing that had been missed by Hemoccult, and 1 cancer identified by Hemoccult testing had been missed by fecal DNA testing. Adenomas with dysplastic features were also detected more often by DNA testing (32.5% vs 15%). Specificities of tests were 92.4% for fecal DNA testing vs 95.2% for Hemoccult (ie, negative findings in patients who had normal colonoscopies).

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

Although the sensitivity of the panel of fecal DNA markers was 4 times that of Hemoccult II for invasive cancer and twice as sensitive for adenomas with high grade dysplasia with no loss of specificity, this approach to colorectal cancer screening is still not ready for prime time use. As pointed out in an accompanying editorial, this test has a number of significant drawbacks. Previous data from Ahlquist et al[1] indicated 90% sensitivity of fecal DNA testing for cancer and 82% for advanced adenomatous polyps. These somewhat better results may relate to the rate of cancer and advanced adenomas in the respective populations studied. There is no doubt that physicians and their patients need a dependable, inexpensive, and culturally acceptable technique for colorectal cancer screening. It isn't here yet. Virtual colonoscopy continues to provoke interest, but it remains far less accurate than colonoscopy and too expensive and unacceptably uncomfortable. Dr. Woolf points out that the fecal DNA data indicate sensitivity far lower than conventional colonoscopy (perhaps less efficient screening than flexible sigmoidoscopy).[2] Low prevalence of colorectal cancer in asymptomatic individuals (240 cases/100,000 individuals 50 to 59 years of age) means that colorectal cancer will be diagnosed in only 2% of adults who have a positive fecal DNA test. The remaining 98% may remain terrified that the positive screening test indicates cancer that somehow was missed at colonoscopy. Fecal occult blood testing costs somewhere between $6000 and $18,000 per year of life gained. Use of the fecal DNA panel for screening would be at least 200 times more expensive. For some time to come, it will be hard to beat old fashioned expensive sedated colonoscopy as the best available test for screening and therapy that may avert cancer development altogether.

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Atenolol For Hypertension

ABSTRACT & COMMENTARY

Synopsis: *Atenolol is unsuitable as a first-line drug in hypertension.*

Source: Carlberg B, et al. Atenolol in Hypertension: Is It a Wise Choice? *Lancet.* 2004;364:1684-1689.

ATENOLOL IS WIDELY USED AS A FIRST-LINE THERAPY for hypertension because it is beta 1 selective and it has low lipophilicity, which should result in fewer central nervous system side effects. However, recent studies have questioned its effectiveness. Thus, Carlberg and colleagues reviewed available randomized, controlled trials of atenolol in hypertension that evaluated morbidity and mortality. They identified 4 studies that compared atenolol to placebo or no treatment, and 5 that compared it to other drugs. The 4 placebo controlled trials encompassing 6825 patients followed for a mean of 4.6 years showed major differences in blood pressure, as expected by no difference in outcome vs placebo: all cause mortality RR = 1.01; cardiovascular mortality .99; and myocardial infarction .99. The risk of

stroke showed a trend downward on atenolol (RR, 0.85; CI, .72-1.01). In the 5 drug comparison trials encompassing 17,671 patients followed for 4.6 years on average, atenolol was equally effective at lowering blood pressure, but demonstrated a higher mortality (RR, 1.3; CI, 1.02-1.25) and more strokes (RR, 1.3; CI, 1.12-1.50), as compared to other non-beta blocker drugs. Carlberg et al concluded that atenolol is unsuitable as a first-line drug in hypertension.

COMMENT BY MICHAEL H. CRAWFORD, MD

These provocative results cast doubt on the use of atenolol as a first-line antihypertensive agent. What could explain these findings? Atenolol is less lipophilic. Animal studies have shown that the amount of beta-blocker in the central nervous system correlates with anti-ventricular fibrillation effects. Studies of metoprolol, propranolol, and timolol, which are more lipophilic, have shown reductions in mortality. Also, atenolol is beta 1 selective, but so is metropolol and others. In addition, the effects of atenolol on left ventricular hypertrophy have not been characterized. Finally, atenolol does not improve endothelial function in hypertensives.

