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INSIDE

Financial Disclosure:
Internal Medicine Alert's Editor, Stephen Brunton, MD, is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Endo, EXACT Sciences, and Astra-Zeneca, and serves on the speaker's bureau of McNeil, Sanofi-Aventis, and Ortho-McNeil. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

What is the Risk for Coronary Heart Disease in a Type 2 Diabetic Without Other Risk Factors?

ABSTRACT & COMMENTARY

By Ralph R. Hall, MD, FACP, FACSM

Emeritus Professor of Medicine University of Missouri-Kansas City School of Medicine

Dr. Hall is a consultant for Aventis.

Synopsis: *There is a wide variation in the rate of coronary heart disease (CHD) in diabetes, depending on the population and existing risk factors.*

Source: Howard BV, et al. Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. *Diabetes Care*. 2006;29: 391-397.

HOWARD AND COLLEAGUES STUDIED THE INFLUENCE OF SINGLE and multiple risk factors on the 10-year cumulative incidence of fatal and nonfatal CHD and cardiovascular disease (CVD) in diabetic and non-diabetic men and women, with and without baseline CHD or CVD in a population (n = 4549) with a high prevalence of diabetes.

In both sexes, diabetes increased the risk for CHD (hazard ratio, 1.99 and 2.93 for men and women respectively). Diabetic men and women had a 10-year cumulative incidence of CHD of 25.9 and 19.1%, respectively, compared with 57.4 and 58.4% for non-diabetic men and women with previous CHD. The pattern was similar when only fatal events were considered. Diabetic individuals with one or two risk factors had a 10-year cumulative incidence of CHD that was only 1.4 times higher than that of non-diabetic individuals (14%). However, the 10-year incidence of CHD in diabetic subjects with multiple risk factors was > 40%, and the incidence of fatal CHD was higher in these subjects than in non-diabetic subjects with previous CHD. Data for CVD showed similar patterns, as did separate analysis by sex.

These results and comparisons with other available data show wide variation in the rate of CHD in diabetes, depending on the population

VOLUME 28 • NUMBER 7 • APRIL 15, 2006 • PAGES 49-56

and existing risk factors. Most individuals had a 10-year cumulative incidence of > 20%, but only those individuals with multiple risk factors had a 10-year incidence of CHD that was equivalent to that of patients with CHD. The authors conclude that until more data are available, it may be prudent to consider targets based on the entire risk factor profile rather than just the presence of diabetes.

COMMENTARY

The authors note that there are concerns regarding the specific ethnic group, variation in care that diverse groups may receive, and the use of statins, ACE inhibitors, and aspirin during the time course of this study. Still the evidence is strong that hyperglycemia without other risk factors was not associated with an increased incidence of CVD.

Grundy, in his editorial discussion of this paper adds that this is true at least over a short period of time.[1] He also points out Alexander et al's report from the National Health and Nutrition Survey (NHANES) III who have concomitant metabolic syndrome (and thus multiple risk factors) have increased risk for major coronary events as compared with those without the syndrome.[2]

Eighty six percent of the patients with type 2 diabetes older than 50 years of age in the NHANES III had the metabolic syndrome.[3] Since the vast majority of patients with type 2 diabetes have multiple risk factors, the National Cholesterol Education Program Adult Panel III (ATP III) listed diabetes as a CHD equivalent. According to Grundy they have rejected the concept that risk adjustment should be carried out on each individual. Therefore "a diagnosis of cardiovascular disease triggers a full therapeutic response for secondary prevention."[1] A further justification for this approach is that having an elevated blood glucose may be associated with an increase in the number of risk factors in the future. ATP III set a goal of < 100 for LDL Cholesterol in these patients.

One paragraph in Grundy's editorial sums up the problem and the current solution. "In ATP III, CHD risk equivalent defines the risk of developing a major coronary event (myocardial infarction + coronary death) over 10 years of > 20%. The 20% risk was that of patients with stable angina who have not sustained a myocardial infarction. This risk is lower than for those who have a history of acute myocardial infarction which is about 26%."[1]

The cost-effective analysis by ATP III indicated that cholesterol-lowering drugs were very cost effective to a risk level of 20% or lower. Since the cost of lipid lowering drugs is rapidly declining, the cost effective level may fall below the risk level of 10%.

Not addressed by this study is the impact that a diabetic having 8 or more risk factors will have on Pay for Performance. Patients already on the edge of what they can afford may opt out of the recommendations their physicians make.[4] ■

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Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

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postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. *Diabetes Care*. 2005;28:2626-2632.

