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INSIDE

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For Thyroid, Right Medication at the Right Time Makes a Difference

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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

Synopsis: *Clinicians should consider prescribing levothyroxine at bedtime since this study demonstrates significantly improved thyroid hormone levels compared to morning intake.*

Source: Bolk N, et al. Effects of evening vs morning levothyroxine intake: A randomized double-blind crossover trial. *Arch Intern Med* 2010;170:1996-2003.

Levothyroxine remains one of the most commonly prescribed medications for a common disease, primary hypothyroidism. This treatment is administered with the aim of restoring clinical euthyroidism and maintaining normal serum levels of thyroid-stimulating hormone (TSH). While there exist other choices for treatment, levothyroxine monotherapy at an appropriate daily dose provides uniform levels of both thyroxine and triiodothyronine in the circulation without diurnal variation and, therefore, is the medication of choice in most patients with hypothyroidism.

Since about 70%-80% of the drug is absorbed, mostly in the small bowel, there is consensus that levothyroxine should be taken in the morning before breakfast to prevent interference in its intestinal absorption.[1] Interference with levothyroxine absorption has been documented for several drugs including raloxifene, antacids, cholestyramine resin, colestipol hydrochloride, sucralfate, iron sulfate, activated charcoal, foods, and herbal remedies.[2-4] Therefore, the drug manufacturers' prescribing information directs patients to take levothyroxine once daily on an empty stomach, 30 minutes to 1 hour before breakfast. However, it has not been adequately and systemati-

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cally studied whether intestinal absorption is better when the stomach is empty in the morning or at night. Since many patients are regularly prescribed multiple medications, it would make more sense to know which method of dosing would be more effective clinically.

Bolk et al conducted a randomized double-blind crossover trial among 105 consecutive patients with primary hypothyroidism visiting a Dutch hospital clinic between April 1, 2007, and Nov. 30, 2008. Patients who were pregnant or had a gastrointestinal tract disorder or thyroid cancer were excluded from the study. Patients were instructed during 6 months to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Patients were instructed to take the morning capsule on an empty stomach half an hour before breakfast and the bedtime capsule at night just before going to bed. Plasma thyrotropin, FT_4, T_3, creatinine, and lipid levels were monitored as well as blood pressure, heart rate, body weight, and quality-of-life variables.

Of the 90 patients who completed the trial and were available for analysis, the authors found that compared with morning intake, when levothyroxine was taken at bedtime, it significantly improved thyroid hormone levels. However, quality-of-life variables and plasma lipid levels showed no significant changes with levothyroxine intake at bedtime vs in the morning. Interestingly enough, after the study was completed, and the patients were given a choice, more than half of the patients decided to continue with bedtime intake of levothyroxine. The authors state that the conditions of chronic illness and obesity may be more to blame for the lack of thyroid hormone level changes translating into quality-of-life changes. Additionally, there may be other factors affecting quality-of-life in patients with hypothyroidism such as the newly discovered thyroid hormone metabolite thyronamine (not replaced by levothyroxine treatment) or the presence of an autoimmune disorder (such as Hashimoto's disease).

■ COMMENTARY

Comparative effectiveness research (CER) is designed to inform health care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options. Where evidence does not sufficiently exist, CER may be helpful in identifying new and emerging clinical interventions. Such is the case with the study mentioned above. The authors present data supporting the change in dosing of levothyroxine from morning to bedtime. While the sample size of the study was relatively small, it is a well-designed study and raises an important question: How many of our own patients are truly directed to or actually take levothyroxine on an empty stomach 30 minutes to 1 hour before breakfast?

There is another big picture question to be answered as experts and our political leaders embrace the idea of funding CER at unprecedented levels. As more timely and relevant research is conducted under CER and the results favoring more effective clinical treatment options are disseminated, who will decide when to pull the trigger and incorporate those changes into existing practices, which may often be in direct contrast with the conventional recommendations and guidelines?[5] Will there be the same delays in changing recommendations and practice guidelines as those that exist today? For the concept of CER to be successful, it is vital that not only research data are available, but also that mechanisms are developed to translate those findings in a timely manner into clinical practice. For example, based on the results of the above study, clinicians should direct patients to take levothyroxine at bedtime instead of mornings, provided that it is taken on an empty stomach. But I would have to think twice prior to changing my practice since giving this advice today would place me in direct opposition to the manufacturers' prescribing information. ■

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Questions & Comments
Please call **Paula Cousins**, Senior Managing Editor, at (404) 262-5488.