There are some issues with this analysis. First, few trials have compared different beta blockers in hypertension. Those that used different beta blockers considered them as a group and did not break down the results with regards to the different beta blockers. So, this analysis compares results from studies using various beta blockers alone or versus other classes of antihypertensive agents, as well as studies where not all the patients were hypertensive, such as post myocardial infarction trials. Second, Carlberg et al are from Sweden, as is metoprolol. Perhaps there is some nationalistic bias here, since metoprolol is the only other beta 1 selective agent readily available in the United States. Third, atenolol is usually given once a day to be competitive with other agents, but its half life doesn't really support this dosing frequency. It should probably be given twice a day. Metoprolol, on the other hand, now comes in a sustained release form (Toprol XL), which permits once a day dosing despite its relatively short half life. Many comparison drug trials suffer from not using comparative doses or dosing strategies; comparing different studies compounds this problem even more.

Regardless of these concerns, the data are provocative. The fact that placebo controlled trials of atenolol for hypertension showed no mortality benefit is disturbing, since we have several other agents that have been shown to reduce mortality (eg, ACE inhibitors and angiotensin receptor blockers). Thus, Carlberg et al make a cogent point that perhaps atenolol should not be considered first line monotherapy for hypertension. ■

Micheal H. Crawford, MD is a Professor of Medicine and the Chief of Clinical Cardiology at the University of California, San Francisco.

Natalizumab Injection (Tysabri)

A NEW AGENT HAS RECEIVED EXPEDITED FDA approval for the treatment of relapsing multiple sclerosis (MS). Natalizumab is the first humanized monoclonal antibody to be approved for MS and is believed to work by inhibiting adhesion of molecules to the surface of immune cells, thus preventing these cells from migrating into the brain from the bloodstream. Natalizumab is manufactured by Biogen and marketed by Elan as Tysabri.

Indications

Natalizumab is indicated for the treatment of relapsing multiple sclerosis to reduce the frequency of clinical exacerbation.[1]

Dosage

The recommended dose is 300 mg by intravenous infusion, over 1 hour, every 4 weeks. The patient should be observed during infusion and 1 hour after completion for signs or symptoms of hypersensitivity-type reactions.[1]

Potential Advantages

Natalizumab has a different mechanism of action than existing drugs such as interferon beta-1a and 1b and glatiramer. Addition of natalizumab to interferon beta results in further reduction of exacerbations and reduces the number of lesions detected by MRI.[1]

Potential Disadvantages

Natalizumab requires intravenous infusion over 1 hour while other products can be given by subcutaneous or intramuscular injection. (Mitoxantrone also requires infusion, but is approved for advanced or chronic MS). Serious hypersensitivity reactions have been reported with natalizumab (< 1%). These generally occur within 2 hours of the start of infu-

sion and are characterized by urticaria, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain.[1] Patients should be observed for 2 hours after infusion of the drug. Natalizumab increases circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Other side effects include serious infections (2.1% vs 1.3% for placebo), fatigue (24% vs 18%), arthralgia (15% vs 11%), and irregular menstruation/dymenorrhea (7% vs 2%). Anti-natalizumab antibodies have been detected in about 10% of patients. These have been associated with reduction in serum natalizumab and infusion related reactions.[1] Long-term effectiveness and safety remains to be established.

Comments

Natalizumab is believed to bind to the 4-subunit, and 4 1 and 4 7 integrins expressed on the surface of all leukocytes except neutrophils.[1,2] Integrins on circulating leukocytes bind to vascular cell adhesion molecule that is expressed at high levels in the CNS during MS exacerbations.[3] Animal models indicate that the natalizumab reduces leukocyte migration into the brain, reducing MRI detected plaque formation.[1] The approval of natalizumab was based on 1-year analysis of 2 phase III, randomized controlled studies. One was a placebo-controlled monotherapy trial (AFFIRM) (n = 942) and the other an add-on study with interferon beta-1a (SENTINEL) (n = 1171). In monotherapy, natalizumab reduced the annualized relapse rate by 66% (0.25 vs 0.74) and resulted in fewer patients with MRI detected and gadolinium-enhancing lesions (60% vs 22% with no new or newly enlarging T2-hyperintense lesions and 96% and 68% with no gadolinium-enhancing). In contrast, in the SENTINEL study, natalizumab or placebo was added to interferon beta-1a in patients who had experienced one or more relapses on interferon beta-1a. Natalizumab reduced the annualized relapse rate by 54%, (0.36 vs 0.78) reduced the number of new or newly enlarging, T2 hyperintense lesions and gadolinium-enhancing lesions detected by MRI (no lesions in 67% vs 40%, 96% vs 76%).[1] The wholesale cost of natalizumab is $1808 per 4 weeks. This is 14-47% more expensive than interferon beta and glatiramer.[4]