Warfarin: Blood-Thinner and Bone-Thinner?

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Residency Program Director, Associate Professor of Family Medicine, University of Alabama at Birmingham School of Medicine—Huntsville Regional Medical Campus

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

Synopsis: *Long-term use of warfarin is associated with an increase in osteoporotic fractures.*

Source: Gage BF, et al. Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. *Arch Intern Med*. 2006;166:241-246.

Bleeding is the most common adverse effect of warfarin use, but there are also reports linking it to osteoporosis and fractures in adults[1] and children.[2] Not all studies have confirmed this.[3] The National Registry of Atrial Fibrillation II is a data set that includes Medicare Part A claims records, Medicare Part B records, and hospital chart abstracts from across the United States. The data were collected from 1995 to 1999. Gage and colleagues performed a retrospective cohort study to examine the relationship of warfarin (WARF) use to osteoporotic fractures (OF). They selected a stratified random sample of Medicare patients who were hospitalized with atrial fibrillation (AF). They looked at patients who had sustained vertebral, wrist, hip, and closed rib fractures, which are often related to osteoporosis. They identified patients likely to be taking WARF by searching for claims for prothrombin time (PT) charges. These patients were stratified into those with at least 1 year of use (long term) and those with 90 to 364 days of use (short term). They used multiple PT charges as a surrogate for continued WARF use. After applying reasonable inclusion and exclusion criteria, they identified 4652 patients with long-term WARF use, 1905 with short-term use, and 8007 with no use in the last 3 years. The patients were, on average, age 79 years, predominantly white, and more than half female. Thiazide diuretics, loop diuretics, and β-blockers were the most commonly prescribed additional medications. Of the total 14,564 subjects, 1005 (6.9%) had an OF. The 30-day mortality after suffering a fracture was high, ranging from 24.8% for wrist fractures to 39.0% for hip fractures. Gage et al performed a logistic regression on the 13,881 subjects who survived more than 30 days after the index hospitalization. The odds ratio (OR) of having an OF was significantly increased for long-term WARF use (OR, 1.25; 95% CI, 1.06-1.48). This did not hold true for short-term use (OR, 1.03; 95% CI, 0.82--1.29). Other independent risk factors for fractures were increasing age, high fall risk, hyperthyroidism, neuropsychiatric disease, and alcoholism. Protective factors included black race, male gender, and b-blocker use. When WARF use by gender was examined there was a statistically significant risk for men (OR, 1.63; 95% CI, 1.26-2.10), but not for women (OR, 1.05; 95% CI, 0.88-1.26).

COMMENTARY

Does long-term WARF use place your patient at risk for OF? This is a retrospective, observational, cohort study, so no firm conclusions can be made. We will have to wait for a prospective, randomized, control trial of sufficient size before we can claim anything more than an association. However, increasing age, high fall risk, hyperthyroidism, and alcoholism are acknowledged risk factors for OF; and black race and male gender ameliorate the risk.[4-6] Previous studies (reviews published in *Internal Medicine Alert*[7,8]) have looked at the protective association of thiazide diuretic use and β-blocker use on OF. This study also supports the benefit of β-blocker use. The authors suggest that neuropsychiatric disease contributed to the increase in fractures through an increased risk of falls secondary to medication use.

The basic science behind the risk of fracture from WARF use is that it blocks the y-carboxylation of glutamic acid. Besides residing on clotting factors II, VII, IX, and X, glutamic acid residues are also found on osteocalcin and other bone matrix proteins. Blocking y-carboxylation results in decreased bone formation and increased bone resorption.

This study does raise some interesting questions. Why was the risk significant in men, but not in women? The authors speculate that other factors (most likely preexisting osteoporosis) had a greater influence on OF in women. Does WARF wreak its damage biochemically through y-carboxylation blockade, or do people taking WARF modify their diets in ways that are not bone-healthy? The authors wonder if by limiting their intake of leafy, green vegetables, a rich source of vitamin K

and folic acid, they are controlling fluctuations in their PT/INR at the expense of becoming folate-deficient. A folate-rich diet helps prevent hyperhomocysteinemia, which is also associated with OF.

