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Omega-3 Free Fatty Acids for the Maintenance of Remission in Crohn's Disease

ABSTRACT & COMMENTARY

By Malcolm Robinson MD, FACP, FACG

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

Synopsis: Despite previous positive reports and much lay enthusiasm, omega-3 fatty acid treatment did not prevent Crohn's disease relapse. (Arguments continue as to whether the correct usage should be "Crohn disease" or "Crohn's disease." Most of the literature seems to use the latter designation, and this review will do likewise.)

Source: Feagan Brian, et al. *JAMA.* 2008;299:14:1690-1697.

Current Crohn's disease treatment with steroids, antimetabolites, methotrexate, and TNFa antagonists can help maintain remission, but their use is hazardous (including risk of infection). Omega-3 fatty acids are anti-inflammatory components of marine fish that have been used for treatment of such diseases as rheumatoid arthritis. However, use of omega-3 fatty acids in Crohn's disease has not been consistently effective. One trial suggested that such therapy could reduce recurrence of active disease by 33%, but another found no benefit vs placebo. To definitively determine the utility of omega-3 fatty acids in the prophylaxis of recurrent disease, two randomized double-blind placebo-controlled international studies were conducted between 2003 and 2007 in 98 centers. Ultimately, 377 patients with currently inactive Crohn's disease (but who had had an exacerbation within the past year) received 1 gram q.i.d. of omega-3 fatty acids and 376 got matching placebo for up to 58 weeks. CDAI Crohn's Disease Activity Index had to be < 150 at baseline. About half of the patients had been treated with a tapering course of prednisone or budesonide to attain "inactive disease" status prior to entry. The manufacturer of the omega-3 fatty acid preparation financed this large trial and continued to be involved in the

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design of the study and its interpretation although the distinguished group of investigators seemed primarily responsible. Trials were designed to detect a 15% reduction in relapse rate with 80% power at the .05 significance level. Various problems were encountered including the exclusion of one site that frequently violated the terms of the protocol. The bottom line for results is that there was absolutely no difference between the omega-3 fatty acids and placebo in preserving Crohn's disease remission in these patients regardless of patient subgroups. Adherence to therapy was acceptably high.

As expected from the known properties of the active study drug, serum triglycerides fell vs placebo. Adverse events were uncommon. Authors speculated that the earlier successful report had involved only patients with elevated acute phase reactants at baseline, and the current study might not have enrolled patients at sufficiently high risk of relapse. However, the large subgroup brought into remission with steroids prior to enrollment should have been at an overall high risk of recurrence, and they did no better than the other subgroup that may have been less at risk.

COMMENTARY

The authors of this manuscript commented on the wide use of alternative medicines such as omega-3 fatty acids (and many others) in inflammatory bowel disease patients. Furthermore, such usages are often taking place without the knowledge of treating physicians. Sadly, many patients are self-treating their inflammatory bowel disease with these unproved agents instead of medications that are of proven value for the acute and maintenance treatment of Crohn's disease and ulcerative colitis. We can conclude that omega-3 fatty acids are ineffective for the maintenance of remission in Crohn's disease. Perhaps even more important is the general principle that patients should be closely questioned about their possible use of herbal preparations and other forms of alternative therapy. Physicians should become aware of the literature in this area so they can speak with authority about the actual data that exists in this otherwise cloudy medical arena. ■

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Prevalence of Widespread Cognitive Impairments in the Elderly

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

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

Synopsis: *Cognitive impairment in the U.S. population without dementia is found in 22% of those over age 70. This is more than the number of those with Alzheimer's or other dementias alone, and needs to be recognized and addressed in our healthcare of this group.*

Source: Plassman BL, et al. Prevalence of cognitive impairment without dementia in the United States. *Ann Intern Med.* 2008;148:427-434.

This large population study of U.S. participants born before 1954 began in 1992 to investigate health, social, and economic implications of aging, collecting data from a sample of 22,000. A subset of 1770 individuals age 70 or older was identified to determine the national prevalence of dementia and other cognitive impairments, titled ADAMS (Aging, Demographics, and Memory Study). Partici-

pants were assessed by nurses and psychiatric technicians at their residence, and they completed a battery of neuropsychological measures. Blood pressure, lab testing and videotapes were also collected. Since self-reporting of these issues can be unreliable, proxies (usually spouses or adult children) also provided information. All this data was then analyzed by an expert consensus panel to determine the diagnosis in 2 stages, both with and without the medical records. In the majority of cases the diagnosis did not change with the addition of medical records.

