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Snoring and Excessive Daytime Sleepiness

ABSTRACT & COMMENTARY

Synopsis: *Excessive daytime sleepiness is associated progressively with snoring frequency.*

Source: Gottlieb DJ, et al. *Am J Respir Crit Care Med* 2000; 162:1512-1517.

The sleep heart health study is an ongoing, multicenter investigation into the cardiovascular consequences of sleep-disordered breathing.[1] In this study, 5777 participants (mean age 64, 53% women) were divided into four groups based on Respiratory Disturbance Index (RDI), which is essentially the same as Apnea plus Hypopnea Index (AHI). As expected, sleepiness, assessed by total Epworth Sleepiness Score (ESS), increased with increasing RDI. The mean ESS in subjects with the lowest (< 1.5 events/h) RDI was 7.1, and the ESS for those with the highest (> 30) RDI was 9.7 events per hour. Subjects were also classified by responses to the question, "Have you ever snored?" For those who answered yes, snoring was quantified as not current (or unknown), less than one night per week, 1-2 nights per week, 3-5 nights per week, or 6-7 nights per week. Sleepiness (defined as a total ESS of 11 or more) increased progressively with snoring frequency. Eighteen percent of those with snoring less than one night per week, compared with 39% of those reporting snoring six or seven nights per week, met the definition of "sleepy" used in this study. Snoring was strongly associated with RDI of course, but analysis of variance indicated that snoring is an independent risk factor for sleepiness. Sleepiness also correlated with male gender, increasing age, endorsement of leg cramps "often" or "almost always," and the difference of the usual total sleep time on weekends minus usual total sleep time on weekdays. It was inversely related to self-reported total sleep time on week nights.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

The Epworth Sleepiness Scale[2] is a deceptively simple tool that is the most commonly used measure of sleepiness in clinical practice. (*See Table.*)

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Critics of this tool cite its subjective nature and weak correlation with objectively measured sleepiness. However, the ESS has good test-retest reliability and internal consistency.[3] It has previously been shown to correlate with RDI,[4] with response to treatment of sleep-disordered breathing,[5] to the likelihood of falling asleep while driving[6] and to quality of life.[7] Most importantly, it is easy and rapid to use. An even simpler assessment of sleepiness was recently reported to predict automobile crashes. Drivers who reported becoming so sleepy while driving that they feared falling asleep one out of three times that they drove on a highway had 10 times the rate of automobile crashes as those who did not.[8] The fact that sleepiness is a risk factor for automobile accidents escalates the problems from one of personal to public health.

Like pain, depression, and pornography, self-reported sleepiness is subjective, which makes it difficult to define and to measure. While we are uncomfortable with imprecise and subjective measures, there is little doubt that they can have significant effects on human life.

Table

The Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation: 0 = would never doze; 1 = slight chance of dozing; 2 = moderate chance of dozing; and 3 = high chance of dozing.

Situation	Chance of Dozing
Sitting and reading	_____
Watching TV	_____
Sitting, inactive, in a public place	_____
As a passenger in a car for an hour	_____
Lying down in the afternoon	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____

That sleepiness is associated with snoring should not surprise us. Snoring has previously been reported to be associated with hypertension,[9] pregnancy risk,[10] and, of course, sleep apnea.

There are many take home messages from this paper. We need to query our patients about sleepiness, especially while driving. It might be good to include the ESS in a questionnaire of general health screening. Snoring is not necessarily a benign symptom. And, most of us need to get more sleep. ❖

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Aspirin: What Are the Risks and Benefits?

ABSTRACTS & COMMENTARY

Synopsis: *The risk of GI hemorrhage exceeds the benefit of primary prevention of MI, and the risk of hemorrhagic stroke is about the same as the benefit conferred.*

Sources: Derry S, Loke YK. *BMJ* 2000;321:1183-1187; Hebert PR, Hennekens CH. *Arch Intern Med* 2000;160: 3123-3127.

In the risk of gastrointestinal (gi) hemorrhage associated with aspirin use study, Derry and Loke collected all publications of randomized controlled trials of aspirin used as an antiplatelet agent in order to determine whether the risk of GI hemorrhage associated with aspirin use is reduced when either the dose is reduced and/or a modified sustained release form is used. Twenty-four randomized, controlled trials were included, with 66,000 participants. Eight studies invol-ving 24,954 participants used low dosage aspirin, 50-162.5 mg per day.