Assuming for the moment that WARF causes osteoporosis, how can a physician use the information from this study to best treat his or her patients? Are there alternatives to WARF for the treatment of AF? A Cochrane Review[11] concluded that WARF is the best agent in patients with AF at average or greater risk of stroke, but that aspirin might be as useful in patients at low risk. Can the effects of WARF in osteoporosis be ameliorated? While there are no studies to address this issue, it would be prudent to monitor patients (especially males) taking WARF for osteoporosis with DXA scans and to promote general bone health measures, including calcium and vitamin C intake, smoking cessation, moderation in alcohol use, and physical exercise. Avoiding or discontinuing unnecessary psychotropic medication is always wise. Whether adding an antiresorptive agent (bisphosphonates, raloxifene, estrogen, or calcitonin) would be useful is a matter of speculation, but certainly worth considering. ■

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Stroke vs Stroke Mimics: Diagnosis at the Bedside

ABSTRACT & COMMENTARY

By Dana Leifer, MD

Associate Professor, Neurology, Weill Medical College of Cornell University

Dr. Leifer reports no financial relationship related to this field of study.

Synopsis: *This prospective study demonstrates that clinical features such as focal deficits, a clear time of onset, and absence of non-neurological signs distinguish a stroke diagnosis from other diagnoses at the bedside.*

Source: Hand PJ, et al. Distinguishing Between Stroke and Mimic at the Bedside: The Brain Attack Study. *Stroke*. 2006;37;769-775.

The availability of a growing number of therapeutic options for acute stroke patients makes rapid and reliable diagnosis of stroke at the bedside more important than ever. Modern technology, such as CT and MRI, can often diagnose stroke and rule out other conditions, but to avoid wasting time and resources, accurate diagnosis must be made efficiently by emergency medical personnel in the field and by physicians and nurses in the emergency room.

Hand and colleagues prospectively studied 336 consecutive patients with suspected stroke. Patients were identified by emergency room personnel as soon as possible after arrival and by review of admission registers from the emergency room, stroke unit, and neurology ward. Clinical evaluations were performed by neurology or internal medicine residents, and final diagnoses were determined by the consensus opinion of a panel of experts.

With 350 acute events in 336 patients, the final diagnosis was stroke in 241 cases and stroke mimic in 109, which included 44 episodes that were considered possible stroke or transient ischemic attack. Sixty-two of the stroke mimics were seen within 6 hours. This is an important group because it includes most patients eligible for intravenous thrombolysis or intra-arterial interventions. In this group, seizures accounted for 29% of the diagnoses, syncope in 14.5%, sepsis in 9.7%, toxic/metabolic changes in 9.7%, acute mononeuropathy in 6.5%, space-occupying lesions in 4.8%, acute confusion in 4.8%, vestibular dysfunction in 4.8%, dementia in 3.2%, and migraine in 3.2%. In patients presenting after 6

hours, seizures and syncope were less common and accounted for only 10.6% and 2.1% respectively, but sepsis and space-occupying lesions were more frequent, accounting for 17.0% and 14.9% respectively.

Univariate analysis demonstrated that patients with an uncertain time of onset, seizure at onset, loss of consciousness, non-neurologic symptoms, prior cognitive impairment, no lateralizing symptoms or signs, or signs not consistent with symptoms, were less likely to have a stroke. In contrast, an exact time of onset and any focal neurologic sign or symptom (speech difficulty, visual loss, focal weakness or numbness, upper limb ataxia, extensor plantar) predicted a diagnosis of stroke, as did presence of coronary or peripheral vascular disease and hypertension (SBP > 150, DBP > 90). More severe deficits as measured by the NIH stroke scale (NIHSS) were more likely to be associated with a stroke, as were patients whose syndrome could be classified as a total or partial anterior circulation stroke by the Oxfordshire classification system. Vertigo and leg ataxia were not significant predictors because they occurred frequently in vestibular dysfunction.

Multivariate analysis identified presence of non-neurologic abnormalities and prior cognitive impairment as factors independently predicting that a patient did not have a stroke. Exact time of onset, definite history of focal neurologic symptoms, any abnormal vascular findings (SBP > 150, atrial fibrillation, valvular disease, or absent peripheral pulses), any lateralizing signs, and definite classification by the Oxfordshire system all predicted that a patient had a stroke. The multivariate analysis also confirmed that chance of stroke increased as the NIHSS score increased. The most powerful predictors were definite history of focal neurologic symptoms and NIHSS greater than 10.