Clinical Implications

Multiple sclerosis affects about 1 million individuals, and twice as many women as men. First symptoms generally occur between ages 20 and 40.[5] The clinical patterns of the disease include relapsing-remitting, secondary-progressive, primary-progressive, and progressing-relapsing.[6] None of the currently approved agents is a cure but all have proven partial success in reducing exacerbations and may slow the disease progression.[7] Switching monotherapy or combination therapy may be considered with breakthrough disease.[2] Interferon beta and glatiramer are generally first line monotherapy for relapsing remitting disease. Natalizumab provides an alternative agent to interferon beta and glatiramer with a different mechanism of action. Natalizumab has demonstrated efficacy when added-on to interferon beta-1a. The 2-year results of the AFFIRM and SENTINEL trials are expected in the first half of 2005.

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CME Questions

1. **Which of the following statements isn't true?**
   a. INRs of 2.6 to 2 are associated with less intracranial hemorrhage than INRs of 2 to 3 in patients with atrial fibrillation.
   b. INRs of greater than 3.5 should be avoided in older patients with atrial fibrillation.
   c. The risk of intracranial hemorrhage increased at 85 years old or older in this study.
   d. Previous guidelines recommended lower intensity anticoagulation for prevention of intracranial bleeding in patients with atrial fibrillation older than 75 years of age.

2. **Colorectal cancer screening can most dependably be accomplished by utilization of:**
   a. fecal occult blood testing
   b. virtual colonoscopy
   c. use of a multitarget fecal DNA panel
   d. conventional colonoscopy
   e. None of the above

Answers: 1. (a); 2. (d)

By Louis Kuritzky, MD

Thyroid Status, Disability and Cognitive Function, and Survival in Old Age

There is little disagreement about the merit of treating frank hypothyroidism. Because of conflicting data, much less consensus exists about whether subclinical hypothyroidism (ie, elevated TSH levels with normal T4) should be treated. Since thyroid disorders increase with age, a population of advanced years is an appropriate group in which to evaluate this issue further.

The Leiden 85-Plus Study is a prospective study of all individuals born in 1912-1914 living in Leiden, the Netherlands. Data was prospectively obtained from the entire population who agreed to be enrolled, without exclusions (n = 599), and these subjects were followed from age 85-89.

Outcome measures included cognitive function, degree of disability, depression, and overall mortality, each of which was assessed in relation to baseline and follow-up TSH and T4. The investigation uncovered 39 participants with previously undiagnosed overt hypothyroidism and 30 with undetected subclinical hypothyroidism. There were 2 new diagnoses of hyperthyroidism and 17 new diagnoses of subclinical hyperthyroidism (ie, decreased TSH with normal T4).

Thyroid status was not related to disability, depression, or cognitive function. However, the highest mortality was seen in those with a suppressed TSH level at baseline (subclinical hyperthyroidism). Somewhat surprisingly, subjects with elevations in TSH had the lowest mortality. Based upon these data, Gussekloo et al posit that thyroid replacement in subclinical hypothyroidism is unlikely to be beneficial; indeed, it could even be harmful. ■

Gussekloo J, et al. *JAMA.* 2004;292: 2591-2599.

Inflammatory Markers and the Risk of Coronary Heart Disease in Men and Women

Inflammatory markers have been consistently associated with coronary artery disease (CAD), the most thoroughly studied of which has been C-reactive protein (CRP). Since interleukin-6 (IL6) and tumor necrosis factor alpha (TNFa) are cytokines which induce CRP secretion, their status might also reflect CAD risk. TNFa is not as readily measurable as are its primary receptors, sTNF-R1 and sTNF-R2.

