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Motivating Women to Use Supplemental Calcium

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor, University of Southern California

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

Synopsis: *Women who do not take supplemental calcium frequently need more education, and state they would be positively influenced by their physician's recommendations.*

Source: Tyler CV, et al. *J Am Board Fam Med.* 2008;21:293-299.

In order to help understand why American women persistently have suboptimal calcium intake, the Cleveland Clinic Ambulatory Research Network was used for a nested cross-sectional patient survey of women aged 20 to 64 years old visiting 6 community family health centers. At each site 95% of eligible women agreed to participate, yielding 185 respondents of whom 43% had never used calcium supplements. The mean age of current users was 48 years old, and for non-users 40 years.

The primary reason stated for non-use was a lack of basic knowledge about the importance of calcium. Only 8% stated cost, convenience or taste as obstacles, and 4% blamed side effects such as constipation or upset stomach. Among the non-users, 40% were taking a daily multivitamin, compared to 80% of the users. They also differed from calcium users by being less likely to have a family history of osteoporosis, and less likely to take time for physical exams.

Non-users indicated they would be influenced by their doctor's recommendation: 96% of them agreed that they were "very likely" or "somewhat likely" to use calcium supplements if this occurred.

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■ COMMENTARY

Once again we see here the power of the personal physician's recommendation to influence health behaviors. Although this outpatient-based survey involves small numbers, it does attempt to capture the real-life situation in clinical settings. We know that calcium intake is crucial to preserve bone mass (and possibly other disease prevention), and we also know that achieving the minimum recommended daily intake is apparently very difficult for American women. Fully 75% of women of all ethnic groups had lower than recommended daily intakes of calcium in the last national survey.[1]

These findings provide further evidence that "brief office-based counseling strategies" are crucial for promoting calcium supplementation that may prevent major future disease. If a personal motivator can be identified, such as a family member with osteoporosis, success may be even higher. Since surveys indicate that 3-4 daily servings of dairy products are needed to meet minimum daily calcium requirements, promotion of calcium supplements remains our best hope of meeting this need.[2] This article suggests that daily doses of 500mg of elemental calcium (best absorbed from calcium citrate), combined with 200 IU vitamin D, should be strongly encouraged during routine office visits. ■

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How Often Does Mild Cognitive Impairment Progress to Alzheimer's Disease?

ABSTRACT & COMMENTARY

By F. Tuna Burgut, MD

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This abstract originally appeared in the August 2008 issue of Neurology Alert *and was peer reviewed by M. Flint Beal, MD.*

Dr. Burgut reports no financial relationships relevant to this field of study.

Synopsis: *Over a 5-year period, 16% of elderly people developed mild cognitive impairment (MCI) and had double the risk of developing Alzheimer's disease (AD) than normals; however, 30% with MCI reverted to normal.*

Sources: Manly JJ, et al. Frequency and course of mild cognitive impairment in a multiethnic community. *Ann Neurol.* 2008;63:494-506.

CORRECT IDENTIFICATION OF INDIVIDUALS WITH MCI and understanding the factors that affect the course of this transition between normal aging and AD or dementia is crucial in developing safe and effective disease modifying therapies. However, studies of the prevalence of MCI as well as the progression rates to AD or dementia may vary, depending on the implementation of MCI criteria, referral source, age at assessment, and duration of longitudinal follow-up. Manly et al studied the incidence rate of MCI and the progression of MCI to AD in a large population-based group of elderly adults from diverse ethnic, linguistic, and educational backgrounds over an average period of 4.7 years. They included: 2,364 subjects residing in Northern Manhattan, who were of Hispanic, African-American, and non-Hispanic white ethnicity, age 65 or older, who were at base-

line free of dementia and were followed with neurological, medical, psychiatric, and neuropsychological examinations to determine the incidence rate of MCI and AD. Over 7,504 person-years of follow-up, there were 379 incident MCI cases, in which age, Hispanic/African-American ethnicity, and presence of hypertension were determined as risk factors for development of MCI. The presence of the APOE allele was, surprisingly, not associated with a greater risk for development of MCI.

