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INSIDE

Recent Cholesterol Report Focuses on Prevention of Coronary Artery Disease

By William T. Elliott, MD, FACP

The executive summary of the third report of the national Cholesterol Education Program (NCEP) was published in May. The report, called Adult Treatment Panel III (ATP III), updates national guidelines for the detection and treatment of hypercholesterolemia, last published in 1993. Perhaps the biggest change in cholesterol management in the last 8 years has been the focus on primary prevention of coronary artery disease (CAD). ATPIII provides a tool for physicians to grade their patients' risk of CAD within 10 years. The report suggests aggressive treatment for those with risk factors, including using drug therapy to lower LDL cholesterol to 100 mg/dl. Another significant change is the elevation of diabetes to the equivalent of CAD when considering lipid-lowering therapy. The guidelines also suggest that anyone with an LDL cholesterol greater than 130, HDL less than 40, or a triglyceride level greater than 200 should be considered for drug therapy. The expert panel also recommends that a fasting lipid panel should be the standard screening exam. The executive summary is available in the May 16 issue of *JAMA* (*JAMA*. 2001;285:2486-2497). More information is also available at http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.

Migraine Treatment

The FDA has approved a new triptan for the treatment of migraine. Pharmacia's almotriptan is approved for migraine in adults with or without aura. The drug, which will be sold under the trade name "Axert," is touted as being as effective as sumitriptan but with significantly less side effects, especially chest pain (company data).

Oral Contraceptives

A new low-dose oral contraceptive was also approved in the last month. Berlex's Yasmin contains 30 mcg of ethinyl estradiol and 3 mg of the progestin drospirenone. It is the latter agent that makes this combination unique. Drospirenone, an analogue of spironolactone, has diuretic effects and, thus, is ideal for women with premenstral bloating and water retention.

Metered Dose Inhalers

In a study that could only have come from Scotland (this editor's ancestral homeland), discarded toilet paper tubes have been found to be effective spacers for use with metered dose inhalers. The cardboard tubes were compared to no spacer and the commercially available Aerochamber spacer device. Both the cardboard spacer and Aerochamber performed better than using the MDI without a spacer, with the Aerochamber performing better, but not significantly so. Fowler and associates conclude: "If a spacer is required for reasons other than increasing delivered drug dose, then the addition of a readily available cardboard tube will fulfill many of the required functions with no expense to the patient." (*Chest*. 2001;119:1018-1020).

Antifungal Warnings

The popular antifungal itraconazole (Sporanox—J&J) is warning doctors not to use the drug in patients with congestive heart failure (CHF) or a history of CHF. The warning is the result of a number of deaths from CHF among patients taking the drug. The company has not specified the number of deaths. J&J is also warning doctors not to use itraconazole in combination with the antiarrythmic dofetilide (Tikosyn) or erythromycin, and urges caution when using the drug with calcium channel blockers.

Cholesterol Lowering Therapy

Older patients may benefit more from cholesterol lowering therapy than younger patients according to an Australian study. More than 9000 patients with a history of CAD were studied, of which 3500 were age 65 to 75. Patients were randomized to pravastatin 40 mg/d or placebo, and were followed for an average of 6 years. In patients 65 to 75 years of age, pravastatin therapy reduced mortality by 21% (CI, 7-32%), death from coronary heart disease by 24% (CI, 7-38%), coronary heart disease death or nonfatal myocardial infarction by 22% (CI, 9-34%), myocardial infarction by 26% (CI, 9-40%), and stroke by 12% (CI, 15-32%). For every 1000 older patients treated over 6 years, pravastatin prevented 45 deaths, including deaths from myocardial infarction and strokes. The rate of decrease was similar for younger and older patients, but since older patients were at a higher absolute risk of death and major coronary events, the benefit was greater for those age 65 to 75 (*Ann Int Med*. 2001;134:931-940).