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Does Atorvastatin Have Anti-ischemic Effects?

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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

This article originally appeared in the December issue of Clinical Cardiology Alert. *At that time it was peer reviewed by Ethan Weiss, MD, Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Weiss reports no financial relationship to this field of study.*

Synopsis: *It seems reasonable to assume that atorvastatin has some anti-ischemic properties, based on the strong correlation between subjective angina reduction and reduction in objective ischemia demonstrated on AECG monitoring. However, there was no incremental benefit to the combination of atorvastatin and amlodipine.*

Source: Deanfield JE, et al. Potent anti-ischemic effects of statins in chronic stable angina: Incremental benefit beyond lipid lowering? *Eur Heart J* 2010;31:2650-2659.

Statins are a cornerstone of treatment for patients with coronary artery disease (CAD). Their powerful lipid-lowering and plaque stabilization effects are well known, as is their ability to reduce myocardial infarction (MI) and death. Statins have also been shown to improve endothelial function, but whether this results in less myocardial ischemia in patients with CAD remains unknown. Amlodipine has been shown to reduce episodes of transient myocardial ischemia detected by ambulatory electrocardiogram (AECG) monitoring. Thus, Deanfield and colleagues performed a randomized controlled trial to compare the anti-ischemic effects of atorvastatin and amlodipine in patients with chronic stable CAD.

Patients with chronic stable angina (≥ 2 episodes per week) were recruited from 46 centers in 13 countries. Inclusion criteria included a positive exercise test, documentation of CAD by either coronary angiography or nuclear perfusion scintigraphy, and a total cholesterol ≥ 200 mg/dL. Eligible patients underwent 48 hour AECG monitoring and could be included if they demonstrated ≥ 15 minutes of ischemia and/or ≥ 3 episodes of ischemia. Exclusion criteria were congenital heart disease, uncontrolled hypertension, systolic blood pressure < 100 mmHg, bradycardia, abnormal electrocardiogram, liver or muscle enzyme elevation, or severe dyslipidemia. After a placebo roll-in phase, patients were randomized to amlodipine (5 mg daily, increasing to 10 mg daily), atorvastatin (10 mg daily, increasing to 80 mg daily), or both. The trial continued for 26 weeks and the primary endpoint was the number of ischemic episodes on AECG monitoring at week 26. Patients also underwent exercise testing, angina diaries, and blood tests for cholesterol and c-reactive protein (CRP).

They enrolled 312 patients: 103 were randomized to amlodipine, 104 to atorvastatin, and 104 to the combination of both. Baseline characteristics were similar between groups with a mean age of 62 years and approximately 25% were diabetic. Importantly, baseline LDL, HDL, blood pressure, and antihypertensives and anti-anginal therapy were well matched. Baseline triglycerides were slightly higher in the amlodipine arm.

At 26 weeks, there was objective evidence of ischemia reduction in all groups. AECG monitoring showed an approximate 66% reduction in the number of ischemic events compared to baseline in all three groups ($P < 0.001$). There was no difference between groups. Subjective assessment of ischemia by angina diaries was also reduced equally across all three groups ($P < 0.001$ vs baseline). The number of nitroglycerin tablets used at week 26 was reduced in all groups compared to baseline ($P < 0.001$), but patients receiving amlodipine (alone or in combination) used significantly fewer nitroglycerin tablets than those receiving atorvastatin monotherapy ($P < 0.05$). During exercise testing, fewer patients developed angina in each group at 26 weeks compared to baseline, but there was no difference in time to angina or time to onset of ST segment changes in any group.