After 10,517 person-years of follow-up, there were 309 cases of incident AD. Further examination revealed that subjects with MCI at their initial visit had twice the risk of developing dementia compared to those who did not have baseline MCI. Those patients with MCI involving multiple cognitive domains with memory impairment were at more risk of developing AD. Older individuals with less education, of African-American/Hispanic heritage, with a positive history of diabetes or stroke, and presence of the APOE E4 allele also were at greater risk for developing AD.

An additional finding of the study was the quantitation of reversal rates of MCI to normal status. At follow-up visits of the 564 elderly subjects diagnosed with MCI at the beginning of the study, 30% did not have MCI or dementia at any follow-up visit and 46% were stable with MCI and did not progress to dementia or revert to normal status. The authors determined that elderly subjects with isolated impairment in only one cognitive domain were most likely to revert to normal at follow-up, regardless of the nature of the cognitive domain affected.

■ **COMMENTARY**

Interest is growing in identifying AD at an early "prodromal" phase prior to dementia and there have been several longitudinal studies examining the antecedents of MCI and AD; however, the differences in cohort types, the varying cognitive measures and cut off scores, and the differences in the use of diagnostic criteria with varying longitudinal follow-up periods have made it challenging to arrive at uniform conclusions. However, it is generally well accepted that age, gender, ethnicity, education, comorbid medical and psychiatric conditions, severity and multiplicity of cognitive deficits, apolipoprotein E4 polymorphism, and functional and neuroanatomical changes on neuroimaging are all useful predictors of the development of MCI or conversion to AD. Manly's study is especially important as many of these risk factors were examined in an ethnically and educationally diverse large population-based group. The evaluation of longitudinal outcomes of different MCI subtypes is valuable in understanding the underlying neuropathological mechanisms leading to conversion to AD. Also, the small group of 27 cases who underwent autopsy demonstrated that antemortem diagnosis of MCI or AD had high specificity but low sensitivity for AD, emphasizing the need for larger studies that examine the accuracy of MCI diagnosis with respect to neuropathology.

The average study duration was 4.7 years but certainly a longer follow-up period will provide more information on the progression rates from normal status to MCI and AD. The course of those individuals who revert from MCI to normal status also may change if followed for a longer duration. A shortcoming of this study is the absence of brain imaging, which would allow for characterization of cerebrovascular disease in this predominantly African-American/Hispanic population with a high incidence of hypertension and diabetes, as it is likely that cerebrovascular disease was under-detected in the cohort. ■

Coffee Consumption and Mortality: Reanalyzing the Data

ABSTRACT & COMMENTARY

By Joseph Varon, MD, FACP, FCCP, FCCM

Dr. Varon is Clinical Professor of Medicine and Professor of Acute and Continuing Care at the University of Texas Health Science Center in Houston; and Clinical Professor of Medicine at The University of Texas Medical Branch at Galveston.

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

Synopsis: *Regular ingestion of caffeine, either as coffee, tea or chocolate was followed in 2 large cohorts of men and women for more than two decades. When caffeine was consumed regularly, there was no increase in the overall mortality. Indeed, a modest benefit of caffeine consumption was noted on overall mortality and in particular death related to cardiovascular disorders. This effect was more pronounced in women.*

Source: Lopez-Garcia E, et al. *Ann Intern Med.* 2008; 148:904-914.

THIS STUDY WAS AIMED AT EVALUATING THE effect of caffeine consumption and the risk of death between two large cohorts of health care professionals. These cohorts included the Health Professionals Follow-Up Study (HPFS) and the Nurses Health Study (NHS), which were started in 1986 and

1976 respectively. Participants with pre-existing cardiovascular disease or malignancies were excluded from this study. A total of 41,736 men and 86,214 women were followed until 2004 for the purpose of this study. Participants were sent questionnaires in different years during the study period inquiring as to baseline caffeine consumption and most current ingestion patterns. The investigators estimated that each cup of coffee had 137 mg of caffeine while a cup of tea had 467 mg, a 12-ounce bottle of a soft drink had 46 mg, and a chocolate bar had 7 mg per ounce. Mortality was then followed by either the next of kin, or by accessing the National Death Index. The primary end point of the study was death from any cause and was classified on the basis of the International Classification of Diseases (ICD coding).