Allergy Medicine Wants OTC Status

An unprecedented battle is shaping up in Washington over the status of 3 popular prescription allergy medications. Wellpoint Health, one of the nation's largest HMOs has petitioned the FDA to switch loratidine (Claritin—Schering-Plough), fexofenadine (Allegra—Aventis), and cetirizine (Zyrtec—Pfizer) to over the counter (OTC) status, thus making them available to consumers without a prescription and removing them from HMO drug benefit plans. The 3 drugs currently account for revenues of $4.7 billion. The issue before the FDA is the relative safety of these "nonsedating" antihistamines compared to currently available OTC antihistamines such as diphenhydramine and hydroxyzine. In a bizarre twist, the manufacturers are arguing to keep the drugs available only by prescription, and thus paid for by third-party payors, arguing that the drugs are too new to be considered for OTC status and that allergic rhinitis requires a doctor's diagnoses. Although a panel of the FDA has approved a prescription-to-OTC switch for the 3 drugs, it is unclear whether the FDA has the ability to force the switch against the companies' wishes.

Beta Blockers and CHF

Do beta blockers benefit patients with advanced congestive heart failure? Subsequent articles in the May 31 *New England Journal of Medicine* give conflicting results. In the first study, more than 2000 patients with severe heart failure were randomized to carvedilol therapy or placebo for an average of 19.4 months. Over the study period there were 190 deaths in the placebo group and 130 deaths in the carvedilol group, and a 24% decrease in the combined risk of death or hospitalization with carvedilol (*N Engl J Med*. 2001;344:1651-1658). In the second study, 2700 patients with severe heart failure were randomized to treatment with the beta blocker bucindolol or placebo. The study was stopped early because no significant overall survival benefit was shown with bucindolol (*N Engl J Med*. 2001;344:1659-1667). ■

Formoterol—A New Long-acting Beta Agonist Inhaler

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

The fda recently approved formoterol inhalation powder, a long-acting, inhaled selective beta-2 adrenergic agonist. The drug is the second long-acting beta agonist on the market along with salmeterol (Serevent). Formoterol is approved for the maintenance

treatment of asthma and the prevention of exercise-induced bronchospasm. Formoterol, which has been available in Europe, is marketed as Foradil by Novartis Pharmaceuticals.

Indications

Formoterol is indicated for the long-term maintenance of asthma and the prevention of bronchospasm in adults and children 5 years of age and older. It is also indicated for the acute prevention of exercise-induced bronchospasm in adults and children 12 years of age and older.[1]

Dosage

For the long-term maintenance of asthma, the usual dose is inhalation of the contents of 1 capsule (12 mcg) every 12 hours. The total daily dose should not exceed 2 capsules per day. For the prevention of exercise-induced bronchospasm the dose is 1 capsule (12 mcg) at least 15 minutes before exercise.

Formoterol is available as 12 mcg capsules and is administered with the Aerolizer Inhaler.

Potential Advantages

Formoterol has a faster onset of action than salmeterol.[2] There have been a few case reports of patients with preferential response to formoterol compared to salmeterol.[8,9]

Potential Disadvantages

Some may find the inhalation of dry powder difficult, especially if they are accustomed to aerosolzed inhalers. Since the delivery system is self actuated, drug delivery is sensitive to the patient's inspiratory flow rate.[4]

Formoterol may have a greater potential to cause side effects such as tremors and effect on Q-T interval compared to salmeterol.[3]

Comments

Formoterol is the second long-acting selective beta-2 adrenergic agonist approved for the long-term treatment of asthma. It is administered as a dry powder and does not use a CFC propellant. Salmeterol is available both as an aerosol and dry powder.

These drugs appear to be comparable in improving pulmonary function in asthmatics in single-dose trials.[2,3] The primary difference between formoterol and salmeterol is the faster onset of action of the formoterol which is similar to that of albuterol. With daily twice-daily dosing, the benefit of faster onset may be negligible. Despite its faster onset of action, formoterol is not recommended for rescue use as its long duration of action may mask signs of more serious asthma.[2] However, the faster onset of action of formoterol may be advantageous for the prevention of exercise-induced bronchospasm. In contrast to salmeterol, formoterol has not been approved for the maintenance treatment of bronchospasm of chronic obstructive pulmonary disease but appears to be equally effective.[5,6]

Both drugs are priced similary with a 30-day cost of about $70.

Clinical Implications

Long-acting beta agonists such as salmeterol and formoterol are recommended as alternatives to medium-dose inhaled corticosteroids in the long-term management of moderate to persistent asthma.[7] Formoterol provides a safe and effective alternative to salmeterol. Both are approved for use in adults and children, although salmeterol is approved down to the age of 4 compared to 5 for formoterol. ■

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Once-Weekly Alendronate Tablets

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

Merck & co. has received fda approval to market once-a-week doses of alendronate for the treatment and prevention of osteoporosis. Alendronate is a bisphosphonate that inhibits bone

resorption. It has been available since 1995 as a once-a-day medication and has been widely used to treat and prevent osteoporosis. Alendronate is marketed under the tradename Fosamax®.

