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A Drink a Day for Women's Mental Health

ABSTRACT & COMMENTARY

Synopsis: *Moderate consumption of alcohol in women (about 1 drink daily) was associated with better cognitive scores at 2-year average follow-up in women aged 70 to 81 in the Nurses' Health Study compared to nondrinkers, while excessive drinkers did not show any association with either improvement or decline.*

Source: Stampfer MJ, et al. *N Engl J Med*. 2005:352:245-253.

THE NURSES' HEALTH STUDY ENROLLED 121,700 US FEMALE registered nurses aged 30-55 years in 1976, and has followed them every 2 years since with written questionnaires about lifestyle and health, along with dietary habits added in 1980. This article reports on a study on cognitive function begun in 1995 on participants aged 70 or older who were not institutionalized nor had a stroke (21,202 women).

A new strategy of telephone interviews to measure cognitive function was used, and responses were completed for 93% of the 12,480 women identified after exclusions for antidepressant use and fluctuating patterns of alcohol use. Approximately half were nondrinkers, 44% drank up to one glass daily, and 5% more than one glass. Baseline and follow-up interviews varying from 1.3 to 5.5 years were performed (average, 2-year follow-up). Data on alcohol consumption were collected from the most recent written questionnaire before the baseline interview for beer, red and white wine, and liquor. The accuracy of the questionnaire was validated by a smaller study using weekly dietary records lasting 3 months in which participants weighed or measured all their food and drinks.[1]

The telephone interview was modeled on the Mini-Mental State Exam with added standardized tests of immediate and delayed recall, verbal fluency, digit span backward, and 10-word list for verbal memory. Nurse interviewers were blinded to the participants' drinking status or the study's hypothesis. The telephone interview was also validated in another study, which featured both telephone and in-person interviews and found a correlation of 0.81, and confirmed the natural rate of cognitive decline to be similar in that study and this present one.

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Results without adjustment showed slightly better cognitive scores for drinkers of up to one drink daily (< 15 grams alcohol) compared to non-drinkers. However, the relative risk was more significant after adjustments for potential confounding factors of age, education, and other variables determined by regression models. No difference was found among the types of alcoholic beverage consumed, nor for diabetes. Final results suggested a decrease in the risk of cognitive impairment of 20% for consumption of up to 1 drink/day over the average 2-year follow-up of the study.

COMMENT BY MARY ELINA FERRIS, MD

Previous research from this study group has suggested that moderate alcohol consumption may add protection against cardiovascular disease in women,[2] and this large study now suggests further benefit to mental function. Stampfer and colleagues have validated their research strategies using dietary questionnaires and telephone interviews, but it is impossible to control for all variables in an observational study. Older persons who drink may be generally in better health than nondrinkers, and of course mental function is always hard to accurately measure.

There is ample evidence that excessive alcohol intake is deleterious to multiple body organs, including the brain, and in fact hidden alcoholism among elderly women is a serious concern often undetected by physicians. The accompanying editorial warns that alcohol consumption can be a *double-edged sword* with as many hazards as benefits for our patients. A substantial residue of uncertainty remains with research in this area, requiring more long-term studies to confirm a preventive benefit.

Moderate alcohol consumption may prevent cardiovascular disease and cognitive decline because it increases HDL cholesterol and reduces fibrinogen and other thrombotic factors, which reduce small thrombi in both heart and brain vessels. Although it's too early to promote widespread increased alcohol consumption for elderly women, we can feel reassured that low-to-moderate use may help, rather than harm, our patients. ■

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Sugar is Sweet, but Snoring is Boring

ABSTRACT & COMMENTARY

Synopsis. *Sleep apnea can exacerbate diabetes, and Continuous Positive Airway Pressure (CPAP) can improve glucose control in diabetic patients with sleep apnea.*

Source: Babu AR, et al. *Arch Intern Med.* 2005;165:447-452.

