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INSIDE

Statins and Cancer Protection

ABSTRACT & COMMENTARY

Synopsis: *In an observational study, enabled by a powerful drug-dispensing record linkage system, statin use among a large number of patients treated with cardiovascular drugs was associated with a 20% reduction in incipient cancer diagnosis over a 7-year period. Although not a definitive answer, drugs in this class may have cancer protective properties, and certainly further investigation is warranted.*

Source: Graaf MR, et al. *J Clin Oncol*. 2004;22:2388-2394.

Because of their efficacy in reducing cardiovascular events, and decreasing morbidity and mortality, 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are often used in the treatment of lipid disorders, particularly hypercholesterolemia. Statins inhibit HMG-CoA reductase, an enzyme that is involved in the cholesterol biosynthesis pathway, which in turn directly leads to a decrease in the production of mevalonate, a precursor of cholesterol. Mevalonate is also the precursor of farnesyl and geranylgeranyl moieties, both of which are necessary for the activation of an array of intracellular proteins through farnesylation or prenylation. One protein that is dependent on this farnesylation is the Ras protein, which is important for the regulation of cell differentiation and proliferation. Approximately 30% of all human tumors have a mutation in k-Ras oncogene, and its expression is thought to be related to abnormal cellular growth. Thus, it has been hypothesized that statins, through inhibition of HMG-CoA, and consequently inhibition of the Ras protein, would reduce the expression of the malignant phenotype of a tumor cell and restore normal cellular growth. Several previous studies have implied that statins have antitumor potential.

Graaf and colleagues from the Academic Medical Center, Departments of Clinical Pharmacy and Oncology, in Amsterdam, in conjunction with the Department of Pharmaco-epidemiology and Pharmaco-therapy at the Utrecht Institute for Pharmaceutical Sciences (UIPS) in the Netherlands, conducted a population-based, nested, case-control study to investigate the relationship between statin therapy and the risk of cancer.

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For this, data were collected from the PHARMO record linkage system, which is a database that contains drug-dispensing records for a population of approximately 300,000 individuals residing in eight medium-sized Dutch cities. The current study included all patients with prescriptions for cardiovascular drugs between January 1, 1985, and December 31, 1998. Cases were identified by a diagnosis of incident cancer. Overall, 3129 subjects developed a diagnosis of cancer during this period, and these were matched with 16,976 controls that were free of a cancer diagnosis. Statin use (at least six months worth) was associated with a risk reduction of incident cancer of 20% (adjusted OR, 0,80; 95% CI, 0.66 to 0.96). Additionally, when the patients using the statins were compared to those using other lipid-lowering therapies, an adjusted risk estimate of 0.89 (95% CI, 0.56-1.41) was found.

COMMENT BY WILLIAM B. ERSHLER, MD

Statins as a group are remarkable. Their lipid lowering capacity is irrefutable, and their widespread use has been associated with reduced morbidity and mortality in a wide range of cardiovascular domains.[1] Furthermore, perhaps because of anti-inflammatory properties,[2] amelioration of seemingly diverse clinical disorders such as Alzheimer's disease[3] and osteoporosis[4] has been proposed. The current observational study extends even further, the potential value for these compounds. Although a risk reduction of 20% would be considered modest and possibly even questionable, in light of the number of potential methodological confounders in a study such as this, it is consistent with a similar study in which the risk of incident cancer was reduced by 28% when statin users were compared with users of other lipid-lowering agents (bile acid-binding resins).[5] Furthermore, the investigators went through great effort to appropriately match cases and controls and in other ways minimize these inherent confounders. One example is the use of the PHARMO record linkage system, which captures prescription distribution and diagnoses into a powerful database. The database, however does not include lifestyle factors, such as cigarette smoking, diet or chronic stress, or associated socioeconomic factors, all of which may be relevant in choice of drug, and possibly compliance. Subjects included in this analysis (cases and controls) were all 'cardiovascular' patients, inasmuch as they were prescribed cardiovascular medications. For one reason or another, physicians chose to prescribe statins in some patients and not in others, and those factors that influence prescription pattern may also, through mechanisms unrelated to the drug, relate to cancer development or growth.