COMMENTARY

These results are important because they demonstrate that a few key features make the diagnosis of stroke likely. The results of the study suggest that initial evaluation of potential stroke patients should determine if there is an exact time of symptom onset, any definite history of focal neurologic symptoms, and any lateralizing signs. The key symptoms and signs are straightforward—speech difficulty, visual loss, focal weakness or numbness, arm ataxia. If such symptoms or signs are identified, this study suggests that it is appropriate to activate a rapid protocol for more thorough evaluation by imaging and more detailed clinical evaluation focused on reaching a definite diagnosis and starting treatment.

On the other hand, if focal signs and symptoms are absent or non-neurologic problems are present, diagnoses other than stroke should be considered, and these include potentially serious non-neurologic conditions such as sepsis, syncope, and toxic-metabolic disorders. Although these conclusions may seem obvious to neurologists who have experience with stroke, the study makes a significant contribution because it provides guidelines for non-specialists who may see a stroke patient first, and must recognize that a patient may be having a stroke. ■

Pharmacology Update

Ranolazine Extended-Release Tablets (Ranexa™)

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

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

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

THE FDA HAS APPROVED A NEW DRUG WITH A unique mechanism of action for the treatment of chronic angina. Ranolazine reduces the frequency of chest pains by reducing the demand for oxygen but does not have significant effect on heart rate or blood pressure. Ranolazine is marketed by CV Therapeutics Inc., as Ranexa™.

Indications

Ranolazine is indicated for the treatment of chronic angina in patients who have not achieved adequate response with standard antianginal agents. It should be used in combination with amlodipine, beta-blockers, or nitrates.[1]

Dosage

The recommended initial dose is 500 mg twice daily. It may be increased to 1000 mg twice daily based on clinical need. It may be taken without regard to meals and should be swallowed whole (ie, not chewed, crushed, or broken).[1]

Ranolazine is supplied as 500 mg extended-release tablets.

Potential Advantages

Ranolazine is the first antianginal drug with minimal hemodynamic effects. The addition of ranolazine to patients with symptomatic severe chronic angina on

standard doses of atenolol, amlodipine, or diltiazem provided additional antianginal relief.[1,2]

Potential Disadvantages

Ranolazine is less active in women than men.[1] It produces a dose and plasma concentration-related increase in the QTc interval and reduction in T wave amplitude. The effect is greater in patients with hepatic dysfunction. Most frequent adverse events are dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). Syncope has been reported in 0.7% of patients on the 2000 mg/day dose. In clinical studies, about 6% of patients discontinued treatment due to an adverse event compared to 3% treated with placebo. Potential inhibitors of CYP3A (eg, protease inhibitors, macrolide antibiotics, diltiazem, verapamil) should not be coadministered with ranolazine. Ranolazine and its metabolite are inhibitors of CYP3A and CYP2D6. Dosage adjustments may be needed in drugs metabolized by these isoenzymes. Ranolazine is also an inhibitor of P-gp and dose adjustments may be required with P-gp substrates (eg, digoxin). Concomitant use of agents that prolong QT interval is contraindicated. The absorption of ranolazine is highly variable due to extensive gut and liver metabolism.[1]

Comments

Ranolazine differs from currently available anti-angina agents. Its mechanism of action is believed to be partial inhibition of fatty acid oxidase resulting in facilitated carbohydrate oxidation. Since carbohydrate metabolism results in less oxygen requirement per ATP production the demand for oxygen is reduced.[3] Ranolazine does not have a significant effect on heart rate or blood pressure although blood pressure reduction has been reported in patients with severe renal dysfunction.[1] The approval of ranolazine was based on 2 clinical trials, ERICA (Efficacy of Ranolazine In Stable Angina) (n = 565) and CARISA (Combination Assessment of Ranolazine In Stable Angina) (n = 823). In both placebo-controlled studies ranolazine was added to patients on standard anti-angina medication, amlodipine in ERICA and atenolol, amlodipine, or diltiazem in CARISA. In ERICA, ranolazine (1000 mg twice daily) reduced the frequency of angina attacks (mean of 1/week) and nitroglycerine use (mean of 0.9 doses/week) compared to placebo at 6 weeks. In CARISA, similar reduction was seen (0.8 attacks per week for 750 mg twice daily and 1.2 for 1000 mg twice daily; 1 dose of nitroglycerine and 1.3 respectively).[1,2] In CARISA, ranolazine was also shown to increase time to angina, time to 1 mm ST depression, and exercise duration both at peak and trough drug levels. The time-to-event difference from placebo ranged from 20-30 seconds at trough and 26-41 seconds at peak levels. Ranolazine has also been reported to be effective as monotherapy although this is not an approved indication.[4] Ranolazine can increase QT interval but is otherwise well tolerated. No incidence of torsades de pointes was reported in CARISA. Ranolazine appears to be about ¼ as effective in women compared to men.[1] The wholesale cost for ranolazine ranges from $5.50 to $11.00 per day.