Indications

Alendronate is used for the treatment or prevention of osteoporosis in postmenopausal women.

Dosage

The dose of alendronate for the treatment of osteoporosis is 70 mg once weekly. For prevention, the dose is 35 mg once weekly. It should be taken upon arising with plain water (6-8 oz) at least one-half hour before the first food, beverage, or medication of the day. The patient should not lie down for at least 30 minutes and until after their first food of the day.[1] Patients should also receive supplemental calcium and vitamin D if these are not adequately supplied by the diet. Patients should be advised not to chew or suck on the tablets as this may cause oropharyngeal ulceration. If a dose is missed, patients should be advised to take it the next morning after they remember and return to the originally chosen weekly schedule. Alendronate is not recommended for patients with renal impairment (creatinine clearance < 35 mL/min).[1]

Potential Advantages

Once-weekly dosing may be more convenient as adherence to the strict dosing instructions need to be followed only once weekly instead of daily. Once-weekly dosing also reduces the esophageal exposure to the drug.

A trend toward a lower incidence of esophageal or gastric duodenal irritation was seen with the weekly dosing compared to daily dosing.[2]

Potential Disadvantages

Alendronate must be taken with specific instructions to reduce esophageal irritation. A retrospective database analysis reported that patients taking alendronate and who are elderly or are users of NSAIDs may have a greater risk of clinic visits and hospital admissions for acid-related gastrointestinal (GI) disorders.[3]

Comments

Alendronate inhibits the rate and extent of bone resorption by inhibiting osteoclast activity. This is shown by a decrease in osteocalcin, bone-specific alkaline phosphatase, and urinary markers such as cross-linked N-telopeptides of type 1 collagen. The drug's half life on bone surface is several weeks, and these pharmacodynamics allow for weekly dosing. In a comparative 1-year study, 70 mg once weekly showed the same efficacy as 10 mg daily. The mean increases in bone mineral density (BMD) in the lumbar spine in those who completed the trial were 5.1% (95% CI = 4.8-54%) and 5.4% (95% CI = 5.0-5.8%) for the weekly and daily dosing, respectively.[1,2]

Increases in BMD at the total hip, femoral neck, trochanter, and total body were also similar. Similarly in a 1-year prevention trial, alendronate 35 mg weekly and 5 mg daily produced a 2.9% (95% CI = 2.6-3.2) and 3.2% (95% CI = 2.9-3.5%) increase in BMD, respectively.[1] Long-term studies on fracture rates have not been conducted with the weekly regimens. While complaints such as dyspepsia and abdominal pain have been associated with alendronate administration, the drug did not appear to be associated with serious upper GI events in patients with no recent history of GI events.[4] The daily and weekly regimens are priced the same.

Clinical Implications

Alendronate 35 mg and 70 mg provide an alternative to the daily regimens for the prevention and treatment of osteoporosis. These may be preferred for patients who cannot tolerate the daily dose or cannot follow the strict dosing instructions. Weekly and daily regimens appear to be comparable in efficacy as shown by BMD studies. ■

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Principles of Appropriate Antibiotic Use for Uncomplicated Acute Bronchitis

Source: *Gonzales R, et al. Ann Intern Med. 2001;134:521-529.*

The term "acute bronchitis" usually designates an acute respiratory tract infection in which cough, with or without phlegm, is a predominant

feature. In the United States, about 5% of adults self-report an episode of acute bronchitis each year, and up to 90% of these persons seek medical attention. In 1997, adults in the United States made more than 10 million office visits for bronchitis. As a result, acute bronchitis consistently ranks among the 10 most common conditions leading to outpatient physician visits.