ADAMS participants were divided within 3 general categories: normal cognitive function, dementia, and cognitive impairment without dementia. The latter is defined as mild cognitive or functional impairment that does not meet criteria for dementia, or performance on neuropsychological measures that was at least 1.5 standard deviations below published norms.

For the age group 71-79 years, 16% were found to have cognitive impairment without dementia, and 6% with prodromal Alzheimer's disease; this increased to 29% and 10% for the age group 80-89 years. At 90 years old and above, the prevalence for cognitive impairment without dementia was 40%, and 22% had prodromal Alzheimer's disease.

Of the 856 who completed initial assessments, 241 were selected for follow-up, and 180 completed a 16- to 18-month follow-up assessment. An annualized rate of 12% for progression to dementia was found, with a higher rate of 17-20% for prodromal Alzheimer and stroke groups. Of those who did progress to dementia, 83% had a diagnosis of Alzheimer disease and 17% had vascular dementia.

COMMENTARY

Based on the prevalence identified in this population study, the authors estimate that 22% (or 5.4 million individuals) of the U.S. population over age 70 have cognitive impairment without dementia. They further extrapolate a predicted progression to dementia of 12% per year, higher in those identified with a prodrome of Alzheimer's disease. By age 90 and above, fully 40% have cognitive impairment without dementia, and 22% have a prodrome of Alzheimer's disease.

These new figures are 70% higher than previous findings of frank dementia alone in 14% of this same population group.[1] Again, the numbers increase with age, from 5% of those aged 71-79 years, to 37% of those aged 90 and older having dementia. This data helps us understand the amount of impairment we can expect in our elderly patients, even before obvious dementia develops, and enables us to provide more evidence-based advice for families on what to expect when their elderly relatives exhibit early signs of cognitive impairments. ■

Reference

1. Plassman BL, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology.* 2007;29:125-132.

Increased Incidence of Pneumonia in Elderly Patients on Antipsychotics

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, Huntsville

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

Synopsis: *Current use of antipsychotic medications by the elderly places them at increased risk for hospitalization for pneumonia.*

Source: Knol W, et al. Antipsychotic Drug Use and Risk of Pneumonia in Elderly People. *J Am Geriatr Soc.* 2008;56:661-666.

Three years ago the US Food and Drug Administration (FDA) issued a "black box" warning about the use of atypical antipsychotics to treat behavioral disorders in elderly patients with dementia.[1] Various theories have been proposed to explain the morbidity and mortality associated with antipsychotics, including their anticholinergic and alpha-adrenergic properties. Their use is also associated with an increase in infections, though the mechanism is unclear. These investigators from the Netherlands conducted a nested case-control study using the PHARMO database to determine whether an association exists between use of antipsychotic medications and pneumonia. PHARMO has the pharmacy dispensing records of 950,000+ Dutch patients. The pharmacy records can be linked to hospital discharge records. The researchers selected a cohort of patients, at least 65 years old, with at least one prescription for an antipsychotic medication during the study period (April 1985 to December 2003). Within this group,

they looked at patients with a hospitalization for pneumonia. The index date was defined as the first hospital day. Each patient was paired with four controls (elderly patients without a pneumonia diagnosis). Patients were deemed to be current users of antipsychotic medication if a prescription for one had ended within seven days of the index date, recent past users if the use ended 8 to 30 days earlier than the index date, and past users if the use ended 31 to 365 days earlier. If the prescription was older than a year, the patient was determined to have no exposure.

Almost 23,000 patients received an antipsychotic drug prescription during the study period. Five hundred forty-three (543) patients were hospitalized with pneumonia, 65 of which were determined to be aspiration pneumonia. 2,163 controls were assigned to the cases. The median age of the cases and controls was approximately 81 years. More cases were male (60% vs 30%). Chronic obstructive pulmonary disease, heart failure, diabetes mellitus, Parkinson's disease, cerebrovascular disease, lung cancer, stomach cancer, and use of antibiotics, benzodiazepines, immunosuppressants, acid-suppressants, and drugs with potential extrapyramidal symptoms (all risk factors for pneumonia) were present more commonly in cases than controls. Unexposed cases and controls were the reference groups. Among the 543 cases with pneumonia, fully 243 (45%) were current users of antipsychotic drugs. Only 30% of controls were current users. No difference was seen in recent past or past users. When the researchers looked at duration of drug use in current users, they found a 4.5-fold increase in risk of pneumonia during the first week of use. After 90 days of use, risk returned to baseline. Among the 243 cases of current use of antipsychotic medication, 37 patients were using atypical antipsychotics. They were more likely to develop pneumonia than the cases who were using conventional antipsychotics (adjusted odds ratio 3.1 versus 1.5). Because the number of patients using the atypical antipsychotics was small, the 95% Confidence Interval was broad (1.9-5.1).