Clinical Implications

It is estimated that 6.8 million Americans are annually diagnosed with angina.[5] Many patients may continue to have symptoms after revascularization with PCI or CABG.[6,7] Ranolazine is the first new antianginal agent to be approved in over a decade and its non-hemodynamic profile differs from current agents. It is indicated for use as add-on to standard therapy. The role may best suited for male patients with lower blood pressure or heart rates. ■

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CME Questions

14. The association of long-term warfarin use and the risk of osteoporotic fractures:

a. is stronger in women than men.
b. may be explained by warfarin's promotion of β-carboxylation of glutamic acid.
c. holds for short-term use as well.
d. None of the above.

15. Which of the following statements is *false*?

a. The majority of type 2 diabetics over the age of 50 have the metabolic syndrome.
b. The Adult Treatment Panel III used the history of myocardial infarction to represent the 20% risk level.
c. The Adult Treatment Panel III used the presence of stable angina to represent the 20% risk level.

Answers: 14 (d); 15 (b)

Clinical Briefs

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

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Noninferiority and Randomized Trials

When one reviews the literature it is likely expected that the statistical analyses performed, the complexity of which is often beyond the ken of the practicing clinician, have been appropriately conducted and accurately reflect both the content and intent of the results. Unfortunately, sometimes this is not the case.

Noninferiority trials are usually designed to show that product B, which entered the therapeutic arena after product A, does not fall below a prespecified margin of efficacy compared to product A, in which case product B may be fairly described as "not inferior to product A." This is not the same as saying that product A and B are 'equivalent.' To make that statement, an equivalency trial must be performed, which demonstrates that the efficacy of product B is within prespecified boundaries above and below when compared to product A.

The authors reviewed 116 noninferiority trials and 36 equivalence trials from literature published between 2003-2004. Discouragingly, all but 33 trials had deficits in sample size or its calculation, utilization of confidence intervals, or *P* value calculation. When subjected to the authors' prespecified criteria for adequacy of study design that further included a requirement that authors justify the margins chosen to determine noninferiority, only 7 trials (4.6%) ultimately were fully satisfactory. Twelve percent of the 33 trials which satisfied overall quality concerns were considered 'highly misleading:' ie, equivalence or non-inferiority was claimed when results were insufficiently robust to do so. The authors suggest that their observations call for greater rigor and uniformity both in design and reporting of noninferiority or equivalence trials. ■

Henanff AL, et al. JAMA 2006;295: 1147-1151.

Thyroid Status, and Cardiovascular Risk

Concern has been raised that subtle perturbations of thyroid function might lead to adverse cardiovascular outcomes. Specifically, subclinical hyperthyroidism has had a reputation of being etiologically involved with a greater incidence of atrial fibrillation. To study the relationship between thyroid dysfunctions and cardiovascular outcomes, investigators from the Cardiovascular Health Study followed subjects (n = 3,233) for new onset atrial fibrillation, coronary heart disease, stroke, cardiovascular mortality, and all-cause mortality, looking for a relationship between thyroid status and outcomes.

Study subjects were comprised of mature, community-dwelling men and women (age > 65). Because one purpose of the study was to elucidate the impact of thyroid dysfunction that was not clinically apparent, subjects already on thyroid treatment at baseline were excluded from analysis. At baseline, 18% of subjects had a clinically occult abnormality of thyroid function, the most common of which was subclinical hypothyroidism (ie, normal T4 with elevated TSH).

Only 1.5% of individuals had subclinical hyperthyroidism (ie, TSH subnormal, with normal T3 and T4). However, the risk of developing atrial fibrillation over the study period was twice as great in persons with subclinical hyperthyroidism as in those without thyroid dysfunction. Similarly, the other thyroid dysfunctions (subclinical and overt hypothyroidism) were not associated with adverse CV outcomes.

Mid-life adults with subclinical hyperthyroidism are at increased risk of atrial fibrillation. ■

Cappola AR, et al. JAMA. 2006;295: 1033-1041.