The HPFS participants were followed for 18 years and 6888 deaths were identified. Of them, 2049 had cardiovascular disease-related mortality and 2491 had malignancies. The NHS participants were followed for 24 years with 11095 deaths (2368 from cardiovascular illness and 5011 from cancer). After adjusting for confounding variables, such as cigarette smoking, alcohol intake and regular exercise, an inverse relationship between coffee consumption and death was noted. Mortality from all causes was statistically lower in those participants consuming several cups of coffee per week. This effect was more pronounced among women where there was a decrease of 18% in mortality for those drinking 2-3 cups per day and 26% on those consuming 4-5 cups per day. The majority of the risk reduction was related to less cardiovascular illness. Caffeine ingestion was not associated with the risk of dying from cancer.

■ COMMENTARY

This study showed an inverse association between caffeine consumption and mortality. A number of theories exist as to why caffeine ingestion could cause a decrease in mortality. Many have postulated the beneficial effects of caffeine on inflammation, and endothelial function.[1,2] In a previous study, these same investigators had shown an inverse relationship between coffee consumption with surface adhesion molecules and C-reactive protein.[3] Others have reported that regular caffeine consumption reduces low-density lipoprotein oxidation, therefore modifying atherosclerotic plaques.[4] However, the specific mechanisms explaining the protective effects of caffeine still require studying. For now and until new recommendations arise, a moderate consumption of coffee every day seems to be beneficial. ■

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Viagra for Women?

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

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

Synopsis: *Women who had sexual dysfunction that was believed to be a side effect of antidepressants were more likely to report improved sexual function if they were assigned to the sildenafil, rather than to the placebo arm of a placebo-controlled trial.*

Source: Nurnberg HG, et al. Sildenafil Treatment of Women With Antidepressant-Associated Sexual Dysfunction: A Randomized Controlled Trial. *JAMA.* 2008;300(4):395-404.

This study is the result of an 8-week, prospective, parallel-group, randomized, double-blind, placebo-controlled trial. Investigators at four different institutions (including the famous Kinsey Institute in Bloomington, IN), recruited women between the ages of 18-50 years who developed sexual dysfunction while taking a selective or nonselective serotonin reuptake inhibitor (SRI) for major depressive disorder. To be included in this industry-supported study, the participants had to have had satisfactory sexual function prior to the onset of depression or antidepressant treatment. The definition of sexual dysfunction is worth examining, and is taken from the DSMIV. To meet criteria for antidepressant-associated sexual dysfunction in this study, women had to have at least 1 of the following criteria that caused significant distress: (1) inability to have an orgasm (anorgasmia), according to the woman's opinion; (2) clinically significant orgasm delay with masturbation or intercourse that, according to the woman's opinion,

represented a meaningful delay compared with her usual time to achieve orgasm in response to sexual stimulation before antidepressant medication interfered with her sexual function; or (3) inability to attain or maintain until completion of sexual activity an adequate lubrication or swelling response of sexual excitement that, according to the woman's opinion, interfered with her sexual function (compared with before taking antidepressant medication).[1]