Meta-analysis revealed that, overall, GI hemorrhage occurred in 2.47% of patients taking aspirin compared with 1.42% taking placebo. The number of patients need to harm based upon an average of 28 months of aspirin was 106. Analyzing separately the eight trials that used low-dose aspirin did not change the result (2.3% for aspirin compared to 1.4% placebo.)

Hebert and Hennekens note that while numerous randomized, controlled trials document the conclusive benefit of aspirin in preventing secondary cardiovascular events and in modifying evolving myocardial infarction (MI), there has been insufficient evidence to recommend aspirin for primary prevention of MI. To address this question, Hebert and Hennekens collected four randomized, controlled trials (51,000 subjects) of the use of aspirin in primary prevention of occlusive events, one of which included women as well as men. Analysis revealed that the number to treat to prevent one MI was 150. This is also the number to treat with aspirin to cause one hemorrhagic stroke (whether for primary or secondary prevention).

COMMENT BY MICHAEL K. REES, MD, MPH

Derry and Loke's study documents that about one in 100 patients taking aspirin over a 28-month period experience GI hemorrhage, which is not reduced by either lowering the dosage of aspirin or using a sustained-relief formulation. Aspirin is known to have a significant benefit in secondary prevention of MI; it estimated that the number to treat to prevent one event is 73. But what about the use of aspirin for primary prevention? Does the benefit conferred by aspirin warrant the risk? This is one of the issues addressed in the paper by Hebert and Hennekens.

Many patients believe that taking a daily aspirin is a benign method of preventing that first MI, but this is far from true. The risk of GI hemorrhage exceeds the benefit of primary prevention of MI, and the risk of hemorrhagic stroke is about the same as the benefit conferred. Hebert and Hennekens conclude: "Whether to recommend aspirin therapy for an individual patient involves assessing the patient's cardiovascular risk profile and then weighing the clear benefit of reducing the risk of a first MI against the adverse effects of long-term administration." At least for GI bleed, the risk is not reduced by either reducing the dose of aspirin or using a modified delivery system. ❖

Depression and the Risk of Coronary Artery Heart Disease in the Elderly

ABSTRACT & COMMENTARY

Synopsis: *Treating depressive symptoms in the elderly should not be overlooked since such therapy is important in preventing the onset of symptomatic CHD or even sudden cardiac death in the elderly.*

Source: Ariyo A, et al. *Circulation* 2000;102:1773-1779.

Depression occurs in 19-30% of all elderly patients and only 1% of those so effected receive the necessary treatment for this serious illness.[1,2] Many published studies have suggested that abnormally high depression scores may predispose an individual to an increased risk of developing coronary heart disease (CHD) especially in middle-aged populations, but data regarding the relationship between depression and CHD in the elderly have been sparse.[3,4]

Ariyo and colleagues in the Cardiovascular Health Study Collaborative Research Group have now published the results of a multicenter study that started in 1989 evaluating cardiovascular risk factors in 5888 Americans aged 65 and older. No evidence of CHD was present at baseline in the 4493 participants who subsequently provided annual information regarding their depressive tendencies, which were assessed by using the Depression Scale of the Center for Epidemiological Studies. These

subjects were followed for six years and, in each case, the cumulative mean depression score was assessed and correlated with all cardiovascular events and/or CHD deaths. Among participants with the highest cumulative mean depression scores, the risk of CAD increased by 40% and risk of death by 60% compared with those individuals who had the lowest mean depression scores.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

Many previously published studies have demonstrated that depressive symptoms constitute a risk factor for CHD[3-7] and CHD mortality.[4,6-8] However, the data presented by Ariyo et al differ from previously reported studies because they focused exclusively on the elderly. There now seems to be little question that depressive symptoms constitute an independent risk factor for the development of CHD and total mortality in the elderly and, in addition, this risk appears to increase for those individuals who score higher on the Depression Scale.