As expected there was a significant reduction in LDL cholesterol and CRP with atorvastatin (monotherapy or combination), but not with amlodipine. The reduction in ischemia correlated significantly with the reduction in CRP. There was a greater reduction in blood pressure with amlodipine, but this did not reach statistical significance in this patient cohort with well-controlled blood pressure at baseline. Adverse event rates were similar across groups with approximately 4% discontinuing the study medication in each group. The amlodipine groups had approximately an 8% rate of peripheral edema. There was one case of myalgia in each group, one case of elevated creatine kinase in each group, and no liver enzyme ab-

normalities. The authors conclude that atorvastatin was as potent an anti-ischemic agent as amlodipine.

■ **COMMENTARY**

Statins continue to delight us with new and unexpected salubrious effects. This study does not compare atorvastatin to placebo and, therefore, we cannot absolutely conclude that atorvastatin has anti-ischemic benefits. However, amlodipine has been shown in prior studies to have anti-ischemic effects compared to placebo and this study by Deanfield and colleagues shows a similar reduction in ischemia with atorvastatin and amlodipine. In addition, the strong correlation between subjective angina reduction and reduction in objective ischemia demonstrated on AECG monitoring strengthens their findings. Thus, it is reasonable to assume that atorvastatin has some anti-ischemic properties. This may explain, at least in part, the reduction in ischemia with medical treatment seen in the COURAGE trial.

It is interesting that there was no incremental benefit to the combination of both treatments. They appear to have different effects on inflammation, based on the CRP lowering by atorvastatin and not by amlodipine, yet similar overall effects on ischemia, suggesting different mechanisms of action. However, the lack of additional benefit would argue against this. Further studies are needed to elucidate the mechanism of the anti-ischemic effects. ■

Alcohol Use in Older Women

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: *Although most older women have stable patterns of alcohol use over time, they still need to be periodically questioned about alcohol use since some will increase their intake substantially after age 50, and may develop new risks for alcohol-related problems.*

Source: Bobo JK, et al. Alcohol use trajectories in two cohorts of U.S. women aged 50 to 65 at baseline. *J Am Geriatr Soc* 2010;58:2375-2380.

To investigate the natural history of alcohol intake in women after age 50, two randomly sampled, nationally representative large cohorts of older women initially between the ages of 50 and 65 were followed with biannual questionnaires for concurrent 8-10 year periods. The alcohol use questions covered the preceding 3 months and collected data on days of use and daily amount. These data were used to create group-based models of four drinking trajectories: infrequent or non-drinkers (62% of the largest cohort of 3233 women), increasing drinkers (5%), consistent drinkers (26%), and decreasing drinkers (7%). The percentages from the second cohort of 1017 women were very similar.

The majority of older women studied maintained a stable drinking pattern as they aged: consistent, infrequent, or non-drinkers were 87.7% of the largest cohort and 82.6% of the other cohort. Within the consistent drinkers, there was a trend over time to slightly decrease the amount of drinks per day, from 1.78 to 1.59 drinks in the first group and from 1.62 to 0.99 drinks per day in the second group.

The surprising finding was that 4.9% of the larger cohort and 8.8% of the smaller cohort reported notable increases in the number of drinks per day over the 8-10 years of the study.

■ **COMMENTARY**

This report demonstrates that the vast majority of older women have stable alcohol intake as they age, and may even decrease their intake with time. A similar study of women enrolled at ages 45-64 also found that 81% of baseline drinkers and 88% of non-drinkers reported no change in drinking status over 6 years of follow-up.[1]

The American Geriatrics Society actually has posted clinical guidelines for low-risk alcohol use in older adults on their web site, and recommends no more than 7 drinks/week with a maximum of 2 drinks on any one occasion. However, these amounts have been questioned since safety may be specific to what medications or chronic diseases are present, and there is scant research support for older adults having different guidelines from younger ages if health status is equivalent.[2]

The group that merits our attention are the small numbers that may actually increase their alcohol intake over time and put themselves at risk for alcohol-related complications. The authors promise to publish subsequent reports of which risk factors were associated with increasing and decreasing alcohol use to help us target these groups in the future. ■

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Taking Steps to Be Healthier

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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

Dr. Phillips is a consultant for Cephalon, and serves on the speakers bureau for Resmed and Respironics.