Glucosamine, Chondroitin Sulfate, and Knee Osteoarthritis

Osteoarthritis (OA) is the most common chronic disabling condition in America. Because there are no disease-modifying drugs to treat OA, intervention relies upon symptomatic relief and improvement of function, which are usually concordant. NSAIDs and Coxibs (eg, celecoxib) have been a mainstay of therapy, but heightened awareness of the GI toxicity of traditional NSAIDs, coupled with publicity about cardiovascular risks of coxibs (ie, rofecoxib, valdecoxib) have tempered enthusiasm for their routine use.

Popular opinion, and a modest number of favorable clinical trials, have encouraged utilization of glucosamine and chondroitin for OA. Their apparent lack of toxicity, in the face of recent reappraisal of NSAID/coxib safety profiles, is additionally reassuring. Indeed, metaanalysis of existing trials has also been supportive. A single, large, randomized controlled trial was devised to help clarify uncertainties remaining after the metaanalysis indicated remaining methodologic uncertainties.

Subjects with knee OA (n = 1583) were randomized to glucosamine, chondroitin (or both), celecoxib, or placebo.

Neither glucosamine nor chondroitin, nor the combination was statistically superior to placebo in the overall analysis. In the subgroup with moderate-to--severe pain at baseline (22% of the total population), the combination of glucosamine and chondroitin was superior to placebo. That the overall population did not benefit from chondroitin or glucosamine, coupled with the fact that amongst responders, response time was quicker with celecoxib, suggests a secondary role, if any, for the glucosamine and chondroitin. ■

Clegg DO, et al. N Engl J Med. 2006;354:795-808.

A Not Completely Normal ECG

By Ken Grauer, MD

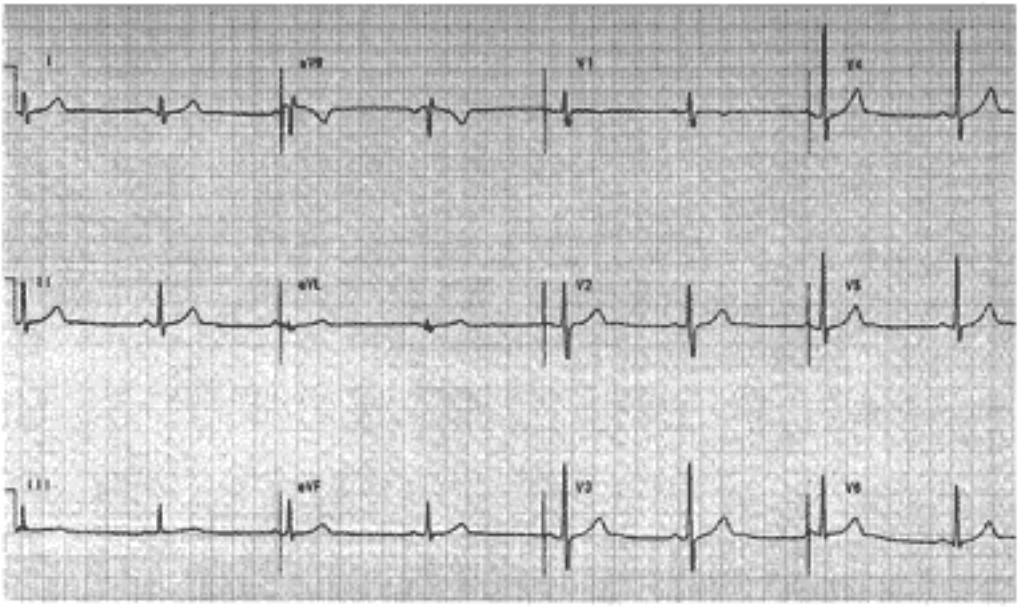

Figure. 12-lead ECG obtained from an otherwise healthy 32-year-old man with atypical chest pain.

Clinical Scenario: The 12-lead ECG in the Figure was obtained from a healthy 32 year old man who had some atypical chest pain. Although there are no ECG findings suggestive of acute ischemia, we disagree with the computer interpretation that said "sinus bradycardia but otherwise normal". Why?

