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INSIDE

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Effects of High and Low Dose Atorvastatin on Major Cardiovascular Events in Patients with Stable Coronary Heart Disease

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

Synopsis: *Compared to patients over the age of 65 years who were receiving 10 mg of atorvastatin daily, the elderly patients who received 80 mg daily experienced significantly reduced major cardiovascular and coronary events and hospitalizations for congestive heart failure; however, it could not be determined whether the clinical benefit was related to the higher statin dose, the lower resultant LDL-cholesterol levels, or to both factors.*

Source: Wenger NK, et al. *Ann Int Med.* 2007;147:1-9.

Cardiovascular risk increases steadily with age and is associated with an increase in the burden of chronic cardiovascular disease (CVD) including coronary heart disease (CHD) and stroke.[1] Large, randomized, placebo-controlled clinical trials have produced statistically significant results which have clearly demonstrated that decreasing low-density lipoprotein (LDL) cholesterol levels with statin therapy will reduce the risk for CHD in older persons.[2-4] The recommendation of the National Cholesterol Education Program Adult Treatment Panel[5] in 2001 that persons older than 65 years of age should not be denied lipid lowering has been further strengthened by later publications[6-7] leading the National Cholesterol Education Program to conclude in 2004 that intensive LDL cholesterol-lowering therapy was justified in high-risk older persons with established CVD.[8] The American Heart Association and the American College of Cardiology guidelines quite recently supported the position that it was reasonable to reduce LDL cholesterol levels to 70 mg/dL or less in any patient with established CHD, including elderly patients even though they were under-represented in many of the clinical trials that were evaluated.[9-10]

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Wenger and her colleagues performed a secondary analysis of the results of the Treating to New Targets (TNT) study[11] evaluating data from that study regarding the efficacy and safety of high-dose atorvastatin treatment in patients 65 years of age or older.[12] In the double-blind TNT clinical trial, 3089 patients 65 years of age and older were randomly assigned to receive atorvastatin in either 10 or 80 mg/d dosage at 256 sites in 14 countries. The primary endpoint was the occurrence of a first major cardiovascular event (ie, death from CHD, nonfatal non procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke). The high-dose atorvastatin group was found to have a 2.3% absolute risk reduction for major cardiovascular events and a 19% reduction in relative risk compared to the low dose atorvastatin group. Mortality rates from CHD, nonfatal non-procedure-related myocardial infarction, and fatal or nonfatal stroke were all lower although the difference was not statistically significant for each individual component. The authors concluded that the analysis of the published TNT data suggested that additional clinical benefit could be achieved by treating older patients with CHD more aggressively by reducing LDL cholesterol levels to less than 100 mg/dL.

COMMENTARY

Secondary analyses and meta analyses of large randomized, placebo-controlled trials have clearly demonstrated that the cardiovascular benefits of statin therapy observed in older patients with CHD are similar to those benefits occurring in younger patients.[2-4,6,7,13] One major trial[7] which was conducted exclusively in older individuals (age 70-82 years) revealed a significant reduction in major cardiovascular events among patients who received statin therapy compared to those who received placebo, but it showed no reduction in risk for stroke although this finding may have been due to the relatively short duration of follow-up in that trial. Other studies have demonstrated the benefits of statin therapy compared with placebo in reducing the risk of stroke in older patients[3,6] and, interestingly enough, the Wenger analysis revealed that the rate of fatal and nonfatal stroke was lower in the 80 mg high-dose group than it was in the 10 mg low-dose atorvastatin group although the difference was not statistically significant.[12] The rate of liver function abnormalities was similar for both dosage groups as it was for both the younger and older groups of patients. The small increase in treatment-related adverse events and trial withdrawals in the 80 mg atorvastatin group was similar to what was observed to occur in the younger patient group and was consistent with what had previously been reported in statin trials.[2] Finally, it is important to note that it could not be determined whether the observed clinical benefit was related to the higher statin dose, to the lower resultant LDL-cholesterol levels, or to both factors and therefore, any benefits observed in patients receiving the higher dose conceivably may also have occurred in those patients who achieve low LDL cholesterol levels even with relatively low dose statin therapy.