This study included 25 patients who had type 2 diabetes and sleep apnea. Their mean age was 50.7 years, and 16 of the 25 patients were men. They were recruited from a sleep clinic, and had fairly severe sleep apnea, with mean Apnea Plus Hypopnea

Indices of 56 events/hr, mean lowest oxygen saturations of 76%, and mean Epworth Sleepiness Scores of 14 (normals for these variables are < 5 events/hr, > 90%, and < 10). Their diabetes was also fairly longstanding and severe; their mean baseline hemoglobin A1C's were 8.3%, Body Mass Indices were 42.7 kg/m^2, and duration of diabetes was 8.3 years. Seventeen of these patients used oral agents, 4 used insulin, and 4 required both oral agents and insulin. After recruitment, participants underwent baseline testing of glucose, HbA1c, food diaries, and 72-hour continuous glucose monitoring. They also had standard in-laboratory polysomnography (sleep studies) and completed questionnaires. Patients were then treated with continuous positive airway pressure for at least 3 months. Half of the patients were compliant with CPAP, defined as use for an average of 4 hours/night. These patients tended to be heavier and male. One-hour post-meal glucose values were significantly lower after all 3 meals for those who were compliant with CPAP, but only after breakfast for the noncompliant group. HbA1C was significantly reduced for the 17 participants with an initial level greater than 7%; there was a highly significant correlation between HbA1c improvement and the number of days of CPAP use in the compliant group, but not in the noncompliant group. Fasting glucose levels fell for the group as a whole, but the change was not significant. There was a significant reduction in the number of glucose values greater than 200 mg/dL in the entire study population.

COMMENT BY BARBARA A. PHILLIPS, MD

We have known for awhile that sleep disturbance and sleep apnea are associated with an increased risk of glucose intolerance and insulin resistance.[1-4] Full-blown sleep apnea is not necessary in order to develop glucose intolerance or insulin resistance. In fact, snoring[5] and sleep deprivation[6] are associated with disruption in glucose homeostasis. In clinical practice, the relationship between sleep and glucose control is obviously most relevant for patients with diabetes. Most recently, Harsch et al demonstrated a rapid improvement in insulin responsiveness in 40 sleep apnea patients who were treated with CPAP, but not all of these patients were diabetics.[7] The current study advances our understanding of the relationship between sleep apnea and diabetes because all of the patients studied were diabetic, and because Babu and colleagues were able to measure CPAP compliance. Strong correlations between compliance and outcome have been reported in other studies of the benefits of CPAP. For example, Pepperell[8] and Becker[9] demonstrated that 4 or 5 hours (respectively) of CPAP use was necessary to lower blood pressure in patients with sleep apnea. The proven benefits of CPAP continue to accrue. Although it is burdensome treatment, it is highly effective treatment for patients who can comply. Reminding patients that effective CPAP use can help improve glucose control and blood pressure should become part of our management of the fast-growing segment of the population who have both the Metabolic Syndrome and sleep apnea.[10]

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How Should We Manage Sub-Clinical Thyroid Disease?

ABSTRACTS & COMMENTARY

Synopsis: *Treatment may be necessary but controversy still exists.*

Sources: Gharib H, et al. *Endocrine Practice*. 2004;10: 497-501; Surks MI, et al. *JAMA*. 2004;281:228-238

These studies note that: ". . .sub-clinical thyroid dysfunction is a common clinical problem with many controversial issues regarding screening, evaluation, and management."

To develop an evidence-based approach to unresolved issues, the American Association of Clinical Endocrinology (AACE), the American Thyroid Associ-

ation (ATA), and the Endocrine Society (TES), jointly sponsored a Consensus Development Conference which was held in September 2002.

The conference followed the principles of evidence-based medicine to make their recommendations. The published recommendations were not reviewed by members of the sponsoring organizations prior to their publication in 2004. After reviewing the recommendations and noting that there was still disagreement regarding some aspects of the recommendations, the leadership of the AACE, ATA, TES, appointed 2 members from each organization who practice clinical thyroidology to review these recommendations. Gharib and colleagues have now published the results of their review of the recommendations.