Interpretation/Answer: The rhythm is sinus bradycardia and arrhythmia at a rate of about 50/minute. PR, QRS and QT intervals are normal. The mean QRS axis is + 70°. There is no ECG evidence of chamber enlargement. Regarding QRST changes, there are very small septal q waves in leads I, aVL, and V_6. ST-T waves are normal. S waves are present across the precordial leads (albeit the S wave is small in lead V_6). The most remarkable finding on this tracing is the relatively tall R wave in lead V_1. Normally the heart's electrical activity is oriented leftward and posteriorly in the transverse plane. As a result, the QRS complex in right-sided lead V_1 is usually either all negative (a QS complex), or almost all negative (a small amplitude positive r wave reflecting septal activation followed by a deep S wave). The finding of R = S in lead V_1 as seen in this tracing therefore represents a relative increase in right and/or anterior forces. Outside of the pediatric age group where this finding is common as a normal variant, the presence of an R wave that equals or exceeds S wave amplitude in lead V_1 should be recognized in adults as more likely to indicate some underlying abnormality. The following differential diagnosis is suggested: i) RBBB (right bundle branch block); ii) WPW (Wolff-Parkinson-White syndrome; iii) RVH (right ventricular hypertrophy); iv) posterior infarction; v) hypertrophic or other cardiomyopathy; or vi) normal variant in an otherwise healthy adult. Normal QRS duration and lack of delta waves rules out the first two possibilities in this example. RVH is unlikely in the absence of supportive findings such as RAE (right atrial enlargement), RAD (right axis deviation), right ventricular strain. Posterior infarction is unlikely in the absence of associated inferior infarction, especially in view of the benign history of this patient. Cardiomyopathies are usually associated with other ECG findings. By the process of elimination, this leaves "normal variant" as the most probable explanation for the relative increase of R wave amplitude in lead V_1. Careful physical examination is advised to ensure no abnormal cardiac findings. Consideration should be given to obtaining an echocardiogram to rule out occult structural cardiac abnormality. ■

PHARMACOLOGY WATCH

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

Can Calcium and Vitamin D Prevent Hip Fractures?

It has been a tough few months for marketers of vitamins and herbal products. Calcium plus vitamin D, saw palmetto, and glucosamine/chondroitin have all been the subject of studies that have questioned their efficacy. The calcium plus vitamin D results are possibly the most disappointing. In further data from the Women's Health Initiative study, 36,282 postmenopausal women ages 50 to 79 were randomly assigned to receive 1000 milligrams of elemental calcium with 400 IU of vitamin D3 or placebo, with the end point being prevention of hip and other fractures. After 7 years of follow-up, bone density was slightly higher, but there was no reduction in hip fractures in women who took calcium plus vitamin D (hazard ratio, 0.88 for hip fracture [95% CI, 0.72 to 1.08]). There was also no reduction in clinical spine fractures (HR, 0.90 [0.74 to 1.10]) or total fractures (HR, 0.96 [0.91 to 1.02]). Calcium plus vitamin D did result in a higher risk of kidney stones (HR, 1.17 [1.02 to 1.34]).

The authors conclude that among healthy postmenopausal women, calcium plus vitamin D supplementation did not significantly reduce hip fractures or reduce risks of kidney stones (*N Engl J Med*. 2006;354:669-683). In an accompanying editorial, Joel Finkelstein, MD, points out that many women who take calcium plus vitamin D "believe that they are completely protected against the development of osteoporosis. This study should help correct this important misconception and allow more women to receive optimal therapy for bone health." He also points out that women should not abandon calcium and vitamin D, neither should they rely on it alone as prevention against osteoporotic fractures (*N Engl J Med*. 2006;354:750-752 [correction published *N Engl J Med*. 2006;354:1102]).

Treatment of Benign Prostatic Hyperplasia

Saw palmetto is used by over 2 million men to treat symptoms of benign prostatic hyperplasia (BPH). Now, a new study suggests that it is ineffective. The study, funded by the National Institutes of Health and the National Center for Complementary and Alternative Medicine, looked at 225 men over the age of 49 with moderate-to-severe symptoms of BPH who were randomized to one year of saw palmetto extract 160 mg twice a day or placebo. The primary outcomes were changes in American Urological Association Symptom Index and maximal urinary flow rates. Prostate size, the residual urinary volume after voiding, quality of life, laboratory values, and adverse effects were also measured. After one year, there were no significant differences between patients treated with saw palmetto or placebo in any of the outcomes. There was also no difference in adverse effects. The authors conclude that saw palmetto does not improve symptoms or objective measures of BPH (*N Engl J Med*. 2006;354:557-566). An accompanying editorial welcomes the scientific rigor of placebo-controlled trials applied to dietary supplements, which are generally not held to standards of safety and efficacy. The authors call for similar studies for other

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commonly used herbal products (*N Engl J Med*. 2006;354:632-634).