In summary, intensive lipid lowering therapy using 80 mg of atorvastatin (compared to 10 mg) in patients over the age of 65 years significantly reduced major cardiovascular and coronary events and hospitalizations for congestive heart failure. Older patients who received the 80 mg dose reduced their risk for major cardiovascular events to about that of patients younger than 65 years treated with 10 mg of atorvastatin. As noted above, it could not be determined whether the clinical benefit was related to the higher statin dose, to the lower resultant LDL-cholesterol levels, or to both factors. However, these findings support the most recent ACC, AHA and National Cholesterol Education Program guideline recommendations[8] for high-risk older patients with established CHD; that is, LDL cholesterol levels should be reduced to 70 mg/dL or lower in all patients with established CHD.[9] ■

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Dietary Intake and Prognosis after Breast Cancer

ABSTRACT & COMMENTARY

By Eileen C. West, MD

Director of Primary Care, Women's Health, Clinical Assistant Professor of Internal Medicine, University of Oklahoma School of Medicine, Oklahoma City.

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

Synopsis: *Patients with early breast cancer did not have fewer recurrences of cancer or improved mortality after eating a diet rich in vegetables and fruit and low in fat.*

Source: Pierce JP, et al. *JAMA.* 2007;298(3):289-298.

Results of the Women's Healthy Eating and Living (WHEL) study were published in a recent issue of *JAMA*. In this multicenter, randomized controlled trial a total of 3088 women diagnosed with early-stage breast cancer (stage I-IIIa) within the previous four years were randomized to a diet rich in vegetables, fruit and fiber and low in fat, vs a regular diet. The two groups had no statistically significant differences in baseline demographics, tumor characteristics, dietary habits, or cancer treatment. The intervention group attended cooking classes, received 12 newsletters, and 18 telephone calls for counseling during the first year. The targets of the intervention group were on an intake of 5 vegetable servings plus 16 oz of vegetable juice, 3 fruit servings, 30 g of fiber and 15%-20% of calorie intake from fat. The control group was given print materials describing the "5-A-Day" dietary guidelines. The main outcome measures were invasive breast cancer event (recurrence or new primary) or death from any cause. After a mean of 7.3 years of follow-up, the authors found no differences in breast cancer events or all-cause mortality between women in the two groups.

Overall, the intervention group succeeded in eating 65% more vegetables, 25% more fruit, 30% more fiber, and 13% less fat than their colleagues ate in the comparison group, based on 24-hour telephone surveys. Investigators measured plasma carotenoid levels and confirmed the sustained change in dietary intake. In 7.3 years, 16.7% of the women in the intervention group developed an invasive breast cancer event, vs 16.9% in the comparison group. Similarly 10.1% of the women in the intervention group died, vs 10.3% in the comparison

group. These numbers did not reach statistical significance at any point.

COMMENTARY

Finding any lifestyle elements which can improve outcomes of breast cancer is a worthy endeavor. Intuitively, it seems that healthy eating can and should improve outcomes of cancer survivorship. There are an estimated 2.4 million breast cancer survivors in the United States alone. Several published studies focused on breast cancer show mixed results. It does appear that a previous trial, the WINS trial, had marginally positive results that were based on lower levels of total energy intake and actual weight loss. Neither of those elements were present in this study. It can be noted that there was less success in the current study at achieving significant reduction in fat calories, and less weight loss in the groups of this trial.

As the authors point out, the WHEL study results are not intended to be applied to primary cancer prevention. Additionally, women who had undergone or were scheduled to undergo chemotherapy were not included, and there were relatively few minority women enrolled in the study.

In summary, although some dietary factors may ultimately prove to be important in reducing the risk for breast cancer recurrence, relatively small changes in vegetable, fruit, and fat intake alone did not make much difference. ■

Retinol Rejuvenation

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

Synopsis: *Application of vitamin A to naturally aged skin reduced fine wrinkling.*

Source: Kafi R, et al. Improvement of naturally aged skin with vitamin A (retinol). *Arch Dermatol.* 2007;143:606-612.

Aged skin is more susceptible to shearing forces, because there is flattening of the rete ridges and subsequent loss of contact between the dermis and the epidermis. In the extracellular matrix, the quantity of protein, composed primarily of collagen, is decreased. This occurs through decreased production and increased catabolism. The collagen quality is degraded. There is also a decrease in dermal microcirculation. All of these factors contribute to poor or delayed wound healing and chronic ulceration. There is "naturally aged skin" (ie, skin that is generally shielded from the sun), and then there is photo-aged skin, where aging is accelerated. Compared to naturally aged skin, photo-aged skin has less procollagen. The fine wrinkling can be reversed with topical retinoids and laser resurfacing. Both treatments increase procollagen synthesis.