Treatment of Sub-Clinical Hypothyroidism

Sub-clinical hypothyroidism is defined as high levels of thyroid stimulation hormone (TSH) associated with normal levels of free thyroxin (free T4) and triiodothyronine (T3). The prevalence is 4-10% in the general population and up to 20% in women older than 60 years of age.

The original panel recommended against the treatment of patients with TSH levels between 4.5 and 10 mU/L; but that treatment was reasonable for patients with TSH levels > than 10 mU/L. The representatives from the reviewing organizations noted that evidence for not treating these patients was lacking and pointed out that thyroid failure was a continuum and, therefore, it might be reasonable to treat these patients.

Treatment of Sub-Clinical Hyperthyroidism

Sub-clinical hyperthyroidism is defined as low levels of TSH associated with normal levels of free T4 and free T3. It is more common in women, blacks, and the elderly.

The treatment panel recommended observing patients with partial suppression of TSH (levels, 0.1-0.4 mU/L), but to treat patients with complete TSH suppression (levels < 0.1 mU/L). The reviewing organizations agreed with these recommendations, but stated that the strength of evidence was insufficient for these recommendations to be definitive.

COMMENT BY RALPH R. HALL, MD, FACP

It is impossible to abstract the thorough academic and clinical approaches used in these evaluations and recommendations. Physicians who care for these patients should read the reports and the article with examples of patient problems that accompanies the paper by Surks and associates.[1]

A recent study, not available when these guidelines were written, lends support to treating sub-clinical hypothyroidism.[2] Serter et al studied 30 female pre-menopausal patients with TSH between 4 and 10 mU/L. Twenty-six healthy, euthyroid, subjects were used as controls. Pre-treatment total cholesterol (TC) and low-density cholesterol (LDL-C) were significantly higher in the sub-clinical hypothyroid group. Treatment targets for TSH were < than 2 mU/L. TC, LDL-C, and the TC/high-density cholesterol (HDL-C) ratio were significantly improved after 6 months of thyroid replacement therapy. Mean changes were -21 mg/dL for the TC and -30.3 mg/dL for the LDL-C and the TC/HDL-C ratio improved from 4.8 to 4.1. The changes are significant enough to substantiality improve the cardiovascular risk profile.

The argument against treating these patients was based on a study that found that 20% of the patients treated for hypothyroidism are treated with too large a dose of thyroxin with resulting TSH levels in the hyperthyroid range. Overtreating patients increases their risk of bone mineral loss and the potential for increased risk of cardiac arrhythmias.

Surks[3] has pointed out that the original panels' review "repeatedly states that the panels' recommendations were for populations and that physicians should use their best clinical judgment for management of individual patients."

The management of sub-clinical hypothyroidism is an instance where a therapeutic trial, for 6 months to 1 year, might be useful. Based on objective findings at 6 months to 1 year, a decision could be made to continue or stop the therapy. ■

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Dr. Hall is a member of the AACE

What's the Correct BP to Reduce Adverse CV Events?

SPECIAL REPORT

By Harold L. Karpman, MD

SEVERAL CLASSES OF PHARMACOLOGICAL AGENTS HAVE demonstrated benefits in hypertensive patients with CAD, but most published studies have, of necessity,

enrolled only patients with an elevated or borderline elevated blood pressure. Recent clinical trials have demonstrated benefits for both angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCB) in patients with coronary artery disease (CAD) with relatively normal or borderline elevated blood pressures. However, few studies have specifically targeted patients with angiographically documented coronary artery obstructions and normal blood pressures.[1-3] Because of the aging population and the increasing prevalence of diabetes, obesity, and lack of exercise, the number of persons with CAD is dramatically increasing and, therefore, it has become critically important for us to acquire prospective, randomized, trial data on the relative impact of various drugs and blood pressure levels on adverse outcomes in patients with CAD.