Synopsis: *Simply increasing the number of steps taken daily reduces obesity and improves insulin sensitivity in middle-aged adults.*

Source: Dwyer T, et al. Association of change in daily step count over five years with insulin sensitivity and adiposity: Population based cohort study. *BMJ* 2011;342:c7249; doi: 10.1136/bmj.c7249.

These Australian investigators set out to see if change in objectively measured physical activity affected risk factors for diabetes in middle-aged Australians. They worked with a subset of the AusDiab study cohort,[1] which was designed to estimate the national prevalence of diabetes and its risk factors. The population presented in this analysis included 592 participants who were evaluated in 2000 and 2005. At enrollment in 2000, these people were about 50 years old, and a high proportion of participants were overweight or obese; the mean body mass index was 27.1 kg/m^2 for men and 26.0 kg/m^2 for women. In addition to the usual anthropomorphic measures, data collected included a questionnaire to report the frequency and duration of physical activity in the previous week, pedometer reading over a 2-day period, smoking status, educational level, food frequency questionnaire, alcohol use, and homeostatic assessment of insulin sensitivity (HOMA insulin sensitivity). At baseline in 2000, average daily step count correlated with self report of walking/moderate activity and with self reported vigorous activity.

Over the 5 years of follow-up, most people gained weight; the men gained an average of 1.3 kg and the women gained an average of 1.6 kg. (Coincidentally, the number of smokers fell from 14.% to 11.2% for men, and from 11.2 to 10.6% for women — what do the Australians know that we don't?) A majority of people also reduced the number and the intensity of steps over the 5-year period. On average, men fell from 10,172 to 9108 steps daily, and women from 10,969 to 8700 steps daily. (For reference, there are about 2000 steps in a mile, and 10,000 steps is close to 5 miles[2]). Despite this overall fall in steps/day for the group as a whole, more than a third had more daily steps by 2005.

Both higher daily steps in 2000 and higher daily steps in 2005 than in 2000 were associated with a lower body mass index, a lower waist-to-hip ratio, and greater insulin sensitivity in 2005. Self-reported physical activity time was also generally associated with improved outcomes for BMI and insulin sensitivity.

Based on the data, the investigators calculated that if a relatively inactive person increased his or her daily steps by 10,000 a day, this would result in a decrease in body mass index of 0.83 units and a 13.85-unit improvement in insulin sensitivity. By increasing the number of daily steps by 2000, the resultant changes would be a decrease of 0.16 units for body mass index and an improvement of 2.76 units for insulin sensitivity. Further calculation demonstrated that the effect of higher step activity on improved insulin sensitivity resulted mostly from reduced adiposity.

■ COMMENTARY

Previous studies have demonstrated that increased physical activity reduces weight and improves insulin resistance.[3-5] What is new about the current study is that this population was not selected or randomized, that physical activity was objectively monitored (with a pedometer), and that the study was long term (5 years).

Addressing obesity is a daily challenge for many clinicians. This report reminds us that a person doesn't have to join a gym or go on an extreme diet to have improvement in weight or insulin sensitivity. Practical information about ways to increase the number of steps taken is available on the internet,[2] as are inexpensive pedometers.

And the benefits of physical activity (especially walking) appear to extend far beyond control of weight and glucose metabolism. Regular, moderate physical activity is associated with a reduction in mortality, reduced risk of coronary heart disease, improved lipid profile, lowered blood pressure, and reduced risk of stroke.[6,7] Further, reduced risk of breast and colon cancer, increased bone density, and reduced risk of dementia have also been reported in those who continue moderate physical activity as they age.[7] We need to remind and encourage our patients to get a move on! ■

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Pharmacology Update

Eribulin Mesylate Injection (Halaven™)

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

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

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

A NEW CHEMOTHERAPEUTIC AGENT HAS BEEN APPROVED FOR the treatment of metastatic breast cancer previously treated with other chemotherapeutic agents. Erbulin mesylate is a member of a new chemical class of halichondrins that exerts its pharmacologic effect by inhibiting the growth phase of microtubules. Eribulin mesylate is marketed by Eisai Inc., as Halaven™.