Kafi and colleagues at the University of Michigan Medical School Department of Dermatology hypothesized that similar therapy directed at naturally aged skin would increase its collagen content. Because laser resurfacing and the usually prescribed retinoids (retinoic acid and tazarotene) cause large wounds and irritation, respectively, when used on naturally aged skin, they decided to use all-trans-retinol, which is a retinoic acid precursor and known to cause less irritation. They enrolled 36 subjects, average age 87 years (range 80-96), 71% female, from two senior centers, excluding those who had used topical medication in the previous 2 weeks or, for women, hormonal therapy in the previous 6 months. Thirteen subjects did not complete the trial for a variety of reasons, but only 3 quit because of skin irritation. Each subject served as his/her own control. The subjects had 4-mm punch biopsies of both arms at baseline and at the end of the study. A 0.4% retinol lotion (mixed up by one of the investigators in his lab) was applied to the sun-protected, upper, inner arm; the vehicle lotion was applied to the other arm. Which arm received the active treatment was randomized. The subjects received treatment three times weekly for 24 weeks and were evaluated at 2, 4, 8, 16, and 24 weeks. The skin was examined by two blinded dermatologists (no jokes please!) for fine wrinkling, tactile roughness, and overall severity. These attributes were scored on a 10-point scale: 0, none; 1-3, mild; 4-6 moderate, 7-9 severe. At the beginning of the study, the fine wrinkling scores for treated and untreated arms averaged slightly more than 7. At the end of the study, the retinol-treated arms averaged 5.61; the untreated arms averaged 7.14. This was statistically significant. The other measures showed similar reductions. Mild adverse reactions (erythema, peeling, pruritis, dryness, burning/stinging) were noted by most participants. Staining for procollagen of the punch biopsies showed an increase in the retinol-treated arms.

COMMENTARY

This is a nice proof-of-concept trial, but it needs to

be repeated in a larger group, and then we'll need evidence that the treatment prevents skin tears and ulcers and improves healing. The dropout rate for skin irritation (8%) doesn't seem too high, but since aging skin is already susceptible to pruritis secondary to decreased sebum production ("xerosis"), this treatment won't be for everyone. Although skin injury prevention was the stated goal of this study, fine wrinkling was the primary outcome measure. Skin products containing retinol are already marketed as a cure for wrinkles. How much are you willing to pay to change fine wrinkling from severe to moderate? ■

Pharmacology Update

Temsirolimus Injection (Torisel™)

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

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

THE FDA HAS APPROVED THE FIRST MTOR INHIBITOR for the treatment of advance renal cancer. Temsirolimus is a more water soluble ester of sirolimus and the latter is the principal active metabolite. It is marketed by Wyeth Pharmaceuticals, Inc. as Torisel .

Indications

Temsirolimus is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma.[1]

Dosage

The recommended dose is 25 mg infused over 30-60 minutes once a week until disease progression or unacceptable toxicity. Due to the potential for hypersensitivity reactions, pre-treatment with an intravenous histamine-1 receptor antagonist (eg, diphenhydramine 25 to 50 mg) given approximately 30 minutes before the drug administration is recommended. Dosage adjustment or interruption of therapy is recommended if the absolute neutrophil count is less than 1,000 mm^3, platelet count less than 75,000/mm^3 or NCI Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or greater adverse reactions.[1]

Temsirolimus is supplied as a 25 mg/ml vial with a diluent vial.

Potential Advantages

Temsirolimus has been shown to be more effective than interferon alfa in improving overall survival.[1,2] Median overall survival times and progressive-free survival were longer for temsirolimus compared to interferon alfa. In addition there were fewer serious adverse events in those treated with temsirolimus compared to interferon alfa.