Nonetheless, the findings from this observational study are intriguing and warrant further investigation. Although the mechanism of protection as proposed in this paper (inhibition of farnesylation and thereby Ras activation) is quite plausible, others are as well. These would include free radical inhibition and modulation of proinflammatory cytokines, which are among the pleiotropic pharmacological effects observed with this class of compounds. By whatever mechanism, it would seem that a well-designed prospective clinical trial might resolve the issue of whether or not a cancer-protective effect exists. The difficulty is going to be finding enough volunteers who are not already taking a drug in this class! ■

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Treatment of Depression: When Do Symptoms Go Away?

ABSTRACT & COMMENTARY

Synopsis: *Physical symptoms are quite common among patients with depression. These symptoms tend to improve during the first month of therapy with serotonin-antagonists. Most symptoms will plateau in months to follow.*

Source: Greco T, et al. *J Gen Intern Med*. 2004;19:813-818.

This study was aimed at evaluating the prevalence, impact on quality of life, and outcome of physical symptoms in patients with depression. It was designed as an open-label, randomized, intention-to-treat trial and was performed within a research network of 37 primary care clinics over a 6-month period. The study was part of the ARTIST (A Randomized Trial Investigating SSRI Treatment) study. Those patients who were deemed clinically depressed by their primary care physician and considered to be candidates for antidepressant therapy with serotonin-antagonists were eligible for inclusion in this trial. Patients were excluded if they had cognitive impairment, terminal illness, residence in an extended care facility, had recent active suicidal attempts or had been under pharmacological treatment for depression in the prior 2 months, had opiate or cocaine use, or if they had a history of bipolar disorder.

Computer-administered telephone interviews were used to conduct baseline and follow interval at 1, 3, 6, and 9 months after enrollment. Depression outcome was measured with 2 measures of core depressive symptoms (the HSCL-20 survey based on the Hopkins Symptom Checklist, and the Patient Health Questionnaire), and medical comorbidity was also calculated for each patient. The prevalence of symptoms was determined at baseline and the follow-up intervals. A linear regression model was constructed to determine the effect of therapy on individual physical symptoms.

Of the initial 601 patients that gave informed consent, a total of 573 patients completed the telephone assessment and completed the trial. Of the 14 physical symptoms assessed, 13 were present in at least a third-to-half of the patients at baseline measurement. In follow-up assessments, every symptom showed the greatest improvement during the initial first month of therapy with serotonin antagonists. This improvement in symptomatology reached a plateau after the first month of pharmacotherapy. In contrast, other non-somatic depression symptoms continued to have a steady and gradual improvement over the 9-month study period.

COMMENT BY JOSEPH VARON, MD, FACP, FCCP, FCCM

Physical, rather than emotional, symptoms are the presenting complaints that the majority of depressed patients voice to their primary care providers. This trial confirms previous studies indicating that many patients with clinical depression have significant physical symptoms.[1-3] The study by Greco and associates is important as it presents interesting and compelling data regarding the improvement of physical symptoms with serotonin-antagonists with a peak during the first month of treatment.[4]

Most standard textbooks still consider that the maximum improvement in depression-related physical symptoms occurs weeks-to-months after the initiation of therapy with serotonin-antagonists. This study reveals that the improvement in physical symptoms will occur primarily during the first month of therapy and then the physical symptoms will plateau. On the other hand, it also notes that the non-physical symptoms of depression continue to improve after the first month.

Clinicians caring for patients with depression in whom somatic symptoms persist beyond one month of antidepressant therapy with serotonin antagonists should consider other treatment strategies. ■

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Dr. Varon is Professor at the University of Texas Health Science Center in Houston.

Hyperkalemia Risk Alert in Managing Heart Failure

ABSTRACT & COMMENTARY

Synopsis: *Patients treated with spironolactone and ACE inhibitors for congestive heart failure (CHF) have a markedly increased risk of hyperkalemia. In severe heart failure, while each of these drugs is effective, their combination may increase the risk of death if hyperkalemia is not prevented or quickly realized and treated.*

Source: Juurlink DN, et al. *N Engl J Med*. 2004;351:543-551.