The results of the reported study could have been influenced by depression produced by other events such as life-threatening illnesses, which are obviously more common in the elderly. Equally important, it should be noted that participants with prior cardiac disease were excluded at the onset so there appeared to be an independent relationship between the depressive symptoms and subsequent cardiovascular events. The prospective nature of this study, the large sample size, the duration of follow-up, and the blinded ascertainment of cardiac events all tend to make the final results even more impressive. As an aside, it should be noted that the results were similar in men and women even though women had higher depression scores at the beginning of the study.

Multiple theories have been advanced as to why depression would be associated with CHD risk. For example, it has been speculated that depressed individuals frequently exercise less, smoke more, and have a higher likelihood of indulging in anxiety-provoking behavior patterns, all of which may increase cardiovascular risk. It has also been speculated that depression produces anxiety, which may result in an increase in autonomic sympathetic activation.[9,10] Many published papers have suggested that there is an inter-relationship between depression and abnormal lipid/glucose metabolism,[11,12] which may encourage the earlier development of CHD. Finally, sudden deaths associated with depressive states have been attributed to an imbalance between the autonomic parasympathetic and sympathetic nervous systems resulting in increased sympathetic activity and induction of lethal ventricular arrhythmias.[13]

The importance of the data presented by Ariyo et al is obvious in that 31 million Americans are 65 or older and, in this group, 5 million are afflicted with depressive symptoms. Between 7-12% of men and 20-25% of women will develop a major depressive episode during their lifetime. The strong relationship between depression and CHD demonstrated in this study makes it mandatory for all primary care physicians to familiarize themselves with the relationship and to vigorously treat depression with drugs and/or psychotherapy early after the onset of depression, much before cardiovascular symptoms and/or sudden cardiac death occur. It would appear that treating this very important risk factor may be equally important as is treating an abnormal lipid panel, or as is advising patients to discontinue cigarette smoking, to bring their weight down to ideal levels, and/or to initiate a regular exercise program. In other words, treating depressive symptoms in the elderly should not be overlooked since such therapy is obviously incredibly important in preventing the onset of symptomatic CHD or even sudden cardiac death in the elderly. ❖

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Chest Radiographs in Acute PE

ABSTRACT & COMMENTARY

Synopsis: *Cardiomegaly is the most common chest radiographic abnormality in acute pulmonary embolism.*

Source: Elliott CG, et al. *Chest* 2000;118:33-38.

A chest radiograph is often the first imaging study done to assess a patient with suspected pulmonary embolism (PE) and it often influences the deci-

sion to perform additional diagnostic testing. The chest radiographic changes of PE have not been studied in a detailed fashion in previous studies due to small sample size or the lack of adequate descriptions of chest x-ray changes. Also, previous studies have not looked at the relationship between chest x-ray changes and right ventricular hypokinesis as seen on echocardiography. Right ventricular hypokinesis has previously been shown to be an important predictor of mortality associated with PE. The purpose of this study was to describe the chest x-ray findings in a large number of patients with acute PE. In addition, Elliott and associates sought to determine the sensitivity and specificity of cardiomegaly or pulmonary artery enlargement for right ventricular dysfunction as verified by echocardiography.

The International Cooperative Pulmonary Embolism Registry (ICOPER) prospectively enrolled 2454 patients who were diagnosed with an acute PE from January 1995 to November 1996. Elliott et al used this registry to prospectively identify patients diagnosed with acute PE (defined as within 31 days of symptom onset) at 52 hospitals in seven countries. They used interpretations of imaging studies provided by physicians at participating sites. The chest x-rays were first characterized as normal or abnormal; if they were abnormal, the participant physicians were asked to note the presence or absence of certain abnormalities.

The three most common modalities by which PE was diagnosed in this population were high probability V/Q scan (30%), high probability perfusion scan (24%), and pulmonary angiogram (19%). Most patients (89%) had symptoms and were hemodynamically stable, whereas only 4% exhibited hemodynamic instability. The most common symptoms included dyspnea (82%), chest pain (49%), and cough (20%).