Potential Disadvantages

Common adverse events (30% or higher) include rash, peripheral edema, asthenia, mucositis, nausea, anorexia, anemia, thrombocytopenia, neutropenia, hypophosphatemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, and elevated AST, serum creatinine, and alkaline phosphatase.[1,2] Serious adverse events include interstitial lung disease, bowel perforation, renal failure, and intracerebral hemorrhage in patients with CNS tumors. Due to risk of abnormal healing, perioperative use of temsirolimus should be undertaken with caution. Strong CYP3A4/5 inducers and inhibitors of CYP3A4 may affect the plasma concentration of the metabolite of temsirolimus.[1]

Comments

Both temsirolimus and its principle metabolite, sirolimus, are inhibitors of the mammalian target of rapamycin (mTOR) kinase. The drugs are believed to act by binding to an intracellular protein (FKBP-12) that interferes with mTOR signaling, resulting in inhibition of cell growth and angiogenesis.[3] Temsirolimus' efficacy was shown in an international, phase III, clinical trial of 626 patients with previously untreated, poor-prognosis metastatic renal-cell carcinoma.[1,2] Subjects were randomized to temsirolimus (25 mg weekly), interferon alfa (3 million units three times weekly up to 18 million units three times weekly), or a combination of interferon (6 million units three times a week) and temsirolimus (15 mg weekly). Overall survival was the primary endpoint and progression free survival and overall response rate were the secondary endpoints. Median overall survivals were 10.9 months, 7.9 months, and 8.4 months respectively. The hazard ratio was 0.73 (95% CI; 0.58 to 0.92) compared to interferon alone. Combination therapy offered no benefit and may be related to greater frequency of dose delays and reductions due to higher frequency of grade 3 or 4 adverse events.[2] Median progression-free survival was 5.5 months for temsirolimus com-

pared to 3.1 months for interferon (hazard ratio, 0.66 [0.53, 0.81]). Overall response rates (8.6% and 4.8%) were not statistically different. Adverse events can be problematic as 66% of patients required one or more delays and 23% required one or more dose reductions. The cost of temsirolimus is $1441 per dose.

Clinical Implications

There are an estimated 51,190 new cases of renal cell carcinoma annually with 12,850 deaths.[4] Surgical resection is the mainstay of therapy. Pharmacologic treatment (eg, interleukin-2 and interferon alfa) has resulted in limited success particularly in more advanced disease. Temsirolimus has demonstrated moderate efficacy in patients with at least three of the six predictors of short survival—serum lactate dehydrogenase level of more than 1.5 times the upper limit of normal, hemoglobin level below the lower limit of the normal range, corrected serum calcium level of more than 10 mg/dL, time from initial diagnosis to randomization of less than 1 year, Karnofsky performance score of 60 or 70, or metastases in multiple organs. Typically these patients have a median survival of 4 to 8 months. Comparative studies with other small molecules such as sunitinib and sorafenib are needed as well as the efficacy of temsirolimus in less extensive disease. Combination use with sunitinib has resulted in dose-limiting toxicity. The role of temsirolimus needs to be defined with further study. The mTOR pathway is a potential treatment option for other cancers such as non-Hodgkin's lymphoma, breast cancer, and glioblastoma multiforme. ■

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CME Questions

39. The reduced incidence of major cardiovascular and coronary events and hospitalizations for congestive heart failure in patients over 65 years of age receiving high-dose (80 mg) of atorvastatin daily is due to:
a. the high statin dose.
b. the lower LDL-cholesterol resulting from the high statin dose.
c. the combination of the high atorvastatin dose and the resultant low LDL-cholesterol.
d. uncertain reasons.

40. What factor has NOT been shown to reduce breast cancer recurrence rates?
a. Reduced exposure to sex steroid hormones
b. Lumpectomy and radiation
c. High-vegetable and fruit, low fat diet
d. chemotherapy

41. Choose the incorrect answer. Applying retinol lotion to the inner arms of octogenarians:
a. reduced fine wrinkling.
b. reduced procollagen content.
c. reduced tactile roughness.
d. increased skin irritation.

Answers: 39 (d); 40 (c); 41 (b)

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.

Rosiglitazone and CV Risk

THE RECENT INDICATION IN AN article by Nissen, et al (*N Engl J Med.* 2007;356:2457-2471) that rosiglitazone (ROSI) might actually increase cardiovascular (CV) risk was met with surprise and dismay by many clinicians and their patients alike. Even though subsequent commentary on the newly-identified risk profile suggested that such conclusions should be considered "preliminary," because CV disease is the predominant cause of death in diabetics—in disproportion to the general population—providers continue to experience consternation.

In an attempt to provide clarification, Home, et al provide data from the RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes), which although not yet completed, offers almost 4 years of followup on over 4,000 diabetics.

In RECORD, subjects not achieving adequate control of diabetes on either metformin or sulfonylurea monotherapy were assigned to combine the two (n = 2,227), or add ROSI (n = 2,220). The primary endpoint of the trial is hospitalization or death from any cause.