There were also many, many exclusion criteria for this study, including any of the following: diagnosis of a sexual disorder other than one associated with SRI treatment or onset of major depressive disorder, genital anatomical deformity, hysterectomy with or without oophorectomy, and at least 6 months of established normal sexual function after the procedure and before onset of depression and antidepressant treatment, uncontrolled psychiatric disorder, diabetes mellitus, cardiovascular disease, alcohol or substance abuse or dependence, stroke, unstable cardiac condition, arrhythmia, or myocardial infarction within the last 6 months, current or anticipated use of nitrate or nitric oxide donor in any form, major relationship changes, proliferative retinopathy, investigational drug use within 3 months, current use of other therapies or medications to treat sexual dysfunction, a sexual partner who has or is receiving treatment for sexual dysfunction, change in SRI antidepressant agent or prescribed dose during the study, use of hormone therapy; pregnancy; lactation; planning to become pregnant during the trial; of child-bearing potential and unwilling, unprepared, or judged unreliable to use an acceptable and verifiable form of contraception during the trial; Papanicolaou test results indicating further assessment; dyspareunia due to anatomical, inflammatory, infectious condition, or clinical estrogen deficiency; amenorrhea over 1 year; or situational sexual dysfunction.

Over a 40-month period, 145 women (recruited from outpatient clinic, newspaper ads and referrals) were assessed for eligibility. One hundred met criteria, and 98 were randomized to either placebo or sildenafil (50mg) 1 to 2 hours prior to sexual activity, optimally at least twice a week. Participants could increase the dose to 2 tablets in consultation with a study investigator. Outcome measures were the changes in four different questionnaires: the Clinical Global Impression (CGI) Scale of sexual function, the Sexual Function Questionnaire, the Arizona Sexual Experience Questionnaire, and the University of New Mexico Sexual Function Inventory-female version. The latter two questionnaires, which have been validated in patients with psychiatric disorders, were used for concurrent validity. The study participants were seen at baseline, 2, 4, and 8 weeks and these questionnaires were given each time. In addition, a variety of biochemical hormone measures were assayed during the study.

The baseline cohort had a mean age of about 36 years, most were married, and they had an average of 3 sexual problems apiece. Only 76 of the 98 women completed the study. Several variables improved for participants in each group. There was a statistically significant difference in the CGI score improvement for the active drug vs placebo drug, and 73% of those taking placebo compared with 28% of those taking active drug reported no improvement (as defined by a CGI score > 3). Women in the sildenafil group were more likely to report improvement in orgasm attainment on 3 of the questionnaires. There were no significant differences in depression over the course of the study, based on the Hamilton depression inventory. Except for increased free testosterone levels and thyoxine among the treatment responders, there were no differences in hormone levels over the course of the study. Most participants, placebo and sildenafil alike, increased the dose to 2 tablets (100mg). No serious adverse events were reported, but women on active drugs were statistically more likely to report flushing, dyspepsia, nasal congestion, and visual disturbances. However, those in the placebo group were more likely to report nausea. The authors concluded, "By treating this bothersome treatment-associated adverse effect in patients who have been effectively treated for depression, but need to continue on their medication to avoid relapse or recurrence, patients can remain antidepressant-adherent, reduce the current high rates of premature medication discontinuation, and improve depression disease management outcomes."

■ COMMENTARY

This article came to my attention because it was heavily publicized in the lay press. And it got published in *JAMA*. This work extends previous work demonstrating that phosphodiesterase type 5 inhibitor treatment improves sexual function in men who experience antidepressant-associated sexual dysfunction.[2] How big a problem is this in women? Depression is a serious, deadly illness, and its treatment is important. Women are about twice as likely as men to experience depression, and antidepressant-associated sexual dysfunction is estimated to occur in 30% to 70% of those who are treated with first- or second-generation SRI's.[3] Further, antidepressant-associated sexual dysfunction is believed to be a rea-

son for antidepressant nonadherence and subsequent depression relapse.[4] This first-ever study of the use of a phosphodiesterase type 5 inhibitor to treat antidepressant-associated sexual dysfunction in women has the potential to greatly expand the already huge market for these agents (though it should be noted that use of phosphodiesterase type 5 inhibitors for women with antidepressant-related sexual dysfunction is most definitely an off-label use, at present). On the other hand, it took investigators at 4 centers more than 3 years to accumulate 100 appropriate candidates for this study, which suggests that women may not be as preoccupied with sexual function or dysfunction as men are. ■

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Pharmacology Update

Aliskiren and Hydrochlorothiazide Tablets (Tektura®HCT)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

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

THE COMBINATION OF THE FIRST DIRECT RENIN inhibitor and hydrochlorothiazide was approved by the FDA this year for the treatment of hypertension. This combination is not indicated for initial therapy but as add-on therapy for those inadequately controlled on either agent alone or as a substitute for titrated components.[1] The combination is marketed by Novartis Pharmaceutical Corporation as Tektura HCT.