In 1999, the randomized aldactone evaluation Study (RALES) clinical trial was published in the *New England Journal of Medicine* showing that spironolactone was highly effective in managing severe heart failure.[1] This was good news since spironolactone is an inexpensive drug and most primary care physicians are familiar with its use as a weak diuretic for hypertension and advanced liver disease. The risk of hyperkalemia using spironolactone is well known, but is generally mild if low doses are used, and low doses were shown to be effective in CHF. In the RALES clinical trial, there was a 30% reduced risk of death over 2 years in patients with severe heart failure, including patients also taking an ACE inhibitor.

However, in real world practice, Juurlink and colleagues found among a large Canadian population that spironolactone use in CHF was associated with increased hospital admissions for hyperkalemia and increased mortality (0.3 per 1000 to 2.0 per 1000 patients). The crux of the problem was the combined use of spironolactone and ACE inhibitors in patient with severe heart failure, often accompanied by some degree of renal insufficiency.

In an editorial in the same issue, McMurray and O'Meara describe the problem as the combined suppression of aldosterone in these elderly patients. In a controlled clinical trial, patients are carefully selected and monitored.[2] In the real world of undifferentiated patients and less stringent monitoring, different outcomes may occur. It is clear that using both spironolactone and an ACE inhibitor in elderly patients with severe heart failure and renal insufficiency is dangerous.

COMMENT BY JOSEPH E. SCHERGER, MD, MPH

Monitoring for serum potassium has been a standard part of patient care for hypertension and CHF. However, ever since the reduction in use of digoxin and diuretics together there has been a relaxation in concern about potassium problems. Now, with the polypharmacy often used with CHF patients, we have a new, clearly delineated concern. Use spironolactone and an ACE inhibitor together with extreme care. What is remarkable about this study is that the follow-up of an excellent clinical trial that showed lives saved resulted in an increased mortality in real world practice. I have not seen such a clear example of how carefully controlled research may result in much different outcomes from regular clinical practice. This result is humbling, and reinforces the caution that must be used when medications which show great promise individually are used together.

This study and the editorial are followed by a review article on managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system.[3] My awareness of the risk of hyperkalemia has been heightened by these articles. Seems like it's back to the days of thinking about potassium very seriously in patients with heart failure when certain medications are used. ■

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Gastroesophageal Reflux Disease, Barrett's Esophagus, and Esophageal Adenocarcinoma

ABSTRACT & COMMENTARY

Synopsis: *Esophageal adenocarcinoma (EAC), GERD, and Barrett's esophagus (BE) are all on the rise, and there is no doubt that BE is a major risk factor for EAC. However, many unanswered questions surround screening GERD patients for BE and cancer.*

Source: Chang JT, et al. *Arch Intern Med*. 2004;164: 1482-1488.

EAC has risen 300-350% since the 1970s from 0.7 to 3.2 per 100,000 population. Squamous carcinoma of the esophagus has declined from 3.4 to 2.2 per 100,000. EAC is particularly likely to occur in white males older than age 65. Regional differences in inci-

idence also exist, eg, twice as many cases in the Seattle area as in Utah. Although the precise pathogenesis of EAC is uncertain, its rise seems to correlate with GERD that may be symptomatic in up to 20% of the US population. Other EAC risk factors include GERD that awakens patients from sleep and reflux symptoms that have been present for more than 5 years. BE is the single most important risk factor for EAC. BE is defined as the replacement of normal squamous mucosa in the distal esophagus with specialized columnar mucosa. This article describes 10%-15% of GERD patients as having BE although these numbers may relate to collection of data primarily in tertiary centers. To confuse issues further, a recent survey of asymptomatic individuals described 25% prevalence of BE. Although some authorities believe that cancer risk is related to the length of BE, others attribute equal cancer risk to very short BE segments. It is said that BE increases the risk of EAC by 30 to 120 times over normal, and this article gives some credence to the notion that chronic GERD may be a predisposition to EAC even in the absence of BE. BE seems to have some genetic characteristics in that relatives of BE patients have variably increased likelihood of having both GERD and BE.