In this interim analysis, there was no statistically significant difference between the groups for CV mortality, MI, or all-cause mortality. The safety monitoring board of this trial, fully cognizant of the Nissen publication, did not feel that, based upon these prospective data, there is any safety concern sufficient to stop the trial. More conclusive information will be available at close of trial. ■

Home PD, et al. N Engl J Med. 2007;357:28-38.

Aldosteronism is a Frequent Cause of Resistant Hypertension in Diabetics

HYPERTENSION (HTN) IS SUBSTANtially more common in diabetics than in the general population. This is of particular concern since cardiovascular disease is also disproportionately the cause of death in persons with diabetes. Most diabetics have essential hypertension, but it is reasonable to suspect that resistant hypertension (defined as BP >140/90 despite at least 3 antihypertensive agents) in this population is sometimes caused by primary hyperaldosteronism (PHA). This report provides details about the prevalence of PHA in diabetics with resistant HTN.

The study population was comprised of diabetics with resistant HTN, who were allowed to continue their medications during the study. Persons already receiving aldosterone antagonists (ie, aldosterone, eplerenone) were excluded from the trial.

Screening lab data included a plasma aldosterone-to-renin ratio, which if abnormal, was followed by a salt loading test. PHA was considered confirmed if the 24-hr urine aldosterone on day 3 of salt loading was > 12 mcg, or if plasma aldosterone was > 5 ng/dL after a 4-hr IV saline load.

Ultimately, 14% of diabetics with resistant HTN were confirmed to have PHA. The authors suggest that screening for PHA is appropriate in the specific group of diabetics with resistant HTN. ■

Umpierrez GE, et al. Diabetes Care. 2007;30(7):1699-1703.

Hydroxychloroquine is Associated with Less Diabetes in RA

ALTHOUGH RHEUMATOID ARTHRITIS (RA) immediately prompts consideration of joint disease and subsequent disabilities, lesser recognized is that persons with RA also suffer a disproportionate burden of cardiovascular disease. OF course, when a patient with RA develops diabetes, their CV risk is greatly magnified.

The antimalarials, of which hydroxychloroquine (HCQ) is an example, have been shown to improve insulin sensitivity and enhance insulin secretion. Indeed, hypoglycemia is a recognized adverse effect of antimalarials. Recently, a cluster of trials with medication, diet, and exercise have indicated that diabetes may be prevented by pharmacotherapies such as metformin, thiazolidinediones, and acarbose. The purpose of this publication by Wasko, et al was to compare the incidence of new onset diabetes in RA patients treated with HCQ (n = 1,808) vs those on other regimens (n = 3,097) over an observation period of 21 years.

The incidence of new onset diabetes was 5.2/1000 patient-years in persons who received HCQ, compared to 8.9/1000 patient-years in the comparison group ($p = < 0.001$). Longer HCQ use was associated with greater risk reductions. Although newer disease-modifying therapies for RA provide excellent therapeutic results, this advantage of hydroxychloroquine may prove to be very attractive for persons identified as high-risk for diabetes. ■

Wasko MCM, et al. JAMA. 2007;298(2):187-193.

A Sensation in the Chest

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.