Indications

Aliskiren/HCTZ is indicated for the treatment of hypertension. It is recommended for use as add-on therapy under the following situations:[1]

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.

1. Blood pressure is not adequately controlled with either agent alone.
2. The patient is experiencing adverse events with either component and the combination permits dosing at a lower dose of that component and still achieve blood pressure control.
3. The combination is substituted for the titrated components for convenience pill burden.

Dosage

The recommended dose of aliskiren/HCTZ is 150 mg/12.5 mg once daily up to 300 mg/25 mg. If blood pressure is not adequately controlled after 2 to 4 weeks of therapy, the dose may be titrated to the maximum dose (300 mg/25 mg). The drug should be taken in a consistent routine manner with regards to meals. High fat meals decrease the absorption of aliskiren. No dosage adjustment is required for hepatic impairment or the elderly. The combination is not recommended for patients with severe renal impairment.[1]

Aliskiren/HCTZ is available as 150 mg/12.5 mg, 150 mg/25 mg, 300 mg/12.5 mg, and 300 mg/25 mg tablets.

Potential Advantages

The combination provides agents with two different mechanisms of action and is more effective than monotherapy with either component alone.[1,2] In addition aliskiren opposes the hypokalemic effect and elevation of plasma renin activity of hydrochlorothiazide.[2,3,4]

Potential Disadvantages

Adverse events that occurred at a higher frequency than placebo include dizziness (2.3% vs 1.0%) influenza (2.3% vs 1.6%), diarrhea (1.6% vs 0.5%), cough (1.3% vs 0.5%), vertigo (1.2% vs 0.5%), and arthralgia (1.0% vs 0.5%).[1] Aliskiren is metabolized by CYP3A4. Ketoconazole and atorvastatin decrease the level while irbesartan increases the level of aliskiren.[1] Aliskiren carries the same pregnancy warning as ACEIs and ARBs.

Comments

The renin-angiotensin aldosterone system (RAAS) is an important target for antihypertensive and heart failure therapy. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists are effective and well tolerated agents currently in widespread use. ACEIs and ARBs act on different parts of the RAAS pathway. As a result, compensatory feedback is activated. ACEIs increase plasma renin activity and angiotensin I while ARBs increase these as well as angiotensin II. In contrast aliskiren does not increase angiotensin I or II but does increase renin levels.

Aliskiren is a direct inhibitor of renin which is the enzyme responsible for the production of angiotensin II. In clinical trials, over 2700 subjects were exposed to aliskiren/HCTZ.[1] The combination provides more effective blood pressure reduction than either drug alone.[1,2] The placebo-adjusted systolic/diastolic blood pressure decrease ranged from 10-14/5-7 mm Hg for the combination (150 mg-300 mg/12.5 mg-25 mg) compared to 5-8/2-3 mm Hg for aliskiren and 6-7/2-3 mm Hg for hydrochlorothiazide.[1] The combination is well tolerated with less than 5% of subjects discontinuing as result of adverse events.[2]

Clinical Implications

Clinical experience with aliskiren is still limited. ACEIs and ARBs are still preferred due to their vast clinical experience. The combination of aliskiren/HCTZ is an effective alternative for patients inadequately controlled on other blood pressure regimens. ■

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CME Questions

31. Which of the following are most likely to initiate supplemental calcium use among American women?

a. low cost preparations
b. television advertising
c. recommendation of their doctor
d. government nutritional guidelines

32. In the study by Lopez-Garcia and coworkers, women ingesting 2-3 cups of coffee per day had mortality rate that was decreased by:

a. 3%
b. 7%
c. 18%
d. 33%
e. 38%

Answers: 31 (c); 32 (c)

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.