Chang and associates suggest that screening is appropriate for white male patients with more than 5 years of GERD occurring 2 times weekly who are older than age 50. They urge that patients without dysplasia should be screened every 3 years and that those with low grade dysplasia should have endoscopic surveillance annually. For high-grade dysplasia (particularly if multifocal or nodular), esophagectomy is recommended. In poor surgical candidates, nonsurgical ablation can be considered (despite poor and inadequate efficacy data). Although there is general agreement among pathologists about the presence of high-grade dysplasia (85%), the natural history of high-grade dysplasia is uncertain with 13-16% of patients with high-grade dysplasia progressing to EAC over periods of 3-7 years.

Esophagectomy is a procedure with substantial morbidity and mortality. No data confirm the use of any medical or surgical therapy for the prevention of the development of BE or progression to EAC. Several cost-effectiveness models of screening were described. One such model supported screening only of men older than age 50 with GERD, then surveillance only for those with both BE and dysplasia (cost, $10,440 per quality-adjusted life year), and another found similar costs-benefits for screening all 55 year old men with BE every five years. Chang et al remind us that there were 7860 cases of EAC in 2002 as compared to 107,300 new colon cancers and 169,400 new lung cancers.

COMMENT MALCOLM ROBINSON MD, FACP, FACG

There seems little doubt that GERD and BE predispose to esophageal adenocarcinoma (EAC). However, the arguments for expensive and widespread endoscopic surveillance seem less compelling. In addition to the almost infinitesimal risks of EAC for most patients with GERD, even BE patients will mostly have normal life expectancy with only 1-2% of deaths over 9-10 years of follow-up being due to EAC. The diagnosis of BE in any otherwise healthy patient has a number of potentially evil consequences including chronic psychological distress, and possible uninsurability (life, health, and disability). Nevertheless, the American College of Gastroenterology currently does somewhat indefinitely suggest possible screening of GERD patients for BE (nothing cited about age or duration of symptoms). Although I am a proud member of the ACG, it is hard not to think of this suggestion in the same light as asking a barber about desirability of a haircut. One hopes we will have clearer and increasingly data-based guidelines regarding GERD, BE, and EAC in the future.

Optimal Frequency of BNP Testing

ABSTRACT & COMMENTARY

Synopsis: *At this time, BNP seems to be a useful initial test that should not be repeated during short hospital stays.*

Source: Wu AHB, et al. *Am J Cardiol.* 2004;93: 1562-1563.

Since B-type natriuretic peptide (BNP) is elevated in patients with congestive heart failure, serial testing may be useful for determining the response to therapy. In order to establish the usefulness of serial testing, knowledge of the assay variability is required. Thus, Wu and colleagues performed a retrospective study of laboratory records at 2 large metropolitan hospitals to determine the optimal frequency of BNP measurements for this purpose. The study population consisted of 2748 samples from 1926 patients admitted for heart failure, approximately one-third of whom had a greater than or equal to 2 BNP measures done in the first week after hospitalization. Only patients with a greater than or equal to 2 BNP measures at 22 days were included. Their previous studies, in normal subjects and stable heart failure subjects, suggested that a difference of

100% in BNP values was the biologic variation cut point.

The likelihood of finding a significant difference in BNP values was lowest when blood was retested the next day (22%) or in 2 days (39%). The likelihood of finding a significant difference was highest when samples were 6 or 7 days apart (50%). Thereafter, the percentag, with a significant difference, fell off again. Overall, two-thirds of significant differences were decreases in BNP, suggesting that most patients improved. Wu et al concluded that daily, or every other day, monitoring of BNP, in patients admitted with heart failure, does not appear warranted.

COMMENT BY MICHAEL H. CRAWFORD, MD

This observational study, based upon laboratory records, is sobering, considering the widespread use of serial BNP testing today. However, it is in line with other recent studies that have not shown value for the indiscriminate serial use of BNP testing in hospitalized patients. The results are also in line with our thinking about heart failure treatment. Some patients will get immediate benefit from diuretics, which may be reflected in the one-fourth to one-third of patients whose BNP values do change significantly over the first 2 days, but many hospitalized patients (50% in this study) may take 6 or 7 days to improve enough to overcome the effects of cardiac structural changes on BNP level, such as left atrial dilation. Also sobering is the magnitude of change required to be biologically significant, 100%. This value is based upon their previous work showing that a significant serial BNP change in normal subjects was 129% and for stable heart failure subjects was 77%. They used the average difference of 100% for this study. Had they used the lower value, perhaps BNP would have looked somewhat better, but I doubt it would have materially changed the results. At this time, BNP seems to be a useful initial test that should not be repeated during short hospital stays. ■

Dr. Crawford is Professor of Medicine, Associate Chief of Cardiology for Clinical Programs University of California,San Francisco.