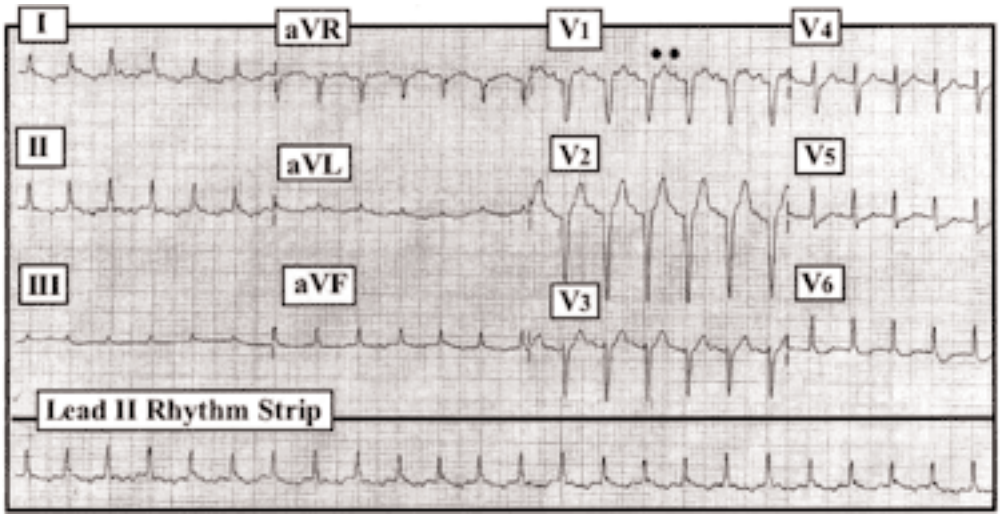

Figure. 12-lead ECG obtained from a 59-year-old man who was admitted to the hospital for chest discomfort.

Clinical Scenario: The ECG in the Figure was obtained from a 59-year old man with hypertension. He was admitted to the hospital to rule out acute infarction because of an "unpleasant sensation" in his chest. He was hemodynamically stable, and in no distress at the time this initial tracing was done. Comments?

Interpretation/Answer: There is a regular, narrow-complex tachycardia at a rate of approximately 150 beats/minute. Atrial activity seems to be present, although it is difficult to determine the nature of the atrial activity that is seen. No clear upright P wave is seen in lead II. This should make one suspect that the rhythm is not sinus tachycardia. After lead II, the next best lead to look at when assessing the nature of atrial activity is usually lead V1 (which anatomically lies just above the atria). Two little dots that we have drawn in this lead suggest that there is underlying atrial activity that occurs at a regular but very rapid rate.

It is helpful to keep in mind the differential diagnosis of a regular SVT (supraventricular tachycardia). Three entities make up over 90% of this differential: i) Sinus tachycardia; ii) Atrial flutter; and iii) PSVT (paroxysmal supraventricular tachycardia). Although other entities (such as junctional tachycardia) are possible, they occur much less often, especially when the heart rate exceeds 130/minute. In this particular case, sinus tachycardia is unlikely because no clear upright P wave is seen in lead II. Since the most common atrial rate of untreated flutter is 300/minute (250-350/minute range), atrial flutter with 2:1 AV conduction should always be suspected as a possible cause whenever a regular SVT is seen at a rate of close to 150/minute, especially in the absence of well defined P waves. In this case, application of a vagal maneuver slowed AV conduction enough to confirm the presence of underlying flutter activity at a rate of close to 300/minute. There is no ECG evidence on the tracing of acute infarction (and troponins were negative). The patient's chest pain resolved once he converted back to normal sinus rhythm. ■

In Future Issues: **The Role of Surgery in Gastroesophageal Reflux Disease**

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.

SSRIs Associated With Low Rate of Birth Defects, Studies Show

In this issue: *SSRIs are safer in pregnancy than previously thought; Estrogen therapy in younger women may be of benefit in preventing cardiovascular disease; Warfarin is substantially better than antiplatelet therapy in preventing stroke in patients with atrial fibrillation; The FDA tightens regulations regarding dietary supplements, Lyrica is approved for treatment of fibromyalgia.*

SSRIs are associated with a low rate of birth defects according to 2 new studies in the *New England Journal of Medicine*. SSRIs are often taken by women in their childbearing years, but the risk of birth defects has been unclear. Paroxetine (Paxil) specifically has been associated with omphalocele and heart defects, but there is little data on the risk of other SSRIs. In the first study from Boston University and Harvard, researchers assessed the association between first-trimester maternal use of SSRI and birth defects among nearly 10,000 infants with and over 5,800 infants without birth defects who participated in the Sloan Epidemiology Center Birth Defects Study. Use of SSRIs was not associated with significantly increased risk of craniosynostosis (odds ratio 0.8), omphalocele (odds ratio 1.4), or heart defects overall (odds ratio 1.2). Analysis of specific SSRIs and specific deficits showed significant associations between use of sertraline (Zoloft) and omphalocele (odds ratio 5.7) and septal defects (odds ratio 2.0) and between use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio 3.3). There were no significant associations with other defects with other SSRIs or non-SSRI antidepressants. In the other study, researchers from the CDC and University of British Columbia looked at data obtained on 9,622 infants with major birth defects and 4,092 control infants born between 1997 and 2002. Records were obtained from birth defects surveillance systems in 8 U.S. states and controls were selected randomly from the same geographic areas. Mothers were interviewed regarding exposure to potential risk factors including medications before and during pregnancy. No significant associations were found between maternal use of SSRIs overall during early pregnancy and congenital heart defects or most other categories or subcategories categories of birth defects. Maternal SSRI use was associated with amencephaly (odds ratio 2.4), craniosynostosis (odds ratio 2.5) and omphalocele (odds ratio 2.8). Their conclusion was that maternal use of SSRIs during early pregnancy was not associated with significantly increased risk of congenital heart defects or most other categories or birth defects. There was an association with SSRI use and 3 types of birth defects, but the absolute risk was small and further studies are warranted (*N Engl J Med* 2007; 356:2675- 2683, 2684-2692). An accompanying editorial points out that 2 previous stud-