Chest x-rays were available for 2322 patients (95%), and of those, 1759 (76%) were abnormal. The most common abnormalities were cardiac enlargement (27%), pleural effusion (23%), and elevated hemidiaphragm (20%). When looking only at patients whose PE was not diagnosed until autopsy, the results were similar except pulmonary congestion (44%) was more common than cardiac enlargement (41%), pleural effusion (36%), or elevated hemidiaphragm (26%). When looking at subsets of patients according to presenting symptoms, they found that cardiomegaly was still the most common abnormality for patients presenting with dyspnea alone (29%) and with syncope or hypotension (27%). They also evaluated patients by the different types of surgery they had undergone prior to PE. They found that those who had undergone thoracic or abdominal surgery were much less likely to have normal radiographs (4% and 16%, respectively) than those that had undergone genitourinary (37%), orthopedic (28%), or gynecologic (28%) procedures.

X-rays were available for 1084 out of 1135 patients (96%) who had an echocardiography. They demonstrated that cardiomegaly on chest x-ray had a low sensitivity (0.48) and specificity (0.63) for echocardiographic evidence of right ventricular hypokinesis. The findings were similar for enlargement of the pulmonary artery on chest x-rays (sens. 0.38, spec. 0.76).

COMMENT BY DAVID OST, MD

In its clinical practice guideline regarding the diagnostic approach to acute venous thromboembolism, the American Thoracic Society concludes that the chest radiograph cannot be used to conclusively diagnose or exclude a PE. Instead, it should be used to diagnose other diseases that may mimic or coexist with PE. However, it is still of value to know which signs on a chest x-ray are more commonly seen with PE in the right clinical circumstance. Elliott et al's study demonstrates that cardiomegaly is the most common chest x-ray abnormality associated with PE. Previous studies have come to different conclusions. Stein et al found atelectasis, pleural effusion, and pleural based opacity to be the most common abnormalities. The urokinase pulmonary embolism trial found an elevated diaphragm was the most common abnormality. However, Elliot et al's study has the advantage of having a much larger study population than previous studies. Also, Elliott et al were not looking for abnormalities specific to PE since they did not exclude patients with known cardiopulmonary disease. This study also found that patients who are older than 70 are more likely to have abnormal radiographs than patients younger than 70, which is a different result than that obtained in the previous study. This paper also highlights how insensitive and nonspecific chest x-ray findings are for right ventricular dysfunction in acute PE. This is important because, as already mentioned, this is an important predictor of mortality. As Elliott et al point out, the sensitivity and specificity of chest x-ray findings suggestive of right ventricular hypokinesis are likely overestimations since not all patients received echocardiographs. ❖

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Lopinavir and Ritonavir Capsules and Oral Solution (Kaletra—Abbott)

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

A new combination protease inhibitor is the latest anti-HIV medication to be approved by the FDA. Abbott's Kaletra combines lopinavir with a low dose of the previously approved ritonavir (Norvir). The combination takes advantage of ritonivir's ability to inhibit the metabolism of lopinavir, increasing its plasma levels. Kaletra, which is to be used with other anti-HIV drugs, was given an accelerated approval by the FDA.

Indications

Lopinavir/ritonavir is indicated in combination with other antiretroviral drugs for the treatment of HIV infections in adults and pediatric patients as young as 6 months.[1]

Dosage

The recommended dose of lopinavir/ritonavir is 400 mg/100 mg (3 capsules or 5 mL) twice daily taken with food. A dose increase to 533 mg/133 mg (4 capsules or 6.5 mL) twice daily should be considered when used in combination with efavirenz or nevirapine in treatment of experienced patients where reduced susceptibility to lopinavir is suspected.[1] The pediatric dose is 12 mg/kg twice daily in patients 7 kg up to 15 kg body weight, 10 mg/kg twice daily in those 15-40 kg, and an adult dose for those more than 40 kg.

To optimize bioavailability and reduce variability, lopinavir/ritonavir should be taken with food.

Kaletra is available as capsules containing 133.3 mg of lopinavir and 33.3 mg of ritonavir and 400 mg of lopinavir and 100 mg of ritonavir per 5 mL. The oral solution contains 42.4% of alcohol.

Potential Advantages

The combination has a low pill burden (3 capsules twice daily) that simplifies therapy and promotes adherence. Lopinavir/ritonavir is indicated for patients as young as 6 months of age—the broadest pediatric indication for a protease inhibitor.