The Nurses Health Study (n = 121,700) and the Health Professionals Follow-up Study (n = 51,529) provided subjects who gave baseline blood samples, all of whom were free of known CAD at the time. Over approximately 8 years of follow-up, data from 515 men and women who had suffered an MI were compared with controls matched for age and smoking status.

Initial analysis indicated that increased levels of sTNF-R1 and sTNF-R2 were associated with CAD in women, but not men. However, after adjustment for other risk factors, only CRP remained a significant predictor of CAD. For instance, lower HDL levels were also associated with higher levels of inflammatory markers, and mitigated some of the predictive value of inflammatory markers. CRP remains a consistent predictor of CAD risk. ■

Pai JK, et al. *N Engl J Med*. 2004;351: 2599-2610.

Self-Measured Home BP in Predicting Ambulatory Hypertension

Ambulatory blood pressure monitoring (ABPM) provides the best metric of overall blood pressure burden. Several factors have compromised use of ABPM as a primary metric in managing hypertension (HTN): its cost, inconvenience, relative lesser availability, and less frequent incorporation in major clinical trials than simple office blood pressure. Home blood pressure (HBP) is increasingly recognized as a valued measurement, especially when OBP is suspected of reflecting white coat hypertension, or when ABPM is not available.

This study evaluated the threshold of HBP that would capture 80% of persons who, as demonstrated by ABPM BP >135/85, have borderline or stage 1 HTN. Subjects (n = 48) who had demonstrated at least 2 elevated BP readings in an office setting underwent ABPM and HBP.

As has been repeatedly demonstrated in other trials, HBP correlated better with ABPM than OBP. The threshold of HBP, at which 80% of persons with HTN (as defined by ABPM >135/85) would be detected, was determined to be 125/76. Persons with HBP > 135/85 are designated as hypertensive. Those with HBP < 125/76 are considered normotensive (regardless of OBP measurement), and those between 125/76-135/85, being indeterminate, merit consideration of ABPM to further refine their burden of blood pressure. ■

Mansoor GA, et al. *Am J Hypertens.* 2004;17:1017-1022.

Are P Waves "Married"?

By Ken Grauer, MD

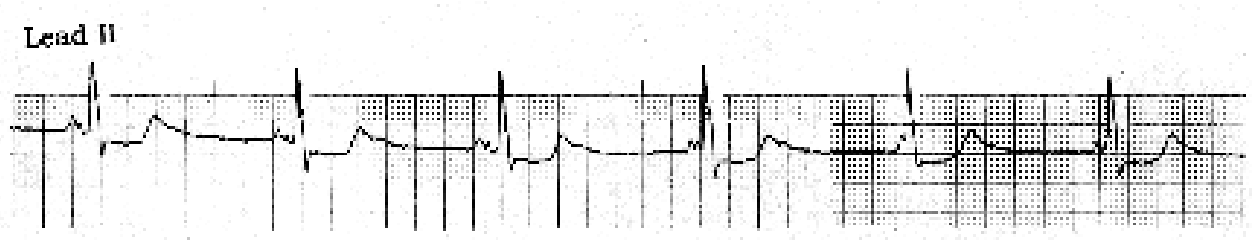

Figure. Rhythm strip from an elderly woman with cardiomyopathy and known bundle branch block.

Clinical Scenario: The Rhythm strip shown in the Figure was obtained from an elderly woman with a history of cardiomyopathy. She has a known history of bundle branch block (ie, RBBB). How would you interpret the rhythm?

Interpretation/Answer: The 5 key components of rhythm analysis are: i) Assessment of the presence and nature of arial activity; ii) determination if the QRS complex is wide or narrow; iii and iv) determination of rate and regularity; and v) looking to see if atrial activity is related to neighboring QRS complexes. Use of the saying, "Watch your P's and Q's, and the 3 R's" (rate, regularity, related) is an easy way to remember these 5 components.