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ies had suggested a relationship between paroxetine and cardiac malformations including ventricular septal defects, an association that was not found in these current studies. Although a small rate of congenital heart malformations, including right ventricular outflow tract lesions, were found the rate was still low, less than 1%. The editorialists, Dr. Michael Green from Massachusetts General states, "The 2 reports in this issue of the Journal, together with other available information, do suggest that any increased risks of these malformations in association with the use of SSRIs are likely to be small in terms of absolute risks." (*N Engl J Med* 2007; 356:2732-2733). ■

Estrogen for Younger Postmenopausal Women

Another follow-up study from the Women's Health Initiative suggests that estrogen therapy in younger postmenopausal women may be of benefit in preventing cardiovascular disease. Analysis was done on the "estrogen-only" wing of WHI in women who had undergone hysterectomy prior to enrolling in the study and were not treated with progesterone. Women age 50 to 59 were treated with 0.625 mg per day of conjugated equine estrogens or placebo. CT heart scanning was done at entry to the study and after a mean of 7.4 years of treatment and 1.3 years after the trial was completed. The endpoint of mean coronary-artery calcium scores was lower among women receiving estrogen (83.1) than those receiving placebo (123.1) (P = 0.02 by rank test). After adjusting for coronary risk factors, the odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared to placebo were respectively 0.78, 0.74, and 0.69. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P = 0.01), 0.55 (P < 0.001), and 0.46 (P = 0.001). For women who had calcium scores greater than 300 the multivariate odds ratio was 0.58 (P = 0.03) in an intention-to-treat analysis and 0.39 (P = 0.004) among women with at least 80% adherence. The authors conclude that in women age 50 to 59 years old at enrollment, estrogen treatment resulted in a lower calcified plaque burden in the coronary arteries compared to placebo. They also point out that estrogen has complex biological effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways (*N Engl J Med* 2007; 356:2591-2602). An accompanying editorial points out that not only did women in this analysis who were treated with estrogen have lower calcium scores, women in whom hormone replacement therapy was initiated at a younger age also had a 30% reduction in total mortality and did not have significant increases in any adverse outcomes examined. This supports the "timing hypothesis" for hormone replacement therapy that suggests that the cardiovascular benefits of hormone replacement are only evident if treatment is started before atherosclerosis develops. (*N Engl J Med* 2007;356:2639-2641). ■

Warfarin Better for Atrial Fibrillation Patients

Recent meta-analysis has confirmed the value of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation. Twenty-nine trials involving more than 28,000 patients were reviewed. Compared with control, warfarin and antiplatelet agents reduce stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%) respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy, and increases in extracranial hemorrhage assisted with warfarin were small. The authors conclude that warfarin is substantially more efficacious at preventing stroke in patients with a fibrillation than is antiplatelet therapy (by approximately 40%). (*Ann Int Med* 2007; 146: 857-867). ■

FDA Actions

The FDA has strengthened its regulations regarding dietary supplements, issuing a "final rule" requiring current good manufacturing practices for dietary supplements. The rule ensures the supplements are produced in a quality manner, do not contain contaminants or impurities, and are accurately labeled. Manufacturers will also be required to report all serious dietary supplement-related adverse events to the FDA by the end of the year.

Pregabalin (Lyrica-Pfizer) has been approved for the treatment of fibromyalgia, the first drug approved for this indication. Fibromyalgia, which is characterized by pain, fatigue, and sleep problems, affects up to 6 million people in United States. Approval was based on 2 double-blind, controlled trials involving 1,800 patients that showed improvement in pain symptoms at doses of 300 mg or 450 mg per day. The drug has already been approved for partial seizures, postherpetic neuralgia, and diabetic neuropathy. ■