COMMENTARY

The authors speculate as to the mechanism whereby antipsychotic drugs increase the risk of pneumonia in the elderly. They list decreased cough reflex, dysphagia, dyskinesia, xerostomia, sedation, and immune system dysfunction as possibilities. A previously published study found no increased risk of mortality from pneumonia in patients taking atypical antipsychotics, however, there was an increased risk with conventional antipsychotics.[2]

The indications for use of antipsychotic drugs in the elderly are no different than in other patients: schizophrenia, bipolar disorder, acute mania, and acute agitation. However, we are seeing increased use, especially of atypical antipsychotics, in patients with dementia and "behaviors."This is disturbing, because these medications are associated with greater morbidity and mortality.[3,4,5] As the medical director of a long-term care facility, I am frequently on the receiving end of pleas such as, "Dr. Wilke, Mr. Smith in Room 8 is yelling out again. Isn't there anything you can give him?" I've heard Mr. Smith, and there is a real temptation to comply with the nursing staff's request. The unspoken request is that I sedate Mr. Smith. Is sedation in his best interest or that of the staff? When I remind the staff of this, I am rejoined, "Well, how about for just a short while?" While this is appealing, even short-term use can result in serious events, including hospitalization and death.[6]

Are the atypical antipsychotics inherently more dangerous than conventional ones? It depends on through whose lens you're viewing. If you are a gastroenterologist, you could point to a recent study that suggests that conventional antipsychotics are associated with a greater risk of hospitalization for acute pancreatitis than atypical ones.[7] From an orthopedist's point of view, atypical antipsychotics with a high degree of somnolence (olanzapine [Zyprexa®] and quetiapine [Seroquel®]) may lead to unintended injury.[8] All antipsychotic medications appear to increase the risk of hospitalization for femur fracture. My advice is to use antipsychotic medications sparingly in the demented elderly and only when they are indicated (dementia with psychosis). And when Mr. Smith yells out, search for other reasons for his behavior (undertreated pain, for instance). ■

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Pharmacology Update

Regadenoson Injection (Lexiscan™)

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

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 relationship to this field of study.

Regadenoson, the first selective A2A adenosine receptor agonist, has been approved for use as a pharmacologic stress agent for nuclear medicine stress testing (radionuclide myocardial perfusion imaging). Currently available pharmacologic stress agents include adenosine and dipyridamole, which are FDA approved for this indication, and dobutamine which is used off label. Regadenoson injection was developed by CV Therapeutics and will be marketed by Astellas Pharma US Inc as "Lexiscan."

Indications

Regadenoson is indicated as a pharmacologic stress agent for radionuclide myocardial perfusion imaging in patients unable to undergo adequate exercise stress.[1]

Dosage

The recommended dose is 0.4 mg (5 ml) by rapid intravenous injection to be followed by saline flush and radiopharmaceutical.[1]

Regadenoson is supplied as single-use vial and syringes containing 0.4 mg/5 ml.

Potential Advantages

Regadenoson appears to be associated with less flushing, chest pain, and dyspnea compared to adenosine.[1,2,3] It can be administered by a rapid intravenous injection compared to continuous infusion required for adenosine and dipyridamole.