Potential Disadvantages

Ritonavir is a potent inhibitor of cytochrome P450 CYP3A and, to a lesser degree, CYP2D6. Kaletra has the potential to inhibit the metabolism of numerous other drugs. Flecainide, propafenone, ergot derivatives, pimozide, midazolam, triazolam, rifampin, lovastatin, simvastatin, cisapride, astemizole, terfenadine, and St. Johns' wort are either contraindicated or should not be co-administered with Kaletra.[1]

In addition, there are numerous other potential significant drug interactions that may require adjustment of doses and/or monitoring. For example, carbamazepine, phenytoin, phenobarbital, efavirenz, and nevirapine can induce the activity of CYP3A resulting in the reduction of lopinavir levels.

Significant dose reduction of rifabutin is recommended if it is co-administered with Kaletra. A complete list of potentially drug-drug interactions is provided in the product labeling.[1]

The most common side effects associated with lopinavir/ritonavir is diarrhea (14-24%) and nausea, which appears to occur more frequently in antiretroviral-naive patients (6-15%). Laboratory abnormalities include elevation of total cholesterol (6-27%) and triglycerides (5-26%). Higher incidences have been observed in antiretroviral-experienced patients.[1] Pancreatitis, new onset diabetes, exacerbation of pre-existing diabetes, and hyperglycemia have been reported although causal relationships have not been established.[1]

Comments

Lopinavir/ritonavir is a novel combination that uses a metabolite enzyme inhibitor to enhance the plasma level of the active drug. When administered as the fixed combination, the plasma levels of lopinavir are 15-20-fold higher than those of ritonavir. The plasma levels of ritonavir are less than 7% of those achieved after a therapeutic dose of ritonavir and the in vitro antiviral activity is about 1/10th of that of lopinavir. The antiviral activity of Kaletra is solely attributed to lopinavir and apparently does not, at least in vitro, influence the selection of lopinavir-resistant virus.[1] It is not clear how the low subtherapeutic doses of ritonavir will affect ritonavir resistance or other protease inhibitors that are cross resistant to ritonavir. The approval of lopinavir/ritonavir, like other anti-HIV agents, was based on improvement in HIV viral RNA levels and CD4 counts. In an ongoing trial (n = 653), lopinavir/ritonavir plus stavudine and lamivudine was compared to nelfinavir plus stavudine and lamuvidine in treatment-naive patients with mean baseline plasma HIV RNA of 4.9 $\log^{10}$ copies/mL.

Through 24 weeks, 79% of lopinavir/ritonavir patients had HIV RNA below 400 copies/mL compared to 70% for the nelfinavir combination. Discontinuation due to side effects were comparable, 2%.[1] In patients

who were one protease inhibitor experienced and non-nucleoside reverse transcriptase inhibitor-naive (n = 70), lopinavir/ritonavir and nevirapine and two NRTIs achieved HIV RNA levels less than 400 in 75% of patients after 72 weeks. These patients have mean baseline viral levels of 4.0 $\log^{10}$. Full details of these studies are not available as results have not been published.

Clinical Implications

Lopinavir/ritonavir provides an alternative to other protease inhibitors on the market. Its twice-daily dosing and low pill burden may favor medication adherence, but the drug combination is saddled with multiple drug-drug interactions since ritonavir is a potent inhibitor of CYP3A and to a lesser degree CYP 2D6. These cytochrome P450 enzymes are responsible for metabolizing a wide variety of drugs and endogenous chemicals.[2,4] In addition, ritonavir is also an inducer of CYP1A4, glucuronosyl transferase, and possibly, CYP2C9 and CYP2C19.[3] As a result, numerous drugs are contraindicated with lopinavir/ritonavir and many require dosage adjustments and/or monitoring. Abbott has agreed to develop educational material for patients and to provide information regarding drug interactions as part of its Phase IV commitments.[5] Kaletra will be priced competitively to nelfinavir. ❖

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CME Questions

46. Sleepiness is associated with:

a. female gender, automobile accidents, accidents, and a large difference between sleep times on weekend and weekday nights.
b. male gender, snoring, and automobile accidents.
c. younger age, automobile accidents, and male gender.
d. a large difference between sleep times on weekend and weekday nights, snoring, and female gender.
e. male gender, younger age, and snoring.