Pharmacology Update

Estradiol Transdermal System (Menostar)

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

THE FDA HAS APPROVED A LOW DOSE ESTRADIOL transdermal patch for prevention of osteoporosis in menopausal women. Menostar provides the lowest dose of estrogen of any product on the market, so low in fact that concomitant progestins are only required once or twice per year for women with an intact uterus. This estradiol transdermal system is manufactured by 3M Pharmaceuticals and marketed by Berlex.

Indications

The estradiol transdermal system is indicated for the prevention of postmenopausal osteoporosis.[1]

Dosage

The transdermal system should be applied to a clean, dry area of the lower abdomen once weekly. The site should be rotated with an interval of at least 1 week. It is recommended that women with an intact uterus be treated also with a progestin for 14 days every 6-12 months and undergo an endometrial biopsy yearly or as clinical indicated.[1]

The transdermal system releases 14 mcg of 17-estradiol per day.

Potential Advantages

Menostar delivers the lowest dose (14 mcg) estrogen currently available with the next lowest dose being 25 mcg daily. Menostar has been shown to produce an increase in bone mineral density (BMD) of 3% above baseline at the lumbar spine and 0.84% above baseline at the hip after 2 years of treatment.[1]

Potential Disadvantages

Menostar is not indicated for the treatment of postmenopausal symptoms and there are no data regarding fracture prevention. Even with this low dose of estrogen, progestin therapy is still recommended in patient with intact uterus albeit less often.

Comments

Menostar is the latest estrogen formulation to be approved at a time when estrogen therapy has come under increased scrutiny. It is approved only for the prevention of osteoporosis. The efficacy and safety was assessed in a 2-year, randomized, placebo-controlled, multicenter study in 417 postmenopausal women ages 60 to 80. BMD was increased by 3% above baseline at the lumbar spine compared to 0.4% for placebo. At the hip the increase was 0.84% vs -0.71% respectively.[1] Application site reactions were reported to be 9%. Menostar is more expensive then the previous low dose estradiol patches. Its average wholesale cost is $49.50 for 4 patches (one month) compared to $33.91-$38.13 for Climara, Alora, or Esclim.

Clinical Indications

Since the findings of the Women's Health Initiative (WHI) and the Women's Health Initiative Memory Study (WHIMS) estrogen have fallen out of favor in general and specifically for preventing osteoporosis. Bisphosphonates are now the preferred therapy for both preventing and treating osteoporosis. The American College of Obstetrics and Gynecology does not recommend hormonal treatment solely for the prevention of osteoporosis.[2] Hormonal treatment may be appropriate, however, for the control of postmenopausal symptoms. It is not known whether Menostar is effective in managing these symptoms and it is not FDA approved for this indication. ■

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CME Questions

7. **Which of the following answers is definitely false?**
   The risk of esophageal adenocarcinoma in Barrett's esophagus without dysplasia is:
   a. so high that such patients must invariably continue annual endoscopic surveillance for life
   b. so low that it may be undesirable to make the diagnosis at all
   c. so low that some believe that no surveillance may be necessary after initial diagnosis
   d. so high that some authorities recommend lifelong PPI treatment even for asymptomatic patients
   e. so low that some authorities doubt the utility of any therapy

8. **What is the mechanism of hyperkalemia in patients receiving spironolactone and an ACE inhibitor?**
   a. Increased production of aldosterone
   b. Stimulation of the renin-angiotensin-aldosterone system
   c. Decrease production of aldosterone
   d. Excessive dietary potassium

9. **In the recent report of cancer development in statin-treated patients, the observed reduction in cancer incidence among statin users was approximately:**
   a. 5%
   b. 20%
   c. 50%
   d. 95%

Answers: 7 (a); 8 (c); 9 (b)

By Louis Kuritzky, MD

Folate Therapy and In-Stent Restenosis and Coronary Stenting

OBSERVATIONAL DATA HAVE SUPported the role of homocysteine (HCS) as a cause of or contributor atherosclerosis. Randomized trials of interventions to reduce HCS have provided conflicting results, although some of the most positive results in favor of interventions to lower HCS (specifically, folate-based treatment) have been in the realm of coronary stent restenosis. Lange and colleagues provide a randomized trial of HCS lowering after coronary stent placement.