In this example, P waves are present and precede each QRS complex. However, they are not related to neighboring QRS complexes, because the PR interval constantly changes (ie, P waves aren't "married" to the QRS). Not only is the PR interval too short to conduct, but it blends into the initial part of the QRS complex the latter part of the tracing. The atrial rate is variable. In contrast, the ventricular rate is regular, with an R-R interval of just over 7 large boxes in duration (corresponding to a ventricular rate of about 43/minute). The QRS complex is widened. Whether this reflects an AV nodal escape rhythm with the patient's chronic conduction defect (bundle branch block) pattern or a slightly accelerated ventricular escape rhythm is impossible to tell from this single rhythm strip.

Our interpretation of this rhythm is sinus bradycardia and arrhythmia, with resultant AV dissociation and QRS widening from either an AV nodal escape rhythm with bundle branch block or ventricular escape. The point to emphasize about this example of AV dissociation is that since P waves never have a chance to conduct at any point on this tracing. One cannot determine from this tracing alone if any degree of AV block is present. It could well be that if sinus node activity sped up, then normal AV conduction would resume. Or the patient could be in second or third degree AV block. ■

In Future Issues:

Abnormal Bleeding Risk with SSRIs

PHARMACOLOGY WATCH

Hypertension: Therapy vs Calcium Channel Antagonists

Pharmacotherapy of hypertension has been much in the news in the last 2 months. Standard therapies such as atenolol have been challenged, while calcium channel antagonists may be making a comeback.

Researchers from Sweden performed a meta-analysis of 9 randomized, controlled trials that looked at the effectiveness of atenolol on cardiovascular morbidity and mortality in patients with hypertension. Four of the studies compared atenolol with placebo or no treatment, and 5 studies compared atenolol with other antihypertensive drugs. Although atenolol was effective at lowering blood pressure, there were no outcome differences with regard to all cause mortality (RR 1.01; 95% CI, 0.89-1.15), cardiovascular mortality (RR 0.99; 95% CI, 0.83-1.18), or myocardial infarction (RR 0.99; 95% CI, 0.83-1.19), compared to placebo. The risk for stroke was lower with atenolol, compared to placebo (RR 0.85; 95% CI, 0.72-1.01). When compared with other antihypertensives, no difference in blood pressure lowering was noted between treatment groups, but the meta-analysis revealed a higher mortality with atenolol, compared with other treatments (RR 1.13; 95% CI, 1.02-1.25). This included a higher risk of cardiovascular mortality and stroke. The authors suggest that the results "cast doubts on atenolol as a suitable drug for hypertensive patients." They further postulate that atenolol's low lipophilic profile, which theoretically may reduce its ability to prevent cardiac arrhythmias, could be responsible for these findings (*Lancet.* 2004; 364: 1684-1689). Some have criticized the study because it did not include newer well-designed trials in which atenolol was used in combination with other drugs including diuretics. In these studies, including ALLHAT and SHEP, the addition of atenolol resulted in overwhelming benefit. In the meantime, use of atenolol as monotherapy needs to be reevaluated, however, addition of atenolol to an existing regimen will probably remain a part of most clinical guidelines.

GEMINI Trial

Speaking of beta-blockers, a new study suggests that carvedilol may be a better choice for diabetic patients than metoprolol. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial was designed to compare the effects of beta-blockers with different pharmacological profiles on glycemic and metabolic control in diabetic patients who were already receiving renin-angiotensin system (RAS) blockade with either a ACEI or ARB. Over 1200 patients with diabetes and hypertension were randomized in GEMINI. The main outcome was change in baseline HbA1c after 5 months of therapy. A difference was noted in mean change of HbA1c for baseline between the drugs (0.13%;95%CI -0.22%-0.4%. *P*=.004) The mean HbA1c increased with metoprolol (0.15% [0.04%]; *P* < .001), but not for carvedilol (0.02% [0 .04%]; *P* =

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Telephone: (404) 262-5416. E-mail: leslie.hamlin@ahcpub.com.