Treatment of Osteoarthritis of the Knee

Glucosamine and chondroitin sulfate is used by millions to treat osteoarthritis. In another study supported by the NCCAM, along with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1583 patients with osteoarthritis of the knee were randomized to 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, combination of glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or placebo for 24 weeks. Acetaminophen was allowed as rescue analgesia. The primary outcome was a 20% decrease in the pain from baseline at week 24. Glucosamine and conference sulfate were no better than placebo in reducing the pain by 20%, except for combined therapy (glucosamine plus chondroitin) in patients with moderate-to-severe pain at baseline (79.2% response vs 54.3% response placebo, $P = 0.002$). Adverse events were no different in all groups. The authors conclude that overall glucosamine chondroitin did not reduce pain effectively in patients with osteoarthritis of the knee, except in the subgroup of patients with moderate-to-severe knee pain (*N Engl J Med*. 2006;354:795-808). An accompanying editorial recommends telling patients that neither glucosamine nor chondroid alone has been shown to be more effective than placebo in treating knee pain. They suggest that glucosamine sulfate plus chondroitin sulfate may be tried in patients with moderate-to-severe knee pain, but should be discontinued after 3 months if there is no benefit (*N Engl J Med*. 2006;354:858-860).

Refractory Asthma and TNF—Connection?

Refractory asthma is a condition with a high mortality rate and limited treatment options. A new study suggests that the tumor necrosis factor (TNF) axis is up-regulated in refractory asthma, creating the possibility of treating refractory asthma with TNF inhibitors. Researchers from the United Kingdom measured markers of TNF alpha activity in 10 patients with refractory asthma, 10 patients with mild/moderate asthma, and 10 controls subjects. Patients with refractory asthma increased expression of TNF alpha markers compared to those with mild-to-moderate asthma and controls. Study subjects with refractory asthma were subsequently randomized to receive the TNF alpha receptor etanercept 25 mg twice weekly in a placebo-controlled, double-blind, crossover pilot study. Ten weeks of treatment with etanercept was associated with a significant increase in concentration of methacholine required to provoke a 20% decrease in FEV1 ($P = 0.05$), an improvement in asthma related quality-of-life score ($P = 0$ .02), and a 0.32 liter increase in post bronchodilator FEV1 ($P = 0.01$) compared to placebo. The authors suggest that the TNF alpha axis is upregulated in refractory asthma, and that etanercept may be beneficial in these patients (*N Engl J Med*. 2006; 354:697-708). An accompanying editorial reports that several studies of TNF inhibitors in patients with refractory asthma are ongoing, suggesting that we soon should have an answer as to whether these agents are effective for treating this difficult clinical entity (*N Engl J Med*. 2006;354:754-758).

FDA Actions

The FDA has approved anidulafungin, Pfizer's new anti-fungal for the treatment of candidemia. The drug is a new molecular entity that is given intravenously. It is approved for a variety of Candida infections including esophagitis, sepsis, abdominal abscesses, and peritonitis. It will be marketed by Pfizer as Eraxis.

The FDA has approved lubiprostone for the treatment of chronic idiopathic constipation in adults. The drug is a selective chloride channel activator that increases intestinal fluid secretion and motility. The drug will be marketed by Sucampo Pharmaceuticals as Amitiza.

CV Therapeutics has received approval to market ranolazine, the first of a new class of agents for the treatment of chronic angina. The drug is an orally available extended-release anti-anginal drug that acts without reducing heart rate or blood pressure. The drug's mechanism of action has not been fully characterized, but it is felt that it works by affecting changes in cardiac metabolism. Because ranolazine prolongs QT interval, it should be reserved for patients who have not achieved adequate response with other anti-anginal drugs, and should be used in combinations with amlodipine, beta-blockers, or nitrates. CV Therapeutics will market ranolazine as Ranexa.

The FDA has approved an oral vaccine for the prevention of rotavirus gastroenteritis in infants and children. The oral vaccine should be initiated in infants 6 to 12 weeks old, with 2 subsequent doses of 4 to 10 week intervals. The vaccine should be completed before the child reaches 32 weeks of age. Based on clinical trials, the vaccine appears to be 98% effective for preventing gastritis caused by targeted rotavirus serotypes, and 74% effective at preventing gastroenteritis of any severity. Rotavirus vaccine will be marketed by Merck as RotaTeq. ■