47. The lopinavir/ritonavir combination:

a. has a low pill burden that simplifies therapy and promotes adherence.
b. is indicated for patients as young as 6 months of age—the broadest pediatric indication for a protease inhibitor.
c. has numerous potential drug interactions that may require adjustment of doses and/or monitoring.
d. All of the above

By Louis Kuritzky, MD

Predicting LVH in Hypertensive Men

The presence of left ventricular hypertrophy (LVH) in patients with hypertension is a marker of high risk. The same is true of proteinuria (PRO). JNC VI suggests intensified treatment in persons with manifest target organ damage, such as proteinuria and LVH. The most accurate method for determination of LVH is echocardiography; the most accurate method for determination of proteinuria (or microalbuminuria) is 24-hour urine quantitation. Both measurement tools are cumbersome, and echocardiography is prohibitively expensive. Whether detection of proteinuria by a spot urine specimen might correlate with LVH has not been prospectively studied and is the subject of this report. Subjects were previously untreated hypertensive African-American men (n = 109). Each subject underwent echocardiography and a single afternoon random urine albumin.

There was a significant correlation between LVH and PRO, independent of other variables related to left ventricular mass or albuminuria. The magnitude of the correlation was similar to that of systolic BP and LVH.

Post et al conclude that obtaining a single random urine for protein is an important predictor of LVH. Since the presence of LVH is an ominous predictor for hypertensive patients, and only a few patients with hypertension actually receive echocardiography due to its expense, the presence of increased protein excretion on a random afternoon sample might be considered a suitable surrogate marker for increased likelihood of LVH. ■

Post WS, et al. Am J Hypertens 2000; 13:1168-1172.

Patients' Knowledge of End of Life Options

End of life (eol) decisions may include such issues as the right to refuse or withdraw life-sustaining treatment, advance directives, legalized physician-assisted suicide, and the double effect (i.e., the legality of administering pain medication that might have the additional effect of hastening death). Despite the widespread familiarity of clinicians with such issues, it remains equally pertinent that the public at large be conversant and informed about such issues. That our populace may be inadequately informed is echoed by results of a recent national poll in which more than one-third of persons were not familiar with the terms "hospice" or "palliative care." This report specifically assessed outpatient adults' (n = 1000) knowledge in four primary areas: refusal and withdrawal of life-saving treatments, physician-assisted suicide, active euthanasia, and the doctrine of double effect.

Subjects were presented with clinical vignettes, such as a patient with terminal cancer, and asked whether the patient had a legal right to refuse potentially curative treatment, IV fluids, or feeding tube. Also, they were queried as to whether the physician could legally turn off a ventilator, inject medication to hasten death, or prescribe a medication that the patient would be enabled to end life if so desired.

Most persons did understand that (in Oregon), patients could refuse life-saving treatment. Less than half understood that patients could withdraw life-sustaining treatment. Only about one-quarter of persons could properly identify assisted suicide as a legal option.

To maximize the benefits of EOL options, the public must be adequately informed of these choices. Even in Oregon, where one would anticipate that knowledge of such issues might be higher than other locales due to recent intense media publicity, there remains substantial room for improvement in public knowledge of EOL options. ■

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PLA2 as A Predictor of CHD

The west of scotland coronary Prevention Study evaluated 6595 men with LDL 174-232 mg/dL without history of myocardial infarction treated with pravastatin or placebo. Evolution of knowledge about atherosclerosis and its consequences has focused attention upon the role of plaque susceptibility and stabilization as crucial factors determining manifest vascular end points. Phospholipase A2 (PLA2) is an enzyme that may affect atherosclerosis, since it is found in the media of arteries, and is believed to play a role in LDL modification, potentially inducing atherogenic changes in the vascular wall. Using the West of Scotland Study population, Packard et al measured PLA2 at baseline.

Increased levels of PLA2 were independently associated with a significantly greater risk of the composite end point of nonfatal MI, cardiac death, or revascularization. The risk at the highest quintile was about double that for the lowest. The relationship of PLA2 levels in the West of Scotland trial was equally prominent in recipients of pravastatin as it was in placebo subjects. Packard et al conclude that PLA2 is a potential risk factor that may directly affect atherosclerosis. ■

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In Future Issues: Is Grapefruit Juice Harmful?