After successful coronary stenting, subjects (n = 636) were randomly assigned to folate therapy for 6 months (folate, vitamin B-6, and vitamin B-12 given initially IV, then orally) or placebo. Study outcomes included luminal diameter and rate of restenosis.

In the study group as a whole, in contrast to some prior data, folate-based treatment was associated with a higher restenosis rate and a higher percentage of patients requiring repeated revascularization. On the other hand, there was a trend (confidence interval crosses unit risk) towards restenosis benefits in some important subgroups: diabetics, women, and persons with baseline marked elevations of HCS (> 15 micromol/L). These data do not support the routine employment of HCS modulating treatments such as folate based therapy in an effort to reduce rates of restenosis. ■

Lange H, et al. N Engl J Med. 2004; 350:2673-2681.

Quinapril Reduces Markers of Oxidative Stress in the Metabolic Syndrome

THE METABOLIC SYNDROME (MBS) MAY be defined as 3 or more of: increased waist circumference (men > 40 inches, women > 35 inches), triglycerides > 150, reduced HDL (men < 40, women < 50), BP > 130/85, and fasting blood sugar > 100. MBS is highly prevalent and is associated with meaningful increases in risk of stroke and myocardial infarction; since markers of an abnormal pro-oxidative state in MBS may be indicative of pathways to development of atherosclerosis, studies of agents which affect inflammatory or oxidative states are of interest.

The renin-angiotensin-aldosterone system (RAS) appears to modulate vasculopathic changes through inflammation and oxidation, amongst other paths. Quinapril (Q-pril), an ACE inhibitor, has shown efficacy in management of hypertension, but has not been heretofore specifically studied for oxidative effects in a MBS population.

MBS subjects (n = 40) were randomized to Q-pril 20 mg/d or placebo. Markers of oxidation included 8-isoprostane, erythrocyte superoxide dismutase activity, and LDL oxidation lag time. After 4 weeks, favorable effects on all markers were seen. Because a normotensive population was chosen, and blood pressure change over time was not significantly different from placebo, the changes on oxidative state markers appear to be independent of blood pressure. Whether modulation of such surrogate markers will translate into clinically meaningful end points remains to be determined. ■

Khan B, et al. Diabetes Care. 2004 Jul;27:1712-1715.

Donepezil in Patients with Alzheimer's

BECAUSE USE OF CHOLINESTERASE inhibitors is neither inexpensive nor without significant potential adverse effects, their long-term impact on patients with dementing disorders like Alzheimer's Disease (ALZ) is important to define.

Although measurable positive impact upon cognitive tests and global measures of change over the short term are encouraging, long-term results may provide a better vantage point from which to discern the risk-benefit balance of such treatment.

The AD2000 Collaborative Group carried out this study. Subjects (n = 566) were enrolled defined by DSM IV ALZ criteria, although a small minority also suffered concomitant vascular, parkinsonian, or psychotic disorders. All patients were naïve to anticholinergic CNS agents at the outset of the trial.

Study subjects were randomized to placebo or donepezil, beginning at 5 mg/d; long-term treatment was maintained for 3 years at 5-10 mg/d. Outcomes included cognition (by the mini-mental state examination), functionality (by the Bristol activities of daily living scale), requirement for institutional care, and progression of disability.

Although cognition and activities of daily living were statistically significantly improved in the active treatment group, this did not translate into meaningful changes in the most important outcomes: institutionalization, progression of disability, behavioral symptoms, costs, and psychological well-being of the primary caregiver, none of which was favorably impacted by treatment. The study concludes that donepezil is neither clinically effective, nor cost effective. ■

AD2000 Collaborative Group Lancet. 2004;363:2105-2115.

In Future Issues: Lidocane Patch for Diabetic Neuropathy