Potential Disadvantages

Headache and increase in heart rate (>100 bpm) appears more likely with regadenoson compared to adenosine.[1] As with adenosine, the labeling contains warnings/precautions regarding SA and AV nodal block, hypotension, and bronchoconstriction. Similar to adenosine, it should be used with caution in patients with asthma or COPD and resuscitative measures should be available. It also has potential drug-drug interactions with methylxanthine (eg, caffeine) and dipyridamole.[1]

Comments

Regadenoson is an A2A selective adenosine receptor agonist that produces coronary vasodilation and increases coronary blood flow. This selectivity may reduce the potential for AV nodal block and bronchospasm. The efficacy and safety of regadenoson and adenosine were compared in two randomized, double-blind studies (n = 2015) with known or suspected coronary artery disease in whom pharmacologic stress myocardial perfusion imaging was indicated.[1,2] Each patient received an initial scan with a radionuclide gated single photon emission computer tomography (SPECT) protocol with adenosine and was then randomized to regadenoson or adenosine for a second scan with the same protocol. The primary endpoint was the agreement rate between agents. In the first study the agreement rates (± SE) were 61 ± 3 % for adenosine and adenosine and 62 ± 2% for adenosine and regadenoson. For the second study, the rates were 64 ± 4% and 63 ± 3% respectively. Generally, increase in heart rate was greater with regadenoson but symptom scores of flushing, chest pain, and dyspnea was less compared to adenosine.[2] The cost of regadenoson was not available at the time of this review.

Clinical Implications

Currently available pharmacologic stress agents

approved are adenosine and dipyridamole. A large number of studies indicate that these agents have high sensitivity (approximately 90%) for detecting coronary heart disease.[4] Regadenoson offers some potential advantages in terms of administration (rapid intravenous injection vs. infusion). It has a longer half-life (2-4 minutes) than adenosine (5 seconds) but shorter than dipyridamole (40-60 minutes). Whether the reater A2A selectivity becomes a real clinical advantage remains to be established. ■

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CME Questions

24. Omega-3 fatty acids had the following effect on the maintenance of remission in inactive Crohn's disease that had been active within the past year:

a. Omega-3 fatty acids were reproducibly better than placebo
b. Omega-3 fatty acids and placebo were indistinguishable in preserving remission.
c. Omega-3 fatty acids prevented relapse only in the subgroup of patients recently treated with steroid preparations.
d. Omega-3 fatty acids only seemed effective if elevated acute phase reactants such as C-reactive protein were present
e. Omega-3 fatty acids seemed differentially superior in patients with Crohn's colitis vs. those with isolated small bowel disease.

25. Which of the following represent the largest cognitively impaired group in the U.S. population over the age of 70 years?

a. impaired cognition with dementia
b. impaired cognition from Alzheimer's Disease
c. impaired cognition without dementia
d. impaired cognition from vascular disease

26. Which elderly patients taking antipsychotic medications are at greatest risk for pneumonia?

a. past users
b. recent past users
c. current users who have been on the medication for less than a week
d. current users who have been on the medication for more than 90 days

Answers: 24 (b); 25 (c) 26 (c)

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

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.

Diagnosis of Pulmonary Embolism by Multidetector CT

BECAUSE THE CONSEQUENCE OF missed pulmonary embolism (PEM) is so grave, it is essential to continue our evolution of tools which maximize diagnostic sensitivity, offer clinical expedience, and minimize risk for the patient. Recently, the combination of clinical probability assessment (CPA) with d-dimer, venous compression ultrasound (v-US), and helical CT has enjoyed advocacy, but multislice CT (MSCT) provides even better vascular visualization down to the level of segmental and subsegmental vessels.

Righini, et al compared a strategy of d-dimer plus either MSCT alone or d-dimer plus MSCT and v-US in a study population (n = 1,819) all of whom had undergone clinical probability assessment because of suspicion of PEM.

The frequency of PEM confirmation was the same in both groups: 20.6%. During a 3-month follow-up of persons who had screened negative for PE, the incidence of documented episodes of thromboembolism was 0.3% in both groups.

These data suggest that the combination of d-dimer with MSCT is as effective as a diagnostic plan incorporating v-US to both confirm the diagnosis of PEM and effectively exclude those without it. ■

Eighini M, et al. Lancet. 2008;371:1343-1352.

The Impact of Medicare Part D on Medication Nonadherence Among Seniors

ONE OF THE GOALS OF THE Medicare Prescription Drug Improvement and Modernization Act of 2003 (MPD) was to provide more universal coverage for essential medications for senior citizens and the disabled. Because of the expense of medications and consistency of polypharmacy among seniors, medication behaviors such as dose-skipping, dose reduction, or frank medication omission occur all too often.

Prior to MPD as many as 38% of Medicare beneficiaries did not have a source of prescription coverage, but that number has now been reduced to about 10%. Did the MPD reduce cost-related medication nonadherence?