Indications

Eribulin is indicated for the treatment of metastatic breast cancer in patients who have been treated with at least two chemotherapeutic regimens that included an anthracycline and a taxane (either as adjuvant or in a metastatic setting).[1]

Dosage

The recommended starting dose is 1.4 mg/m^2 given intravenously over 2-5 minutes on day 1 and 8 of a 21-day cycle.[1] The dose should be reduced in patients with mild-to-moderate hepatic impairment and moderate renal impairment. The dose should be delayed or reduced based on the severity of hematologic and non-hematologic toxicities.

Eribulin mesylate injection is available as 1 mg/2 mL single-use vial.

Potential Advantages

Eribulin showed an overall survival advantage over treatment of physician's choice (13.12 months vs 10.65 months) in patients with metastatic breast cancer who were previously treated with a median of four regimens that included an anthracycline and a taxane.[1,2] There are no known drug-drug interactions involving CYP450 isoenzymes or P-glycoprotein.[1]

Potential Disadvantages

Dose-limiting adverse events are mainly neutropenia (57% grade 3) and peripheral neuropathy (8% grade 3).[1] Other adverse events include asthenia/fatigue and alopecia. Eribulin may cause QT prolongation. ECG monitoring is recommended in patients susceptible to QT prolongation (e.g., CHF, bradyarrhythmias, or on drugs known to prolong QT interval).

Comments

Eribulin is an inhibitor of microtubules, but unlike other inhibitors such as taxanes and vinca alkaloids, which inhibit both the shortening and growth phases, enibulin only inhibits growth phases.[2] The efficacy of eribulin was shown in a phase III study (EMBRACE). Women with locally recurrent or metastatic breast cancer who had received two or more chemotherapy regimens for advanced disease were randomized 2:1 to eribulin (1.4 mg/m^2 on days 1 and 8 of a 21-day cycle; n = 508) or treatment of the physician's choice (TPC; n = 254).[1,3] Approximately two-thirds of patients were estrogen receptor-positive, 28% negative; 49% progesterone receptor-positive, 39% negative; 16% HER2/neu receptor-positive, 74% negative; and 19% were triple negative. Patients had experienced disease progression within 6 months of their last chemotherapy regimen. TPC included any monotherapy or supportive care. Ninety-seven percent were on chemotherapy with the most common regimens being vinorelbine (26%), gemcitabine (18%), taxane (16%). The primary endpoint was overall survival and secondary endpoints were objective response rate (ORR), progression-free survival (PFS), and duration of response. The median survival was 13.1 months for eribulin and 10.6 months for TPC (hazard ratio, 0.81; 95% confidence interval [CI], 0.66-0.99; P = 0.041). ORR was 12% compared to 5% (P = 0.005). Median PFS was 3.7 months vs 2.3 months

(P = 0.09). The median duration of response was 4.1 months for eribulin (56 responders) and 6.7 months for TPC (11 responders). Serious treatment-related adverse events associated with eribulin were asthenia/fatigue, neutropenia, and peripheral neuropathy. A second trial is in progress (n = 1102), which compares eribulin to capecitabine as second-line therapy for metastatic breast cancer.[4]

Clinical Implications

Metastatic breast cancer has a 5-year survival of 23%.[5] Eribulin provides an alternative third-line therapeutic regimen for patients who have previously been treated but experience disease progression. ■

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CME Questions

4. In the study by Bolk et al, for patients with hypothyroidism, the most optimal time to take levothyroxine is:
a. morning.
b. evening.
c. bedtime.
d. noon.
e. anytime.

5. Which of the following is *not* anti-ischemic?
a. Amlodipine
b. ACE inhibitors
c. Atorvastatin
d. Coronary artery stenting

6. Of the following four drinking trajectories found in older women over time, which has the smallest numbers, but also needs the most attention?
a. Infrequent or non-drinkers
b. Increasing drinkers
c. Consistent drinkers
d. Decreasing drinkers

7. Increasing the number of steps taken daily:
a. reduces weight and increases insulin sensitivity.
b. reduces weight but does not affect insulin sensitivity.
c. increases insulin sensitivity but has no effect on weight.
d. has no effect on weight or insulin sensitivity.