Evaluation of Acute Cough

A wide variety of infections and inflammatory disorders can lead to an acute cough illness. The American College of Chest Physicians defines acute cough illness as lasting less than 3 weeks.[1] Acute upper respiratory tract infections account for approximately 70% of primary diagnoses, with asthma (6%) and pneumonia (5%) being the next most common. Previously undiagnosed asthma is a consideration in patients presenting with an acute cough. The diagnosis of asthma is difficult to establish because many patients with acute bronchitis will have transient bronchial hyperresponsiveness. The primary objective in a healthy adult with uncomplicated acute cough is to exclude the presence of pneumonia. An evidence-based review concluded that absence of abnormalities in vital signs (heart rate > 100 beats/min, respiratory rate > 24 breaths/min, or oral temperature > 38°) and chest examination (rales, egophony, or fremitus) sufficiently reduces the likelihood of pneumonia to the point where further diagnostic testing is usually not necessary.[2]

Microbiology of Acute Uncomplicated Bronchitis

As in community-acquired pneumonia, microbiological studies of uncomplicated acute bronchitis identify a pathogen in the minority of cases, ranging from 16-40%. Specific viruses most frequently associated with acute bronchitis are influenza B, influenza A, parainfluenza 3, respiratory syncytial virus, corona virus, adenovirus, and rhinovirus. To date, only *Bordetella pertussis*, *Mycoplasma pneumoniae*, and *C pneumoniae* (TWAR) have been established as nonviral causes of uncomplicated acute bronchitis in adults.

Treatment of Uncomplicated Acute Bronchitis

Routine antibiotic treatment of uncomplicated acute bronchitis is not recommended, regardless of the duration of cough. The one uncommon circumstance for which evidence supports antibiotic treatment of patients with uncomplicated acute bronchitis is suspicion of pertussis.

Influenza is the most common pathogen isolated in patients with uncomplicated acute bronchitis. The neuraminidase inhibitors zanamivir and oseltamivir have demonstrated some efficacy in reducing illness duration in adults with naturally acquired influenza A and B if treatment begins within 48 hours of symptom onset.[3]

In most cases, cough is the major symptom for which patients seek relief. Randomized, controlled trials have demonstrated a consistent benefit of therapy with albuterol vs. placebo in reducing the duration and severity of cough.[4] Preparations containing dextromethorphan or codeine probably have a modest effect on severity and duration of cough. Cough of more than 3 weeks duration, cough associated with underlying lung disease, or experimentally induced cough have been shown to respond to dextromethorphan or codeine. Elimination of environmental cough triggers such as dust and dander, as well as the use of vaporized air treatments in low-humidity environments, such as high altitude, are also reasonable options.

Clinicians should be encouraged to discuss the lack of benefit of antibiotic treatment for treatment for uncomplicated acute bronchitis and stop prescribing antibiotics for this condition as a standard of practice. Mounting evidence indicates that patient satisfaction with the office encounter does not depend on receipt of antibiotic therapy but instead is related to the patient-centered quality of the encounter.[5]

■ Comment by David Ost, MD, FACP

Most cases of acute bronchitis occur in otherwise healthy adults, in whom this acute cough illness can be called "uncomplicated acute bronchitis." The principles in this guideline are intended to apply to such patients, and do not necessarily apply to patients with chronic lung diseases such as chronic obstructive pulmonary disease.

The recommendations given in this article for discussing the management of acute bronchitis with patients include the following steps:

1. Provide realistic expectations of the duration of the patient's cough, which will typically last for 10-14 days after the office visit.
2. Refer to the cough illness as a "chest cold" rather than bronchitis.[6]
3. Personalize the risk of unnecessary antibiotic use.
4. Explain to patients why we need to be more selective in treating only those conditions for which a major clinical benefit of antibiotics has been proven. Alert them to the current epidemic in antibiotic resistance among community bacterial pathogens and explain the public health concern. ■

Najma Usmani also contributed to this article. Dr. Usmani is an Internal Medicine Fellow, Northshore University Hospital, Manhasset, NY. Dr. Ost is Assistant Professor of Medicine, NYU School of Medicine, Director of Interventional Pulmonology, Division of Pulmonary and Critical Care Medicine, Northshore University Hospital, Manhasset, NY.

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Postmenopausal Estrogen Therapy and Ovarian Cancer

Source: *Rodriguez C, et al. JAMA. 2001;285:1460-1465.*

Rodriguez and colleagues from the american Cancer Society examined the association of postmenopausal estrogen use and ovarian cancer mortality in a prospective cohort study. The American Cancer Society Cancer Prevention Study II enrolled 676,306 postmenopausal women by a baseline questionnaire in 1982. Deaths in this cohort through 1996 accounted for 107,810 (15.9%) of the original group. After exclusions (premenopausal, unavailable information, hysterectomy, ovarian surgery), 211,581 postmenopausal women were left for analysis, with a total of 1497 ovarian cancer deaths. Estrogen use (ever use, past use, current use) was based on responses to the baseline questionnaire. The risk ratio for ovarian cancer mortality was adjusted for age, race, oral contraceptive use, number of live births, body mass index, age of menarche and menopause, and tubal ligation. The statistically significant increased adjusted risk ratios are presented in the Table.