Androgen Deprivation Therapy for Localized Prostate Cancer

After skin cancer, prostate cancer (P-CA) is the most common cancer among American men. Guidelines suggest that for localized P-CA (stage T1 or T2) surgery, radiation, or conservative management (treatment deferred until demanded by disease progression) is appropriate. Despite the absence of major consensus group endorsement, androgen deprivation therapy (ADT) has been sufficiently popular that in a 2003 report, ADT was employed second only to surgery for localized disease.

When employed as an adjunct to radiation or surgery in high-risk P-CA (poorly differentiated or advanced stage), ADT has been associated with as much as 50% or greater mortality reductions.

Lu-Yao et al evaluated data on men aged 66 years or greater (n=19,271) treated with either ADT or conservative management only (ie, no definitive surgical or radiation therapy had been used). The population studied began accruing data in 1992, and men were followed through 2006.

ADT did not show advantage compared to conservative management for either mortality specifically related to P-CA or all-cause mortality. In fact, for the metric of 10-year prostate cancer-specific mortality, ADT was associated with a statistically significant 17% increased hazard ratio. Selecting the subgroup of men with poorly differentiated P-CA did not favorably affect overall mortality either, although in this subgroup there was a favorable impact on P-CA related mortality. Despite its recent popularity, ADT for localized disease has no mortality advantage over conservative management strategies. ■

Lu-Yao GL, et al. AMA. 2008;300(2):173-181.

Heart Failure Complicated by Atrial Fibrillation: Rate or Rhythm Control?

Among patients with atrial fibrillation (AFIB), clinical trial data have confirmed that outcomes using rate control are as favorable as using rhythm control. Since rate control is usually easier to attain, and medications for rate control are generally both less expensive and better tolerated than agents required for rhythm control, rate control is often the preferred strategy.

Patients with heart failure (CHF) who also have AFIB have a worse prognosis. Whether management of AFIB in heart failure is most advantageous with rate or rhythm control has not been fully elucidated, since the trial data upon which rate/rhythm equivalence is based were sparsely populated with heart failure patients.

Roy et al performed a randomized trial of rate vs rhythm control in heart failure patients with AFIB (n=1,376). Patients were followed for approximately 3 years. At the end of this trial, both mortality and all secondary outcomes were essentially equivalent with either intervention, although there was a trend towards greater CV mortality in the rhythm control group. Additionally, rhythm control patients experienced more hospitalizations.

Based upon these results, the authors suggest that rate control is preferred. Because pharmacologic treatments were used rather than radioablation techniques, no conclusions can be drawn about the relative efficacy of the latter. ■

Roy D, et al. N Engl J Med. 2008;358(25):266-277.

Pregabalin for Diabetic Peripheral Neuropathic Pain

Long-standing diabetes is associated with development of diabetic peripheral neuropathy (DPN). As many as 1 out of every 4 patients with diabetes eventually develops diabetic peripheral neuropathic pain (DPNP). In addition to the burden of pain, patients are often much disquieted by the worsening of DPNP symptoms at night which interrupts sleep and produces next-day excessive drowsiness.

Pregabalin is one of two agents approved for the treatment of DPNP in the last 2 years. Because our experience with pregabalin is relatively recent, this report which includes data from 7 randomized trials (total n= 1,510) may help bolster our knowledge base.

Daily pregabalin doses ranging from 150 mg-600 mg were all shown to be more effective than placebo when divided t.i.d.; when administered b.i.d., only a 600 mg daily dose was effective.

The literature has shown that patients with chronic pain report that a 30% reduction in pain from baseline is a clinically meaningful improvement.

Adverse events—most commonly dizziness, edema, weight gain, and somnolence are dose related. Less than 10% of patients discontinue treatment for any of these individual adverse events. ■

Freeman R, et al. Diabetes Care. 2008;31(7):1448-1454.

In Future Issues: **COURAGE and The Management of Stable CAD**