Answers: 4. c, 5. b, 6. b, 7. a.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
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The effects of obesity upon activity of short-acting insulin analogs

Source: Gagnon-Auger M, et al. Dose-dependent delay of the hypoglycemic effect of short-acting insulin analogs in obese subjects with type 2 diabetes: A pharmacokinetic and pharmacodynamic study. *Diabetes Care* 2010;33:2502-2507.

The most recent ADA/EASD algorithm for management of type 2 diabetes (DM2) indicates basal insulin as an appropriate next step if glycemic goals are not attained with metformin and lifestyle interventions. After fasting glucose levels are controlled on basal insulin regimens, it is common to use prandial bolus insulin (especially short-acting insulin analogs) if A1c goals have not been reached. The activity profile of short-acting insulin analogs has been established by trials in either lean healthy subjects or type 1 diabetics; neither population may be pharmacokinetically or pharmacodynamically concordant with DM2, and most are overweight or obese. To examine these issues, obese DM2 subjects (n = 7) received lispro insulin and were monitored for time to peak insulin concentration, maximal attained insulin concentration, and efficacy for reducing glucose.

Absorption of low-dose lispro (10 units) was similar in DM2 and controls, but its hypoglycemic effect was less in obese persons. At higher doses (30 units and 50 units), however, both absorption and efficacy were diminished in obese DM2 subjects. The authors challenge the current perceptions of the utility of short-acting insulin analogs in DM2, reminding us that the purpose of prandial insulin is to provide rapid rise and rapid glucose-lowering effects, both of which appear to be diminished in obese individuals. In any case, these data confirm that clinicians might anticipate proportionately less "bang-for-the-buck" as they up-titrate short-acting insulin analog doses in obese DM2. ■

Atrial fibrillation risk: Choose your parents wisely

Source: Lubitz SA, et al. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *JAMA* 2010;304:2263-2269.

A familial component contributes to atrial fibrillation (a-FIB) risk, such that independent of other risk factors (e.g., hypertension), having a first-degree relative with a-FIB increases risk.

Using data from participants (n = 11,971) in the Framingham Heart Study, Lubitz and colleagues examined the relationship between having a first-degree relative (sibling or parent) with a-FIB and subsequent development of a-FIB during an 8-year window of observation.

Subjects with a positive family history had an increased risk of a-FIB compared to those without a family history (5.8% vs 3.1% over 8 years). Risk increased further with the number of family members affected by a-FIB. The younger the age of a-FIB onset in a family member, the greater the increase in a-FIB risk.

Overall, having a positive family history for a-FIB increased risk of new-onset a-FIB by 40%. Of all risk factors for a-FIB, hypertension is responsible for the largest population-attributable risk; whether treatment of hypertension in persons with demonstrated increased risk for a-FIB because of family history might provide reduction in a-FIB risk remains to be determined. ■

Seeking the best diet for weight-loss maintenance

Source: Larsen TM, et al. Diets with high or low protein content and glycemic index for weight loss maintenance. *N Engl J Med* 2010;363:2102-2013.

Identifying the "best" diet to achieve and maintain weight loss in overweight persons has been an elusive task. Even if a person is successful at reducing weight using a highly calorie-restricted diet over the short term, the choice of a preferred maintenance diet over the long term is ill-defined.

Larsen et al enrolled overweight adults who had successfully lost at least 8% of their initial body weight, and randomized them into diets based upon protein content and glycemic index. Five subgroups were thus defined based upon high or low protein (PRO) and glycemic index (GIN): high GIN + high PRO, high GIN + low PRO, low GIN + high PRO, low GIN + low PRO, and control). All subjects followed their respective diets for 26 weeks.

Both high PRO and low GIN were independently associated with lesser weight regain. Overall, adherence to diet and maintenance of weight loss was best with the high PRO + low GIN diet. It is possible that even greater benefit could have been achieved in relation to protein, because the actual separation of protein content between high PRO and low PRO of 5.4% was substantially less than the intended 12%. ■

In Future Issues: **Bright Light Therapy for Major Depressive Disorder in the Elderly**