.65). Insulin sensitivity also improved with carvedilol but not with metoprolol, and progression to microalbuminuria was less frequent carvedilol than with metoprolol (6.4% vs 10.3%; *P* = .04). The drugs were used in equipotent doses to achieve similar blood pressure lowering effects. The authors conclude that the carvedilol, used in the presence of RAS blockade, does not effect glycemic control, and improves some components of metabolic syndrome relative to metoprolol in patients with diabetes and hypertension (*JAMA.* 2004;292:2227-2236). The study points out again that beta-blockers, with variable pharmacologic effects, may result in different clinical outcomes. Carvedilol is a nonselective beta antagonist, but has alpha 1 antagonist properties and mild vasodilatory properties.

CAMELOT Trial

The calcium channel antagonist amlodipine has beneficial cardiovascular effects in heart patients even if they have normal blood pressure according to new study. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared amlodipine 10 mg, enalapril 20 mg or placebo in patients with documented CAD and diatolic blood pressures < 100 mm Hg. The outcome measures were incidence of cardiovascular events and a second outcome was the use of intravascular ultrasound to measure atheroma volume. Nearly 2000 patients were followed over 24 months. New cardiovascular events (cardiovascular deaths, non-fatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina actors, hospitalization for congestive heart failure, fatal or non-fatal stroke or transient ischemic attack, or new diagnoses of peripheral vascular disease) occurred in 23.1% of placebo treated patients, 16.6% of amlodipine treated patients (HR 0.69; 95% CI, 0.54-0.88 [*P* = .003]) and 20.2% of enalapril treated patients (HR, 0.85; 95% CI, 0.67-1.07 [*P* = .16]). Plaque volume by ultrasound showed a trend towards less progression of atherosclerosis in the amlodipine group vs placebo (*P* = .12), with significantly less progression in the subgroup of patients with higher systolic blood pressures (*P* = .02). Compared with baseline atheroma volume progression in the placebo group (*P* < .001), the study showed a trend towards progression in the enalapril group, and no progression in the amlodipine group. The authors conclude that amlodipine reduced cardiovascular events and slowed progression of atherosclerosis in patients with CAD and normal blood pressure (*JAMA.* 2004;292:2217-2225). An accompanying editorial reviews the data and suggests mechanisms for the findings. More than any other factor, the editorialists suggest that lowering blood pressure to a systolic in the 120 mm Hg range may be the most important factor of all in patients with CAD (*JAMA.* 2004;292:2271-2273).

INVEST Trial

The INVEST study suggests that verapamil is as effective as atenolol with regard to benefit and side effects in diabetic patients with hypertension (*Hypertension* 2004;44:614-615). The PEACE trial looked at patients with coronary disease and normal or slightly reduced left ventricular function to assess whether addition of an ACE inhibitor would convey benefit, and found no benefit for these patients (*N Engl J Med.* 2004; 351:2058-2068).

The Dangers of Vitamin E

And vitamin E? Don't expect it to prevent cardiovascular disease or cancer for that matter. As vitamin E doses increase, so does all cause mortality, according to a large meta-analysis. Nineteen trials, which included nearly 136,000 participants, were evaluated in the analysis, of which 11 tested high dose vitamin E (400 IU/d). The pooled all-cause mortality risk difference for the high-dosage vitamin E was 39 per 10,000 (95% CI, 3-74 per 10,000; *P* = .035). For doses less than 400 IU/d, the mortality risk difference was 16 per 10,000 (CI, -41 to 10 per 10,000; *P* > .2). A dose-response analysis revealed an increase in all cause mortality with vitamin E dosages > 150 IU/d. The authors suggest that an increased mortality with higher doses of vitamin E is biologically plausible. Low doses of vitamin E may have some antioxidant effects, but higher doses may be pro-oxidant, particularly to LDL cholesterol. High doses of vitamin E may also displace other fats soluble antioxidants, disrupting the natural balance of antioxidant systems. Vitamin E may also be a mild anticoagulant, which may explain the increased hemorrhagic stroke seen in some vitamin E trials. This study was felt important enough to warrant early release online, since many people worldwide take vitamin E supplements on a daily basis far in excess of 400 IU/d. The full study will be published in the January 2005 *Annals of Internal Medicine*.

FDA Actions

The FDA has approved a new biologic for the treatment of relapsing forms of multiple sclerosis. Natalizumab is a monoclonal antibody that is given intravenously once a month. It will be marketed by Biogen as Tysabi.