To determine the answer, a representative sample of Medicare enrollees (n = 15,700) responded to questions addressing cost-related nonadherence such as "did you skip doses/take smaller doses of medicine to make it last longer." Because behaviors such as skimping on food, heat, or other basic needs to afford medicine has also been commonly seen in the past, these behaviors were also addressed on questionnaires.

Since MPD, spending less on basic needs decreased from 10.6% to 7.6%. There was also a 15% reduction in cost-related nonadherence overall. Unfortunately, the least healthy individuals (rated as fair to poor health) did not demonstrate the same reductions.

MPD has benefitted Medicare beneficiaries overall. The sickest beneficiaries still experience unabated cost-related nonadherence behaviors. ■

Madden JM, et al. JAMA. 2008;299(16):1922-1928.

Liberty, Justice, and Hypertension Treatment for ALL

THE BENEFITS OF TREATMENT OF hypertension (HTN) include meaningful reductions in stroke, MI, CHF, and overall mortality. Typically, HTN treatment trials enroll adults from middle-aged and early geriatric groups, without a large representation of advanced seniors (> age 80). The gap in knowledge about advanced seniors has been closed by HYVET (Hypertension in the Very Elderly Trial).

A large population (n=3,845) of advanced senior subjects (mean age =83.6) was randomized to indapamide or placebo for 2 years. If BP was not controlled on indapamide monotherapy, perindopril was added (BP target = 150/80). The primary endpoint of the trial was fatal or nonfatal stroke.

Indapamide treatment reduced the primary endpoint by 30%. Additionally, treatment provided a 21% reduction in all-cause mortality and 64% reduction in heart failure (all statistically significant). Differences between placebo and active treatment became visible within as little as 12 months time. Remarkably, the frequency of serious adverse events was lower in the active treatment group than the placebo group. Even change in potassium, a well recognized adverse effect of thiazide diuretics, was not significantly more common in the indapamide treatment group than in the placebo group.

These data support that concept that advanced age should not be a limiting factor in the decision to treat hypertension ■

Beckett NS, et al. N Engl J Med. 2008;358:1887-1898.

What are the 5 Findings?

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.

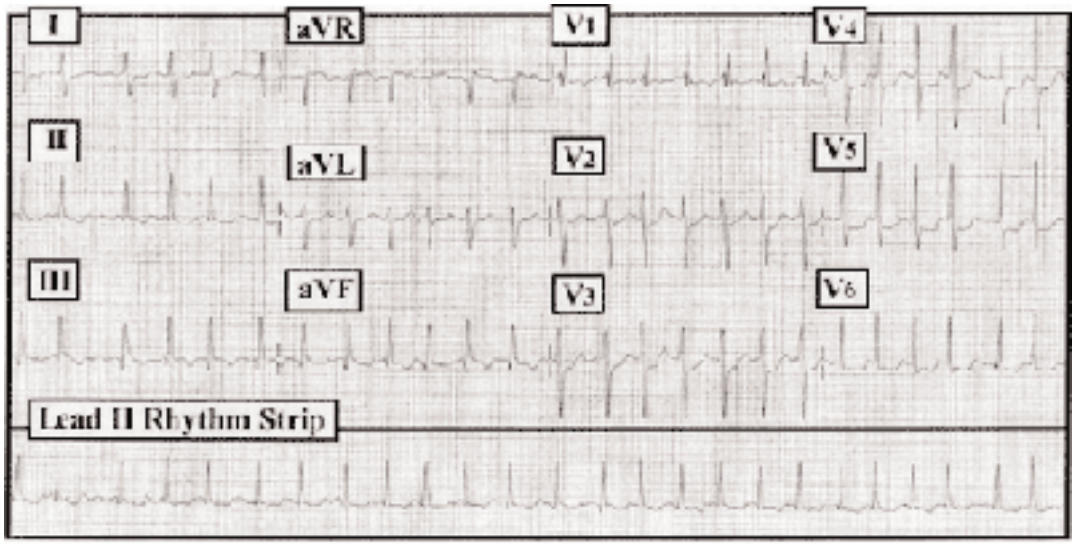

Figure: 12-lead ECG and lead II rhythm strip obtained from a 67-year-old man with new-onset shortness of breath.

Clinical Scenario:

The 12-lead ECG and lead II rhythm strip in the Figure were obtained from a 67-year old man who presented with new-onset shortness of breath. No chest pain. How would you interpret his ECG if told that a previous tracing was "normal"? Can you identify 5 ECG findings that might impact on your diagnosis?