These numbers indicated 64.4 ovarian cancer deaths per 100,000 users of estrogen for 10 or more years, compared with 26.4 for never users. Rodriguez et al further concluded that some risk persisted for up to 29 years after discontinuing estrogen. Rodriguez et al considered a possible mechanism for their conclusion, suggesting that ovarian cancer is more affected by lower gonadotropin levels than higher levels (this would not be consistent with the protective effect associated with oral contraceptives, or that estrogen directly stimulates ovarian cellular proliferation).

Table

Risk Ratio for Ovarian Cancer Mortality

	No. of Deaths	Rate Ratio (similar to Relative Risk)
Ever use	255	1.23 (1.06-1.43)
≥ 10 years of use	31	2.20 (1.53-3.17)

Comment By Leon Speroff, MD

There are so many things about this epidemiologic report that remind one of the similar circumstances surrounding the issue of postmenopausal hormone therapy and the risk of breast cancer.

Rodriguez et al argue that one of the reasons the results suggest causality is that the findings are similar to previously published case-control studies.[1-3] In fact, one of their references, that I did not cite, is a book chapter; in 2 of their cited studies the conclusions for long-term users were not statistically significant; and in the 1 statistically significant result, the finding applied only to serous carcinomas. I am not impressed with the quality of their reporting. Another example of selective reporting is the statement in the introduction of the current report that breast cancer incidence increases only after long-duration estrogen use, citing the Nurses' Health Study report in 1995, and neglecting to point out that the results of the American Cancer Society study with these same authors failed to support the Nurses' Health Study conclusion.[4]

One case-control study that examined long-term use did not find an increased risk.[5] The pooled analysis by Whittemore and colleagues of the 12 case-control studies up to 1992 could find no evidence for an association between ovarian cancer and estrogen therapy.[6] A meta-analysis in 1998 concluded that there was a 27% increase in risk of ovarian cancer with more than 10 years of estrogen use, but among the 6 studies included in this analysis, only 1 reported a statistically significant increase in risk with 10 or more years of therapy; and by definition, even the meta-analysis conclusion of a 27% increase in risk did not reach statistical significance (CI = 1.00-1.61).[7] In a more recent meta-analyis of 15 case-control studies, in the year 2000, Coughlin and associates could not find an association of estrogen therapy with ovarian cancer and no evidence of an effect with increasing duration of use.[8] To be complete, I will add to this list a re-analysis of 4 European case-control studies that found a statistically significant increased risk of ovarian cancer with estrogen use, but responsibly noted that it is essentially impossible to control in observa-

tional studies (case-control and cohort) for the possibility that hormone users and never users have different risks for ovarian cancer because they are not identical populations.[9]

It should also be noted that retrospective analyses have not detected any detrimental effect on prognosis after surgery for ovarian cancer in patients subsequently treated with hormones.[10,11]

The weakest link in the American Cancer Society Study is the fact that information regarding estrogen use was obtained from the single self-administered questionnaire in 1982. Despite the fact that it is touted as a large prospective study, the conclusion with some strength of association (the increase with users of 10 or more years) was based on 31 cases. But most of all, the results of the study do not represent further information added to a uniform, strong, and consistent story in the literature on this subject. Instead, the subject is similar to that of breast cancer risk and hormone therapy—many negative studies with some positive studies. The positive studies exhibit a strength of association that is not huge and could be due to the problems of small numbers and the attempt to compare 2 groups that may be basically dissimilar.