Interpretation/Answer:

Five important ECG findings that we identify on this tracing are:

1. Atrial fibrillation (A Fib) with a rapid ventricular response. This is presumably of new-onset given the patient's acute dyspnea.

2. IRBBB (incomplete right bundle branch block) with a tall positive deflection in lead V1. The typical morphology of RBBB is seen (rsR' in lead V1, and terminal S waves in lateral leads I and V6). However, since the QRS complex is not widened, this is an incomplete RBBB. In the context of new-onset rapid A Fib, acute dyspnea, and the surprisingly tall positive (R') component of the QRS complex in lead V1—the possibility of RVH (right ventricular hypertrophy) and/or pulmonary embolism should be considered.

3. Diffuse ST segment depression (in precordial leads V2 through V6). This could be due to ischemia, "strain," digitalis effect (if the patient was on this drug), hypokalemia/hypomagnesemia, rapid heart rate—and/or any combination of the above.

4. Small, but definitely present inferior q waves. We are told that this patient's previous ECG was normal, so these q waves could be new and indicative of inferior infarction of uncertain age.

5. Distortion of the baseline in the inferior leads. Given new-onset of this patient's symptoms and tachyarrhythmia that occur in the setting of diffuse precordial ST segment depression and possibly new inferior q waves, special attention should be directed at assessing the ST segment in the inferior leads. Baseline distortion from either artifact or "fib waves" makes it impossible to tell if the subtle ST elevation and T wave inversion seen in some of the QRS complexes in leads III and aVF is real. Serum troponins became positive in this patient, confirming that acute infarction did occur. ■

In Future Issues: **The Risks of Abdominal Obesity**

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.

New Study on Thiazolidinediones May Show Benefits

In this Issue: Pioglitazone and heart disease; ARBs manufacturers spend millions to show the non-inferiority of their products compared to less expensive, generic ACE inhibitors; some athletes turn to growth hormone because it is difficult to detect; FDA Actions

The thiazolidinediones rosiglitazone (Avandia) and pioglitazone (Actos) have taken their lumps in the last year, with evidence associating drugs with increased risks of heart failure. Rosiglitazone has also been associated with increased cardiovascular mortality, while evidence suggests that pioglitazone may actually improve cardiovascular outcomes. Now a new study compares pioglitazone with the sulfonylurea glimepiride measuring the progression of coronary atherosclerosis in patients with type 2 diabetes. A total of 543 patients with type 2 diabetes and coronary disease underwent coronary intravascular ultrasonography and were then randomized to receive glimepiride 1 to 4 mg daily or pioglitazone 15 to 45 mg daily for 18 months with titration to a maximum tolerated dosage. Intravascular ultrasonography was repeated in 360 patients at completion of the study. The primary endpoint was percent change in atheroma volume (PAV). Patients were also treated with standard therapy (statins, renin-angiotensin blockers, and aspirin). Glimepiride resulted in an increase in PAV of 0.73% (95% CI, 0.33%-1.12%) while pioglitazone decreased PAV by 0.16% (95% CI, -0.57% to 0.25%) (*P*=.002). Blood sugar control as measured by HbA1c was similar in both groups. Pioglitazone also resulted in increase in HDL cholesterol of 5.7 mg/dL compared to 0.9 mg/dL for glimepiride (P<.001), and pioglitazone lowered triglyceride levels an average of 16.3 mg/dL compared to an increase of 3.3 mg/dL with glimepiride (*P* <.001). Hypoglycemia was more common in the glimepiride group while edema, fractures, and decreased hemoglobin levels were more frequent in the pioglitazone group. The authors conclude that in patients with type 2 diabetes and coronary artery disease, pioglitazone slows progression of coronary atherosclerosis compared to glimepiride (*JAMA* 2008; 299: 1561-1573). An accompanying editorial points out that outcomes such as those found in the study may not translate to improving cardiovascular outcomes, however the results are consistent with a modest clinical benefit demonstrated in the PROACTIVE trial (*JAMA* 2008; 299:1603-1604).

ARBS effective as ACE?

Are angiotensin-receptor blockers (ARBs) as effective as angiotensin-converting-enzyme (ACE) inhibitors in reducing vascular events in high-risk patients? Manufacturers of ARBs have spend millions trying to show the non-inferiority of their products compared to the less expensive, generic ACE inhibitors. The current entry funded by Boehringer Ingelheim, the ONTARGET trial, com-

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pares their product telmisartan (Micardis) with the ACE inhibitor ramipril. In this large double-blind randomized trial of 25,000 patients with vascular disease or high risk diabetes, over 8500 patients received ramipril 10 mg per day, telmisartan 80 mg per day, or the combination of both drugs. The primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Mean blood pressure was slightly lower in the telmisartan and combination therapy group than in the ramipril group. After a median follow-up of 56 months, the primary outcome occurred in 16.5% of the ramipril group, 16.7% of the telmisartan group, and 16.3% of the combination group. The ramipril group had a higher incidence of cough and angioedema, while the telmisartan group had a higher rate of hypotensive episodes. The combination group had a higher risk of hypotensive episodes, syncope and renal dysfunction compared to the ramipril group. The authors conclude that valsartan was equivalent to ramipril in patients with vascular disease or high risk diabetes, and was associated with less angioedema. There was no benefit in the combination of the two drugs (*NEJM* 2008; 358: 1547-1559). An accompanying editorial points out the difficulty in interpreting non-inferiority trials. In this study telmisartan preserved 94% of the benefit of 10 mg of ramipril (95% CI, 85 to 105). It is also the fourth trial showing that combinations of ACE inhibitors and ARBs are of no value in reducing cardiovascular events compared to ACE inhibitors alone. The author concludes that the ARBs provide a similar benefit to prevent ACE inhibitor therapy; however "because ARBs are more costly than ACE inhibitors and have more side effects, their primary value is as an alternative for patients who cannot tolerate ACE inhibitors because of cough." (*NEJM.* 2008; 358:1615-1616).

Athletes and Growth Hormone

As testing for performance-enhancing drugs becomes more prevalent in sports, some athletes have turned to growth hormone because it is difficult to detect. Touted as an anabolic agent that improves athletic performance, the drug is also associated with significance side effects including diabetes, hepatitis, and acute renal failure. Recently a group from Stanford performed a meta-analysis of 44 articles describing 27 study samples in which 303 participants received growth hormone representing 13.3 person-years of treatment. Participants were average 27 years old with lean body mass and physically fit. Lean body mass increased with growth hormone compared to participants who did not receive it (increase 2.1 kg 20.1 kg [95% CI, 1.3 to 2.9 kg]), however strength and exercise capacity did not improve. Lactate levels during exercise were statistically significantly higher in two of three studies, and growth hormone treated participants experienced soft tissue edema and fatigue more often than those who did not receive it. The authors conclude that claims that growth hormones enhance physical performance are not supported by the scientific literature. The drug may increase body mass but it is does not improve strength, and it may worsen exercise capacity and adverse events (*Ann Int Med,* early online release 18 March 2008, print date 20 May 2000).

FDA Actions

Cefixime (Suprax), the only CDC recommended oral treatment for gonorrhea, is now available for the first time since 2002 in a 400 mg tablet. Wyeth Pharmaceuticals discontinued production of the drug when its patent expired. Now Lupin Pharmaceuticals has received FDA approval to market the 400 mg tablets. The company has been marketing the oral suspension since 2004. Cefixime 400 mg as a single dose is recommended treatment for all types of gonorrhea infections (urogenital, rectal, and pharyngeal).

The FDA has approved methylnaltrexone bromide (Relistor) for the treatment of opioid-induced constipation in patients with late stage, advanced illness who are receiving opiates on a continuous basis. The injectable medication is started on an every-other-day basis, then increased to once a day as needed.

The FDA has approved a new biologic, certolizumab (Cimzia) for the treatment of Crohn's disease. Certolizumab is a TNF blocker similar to other drugs used for this indication. The initial dose is one injection every two weeks for the first three injections, then decreasing to once every four weeks. Like other TNF blockers, certolizumab is associated with increased risk of serious infections, lymphomas, and other malignancies.

The FDA has investigated reports of increased depression in patients switched from Wellbutrin XL 300 mg to Teva's generic bupropion XL 300 mg (Budeprion). Nearly 80 patients of the thousands who were changed to the generic noted loss of antidepressant effect following the switch. The agency reevaluated bioequivalency studies and concluded that, although there are small differences in the kinetic profiles the two formulations they were within the establish boundaries of equivalents. They conclude that the generic is bioequivalent and therapeutically equivalent to the branded product. ■