Epidemiologic evaluation of the effects of postmenopausal combined estrogen-progestin therapy will not be forthcoming for several years because of the relative recency of combined regimens. Pointing out that a combination of estrogen and progestin may prove to protect against ovarian cancer (similar to the results seen with oral contraceptives) is justified, but I would not make that the major part of my response to this current epidemiologic report. I would rather emphasize the small numbers, the weak associations, and the mixed story in the observational studies—all indicating either a very small or no effect. ■

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Lansoprazole Treatment of Patients for Chronic Idiopathic Laryngitis

Source: *El-Serag HB, et al. Am J Gastroenterol. 2001;96: 979-983.*

Many physicians accept the notion that gastroesophageal reflux disease (GERD) can underlie a number of extraesophageal syndromes, including laryngitis. Epidemiological data support this concept in a Veterans Administration setting with a high prevalence of laryngeal disorders associated with the diagnosis of erosive esophagitis.1 Additionally, it is widely taught that patients with GERD-related laryngitis often do not have heartburn or erosive esophagitis. It seems reasonable that anti-reflux treatment might be beneficial for treatment of reflux-related laryngitis. However, up to now, no controlled studies have assessed the value of such treatment. This paper describes 22 patients with symptoms and laryngoscopic signs of chronic laryngitis receiving either lansoprazole 30 mg bid or placebo for 3 months. Some had heartburn and some did not. Only a few had erosive esophagitis (3 on lansoprazole and 1 receiving placebo). Twenty patients completed the study (11 on lansoprazole, 9 on placebo). Of lansoprazole recipients, 58% had complete or partial resolution of laryngeal findings vs. 30% of those on placebo (NS). However, lansoprazole led to symptom relief in 55% vs. only 1 patient (11%) on placebo. Initial diagnostic test results such as pH exposure did not predict response. It is suggested that these results support empirical treatment of suspected GERD-related laryngitis with aggressive acid suppressive therapy.

■ Comment by Malcolm Robinson, MD, FACP, FACG

This study is far too small and too heterogeneous to answer any basic questions regarding the proper evaluation, identification, or treatment of patients suspected to have GERD-related laryngitis. Nevertheless, I would agree with El-Serag and Sonnenburg that laryngitis might be related to proximal esophageal reflux. If so, it should

respond to acid suppression. As this paper also comments, further larger studies should be undertaken to help define the appropriate identification of patients most likely to respond to such management. At present, there is still little justification for large-scale use of empirical aggressive antisecretory treatment for primary care patients presenting with unexplained chronic laryngitis. ■

Dr. Robinson is Medical Director, Oklahoma Foundation for Digestive Research; Clinical Professor of Medicine, University of Oklahoma College of Medicine Oklahoma City, Okla.

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Therapeutics & Drug Brief

Use of Statins and Risk of Fractures

Source: *van Staa TP, et al. JAMA. 2001;285:1850-1855.*

Geranylgeranylpyrophosphate (ggpp) is a protein that exerts control over osteoclast-mediated bone resorption. Statins (ie, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) block production of mevalonic acid, a precursor of GGPP. It has been suggested that currently used osteoporosis treatments like bisphosphonates may have an effect upon bone resorption through GGPP suppression in this same pathway. Recent epidemiologic data have suggested that statins may reduce fracture risk.

van Staa and colleagues studied a large population (n = 81,880) of cases from general practices in the United Kingdom of persons who had sustained a fracture (vertebra, clavicle, humerus, radius, ulna, carpal bone, hip, ankle, or foot), and compared this information with an equal body of age and sex-matched controls. Odds ratios were determined for use of statins vs. non-use of statins and likelihood of fracture.

Regardless of statin dose studied, no difference in odds ratio of fracture between current statin users and non users was discerned. This lack of effect was unaltered by duration of use of statin dose. van Staa et al suggest that the previously reported observational reports of statin-associated reduced fracture rates may have been due to the confounding effects of obesity in these patients. ■

The Therapeutics & Drug Brief was written by Louis Kuritzky, MD.

CME questions

Testing form inserted in the July 2001 issue

11. Routine antibiotic treatment of uncomplicated acute bronchitis is not recommended, regardless of the duration of cough.

a. True
b. False

12. The following statements are true of the association between ovarian cancer and postmenopausal hormone therapy except:

a. The epidemiologic data thus far include only women using unopposed estrogen regimens.
b. There is no evidence that short-term estrogen therapy increases the risk of ovarian cancer.
c. Survivors of ovarian cancer should not use postmenopausal estrogen therapy.
d. Hopefully, combined postmenopausal regimens of estrogen and progestin will protect against ovarian cancer like combined oral contraceptives.

13. Use of pH monitoring to demonstrate abnormal esophageal acid exposure reliably predicts a favorable response of laryngeal signs and symptoms to a minimum of 3 months of aggressive PPI treatment.

a. True
b. False

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