Dr. Steven Nissen and his colleagues from The Cleveland Clinic studied the effects of amlodipine and enalapril on cardiovascular events and atherosclerosis progression in 1991 patients with angiographically documented CAD in a carefully performed double-blind, randomized, multicenter, 24-month trial.[4] Patients with CAD and treated blood pressure within the normal range (< 140 mm Hg) were randomly assigned to receive a placebo, a CCB (amlodipine), or an ACE inhibitor (enalapril). Compared with placebo, amlodipine and enalapril reduced blood pressure similarly (approximately 5 mm Hg systolic) when added to beta blockers with or without diuretics. The patients assigned to amlodipine who had an average baseline systolic blood pressure of 129/78 mm Hg experienced a 5/3 mm Hg blood pressure reduction, a 31% relative reduction in adverse cardiovascular events (ie, hospital admissions for angina, coronary revascularizations) and demonstrated a trend toward reduced death, MI, and stroke. The enalapril group had a minimal blood pressure reduction (5/2 mm Hg) but also demonstrated a statistically nonsignificant 15.3% relative reduction in adverse cardiovascular events. An intravascular ultrasound (IVUS) sub study at 38 sites revealed a trend toward less progression of atherosclerosis in the amlodipine group vs the placebo group with significantly less progression in the subgroup with systolic blood pressures greater than the mean. Compared with baseline, IVUS showed significant progression in the placebo group, a trend toward progression in the enalapril group, and no progression in the amlodipine group.

The age-specific increase in risk for CAD mortality associated with usual blood pressures is continuous for systolic blood pressures > 115 mm Hg (ie, the absolute risk for CAD death in 50-59 year-old patients is approximately 3 at a systolic blood pressure of 120 mm Hg, about 8 at 140 mm Hg, and exceeds 30 for 180 mm Hg or higher).[5] This observation would suggest that the management of blood pressure is similar to the current management of LDL cholesterol (ie, lower is better) however, the physiological effects of blood pressure management are more complex because the distribution of systolic and diastolic blood pressures is continuous and it is difficult to the identify the "normal" blood pressure for any specific individual.[6] Nissen et al made their important observations on patients with normal blood pressures who were on appropriate medical therapy (ie, high rates of statin and aspirin use). Their observations that amlodipine used for 24 months results in a 31% relative reduction in adverse cardiovascular outcomes and a significant decrease in the progression of IVUS-measured coronary atherosclerosis suggest that the optimal blood pressure range for patients with CAD may be substantially lower than recommended by current guidelines. Their conclusions are guarded because the sample size consisted of only 2000 patients and because the end points were relatively broad (ie, not the traditional somewhat more rigid end points of death, MI, and stroke).

In summary, the most intriguing result of this study in my mind is to again raise the increasingly asked question of what is the optimal target systolic blood pressure to prevent coronary atherosclerosis progression. The optimal blood pressure level in patients with CAD remains unclear; however, published data suggest that it is clearly lower then the commonly accepted 140 mm Hg range, and more probably is in the 120 mm Hg range.[6,7] Multidrug strategies are usually needed to achieve lower blood pressure targets, especially in patients with diabetes and renal insufficiency, but the benefits appear to far outweigh the risks of these pharmaceutical agents and it now appears quite likely that the CAD population will also benefit substantially by dropping the currently accepted blood pressure guidelines to lower levels. The final answer to what is a normal blood pressure in the CAD population will have to await larger and perhaps longer-term studies of antihypertensive therapies but, for the time being, it would appear prudent to consider resetting the desired systolic blood pressure target range from 140 mm Hg to 120 mm Hg in those patients who can tolerate lower blood pressures without significant symptoms. ■

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Pharmacology Update

Pregabalin Capsules (Lyrica™)

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

PREGABALIN HAS BEEN APPROVED FOR THE MANAGEment of neuropathic pain. It is the second drug to be approved for the treatment of painful diabetic neuropathy (after duloxetine) and the first drug to be approved for both diabetic neuropathy and postherpetic neuralgia. Pregabalin is pharmacologically similar to gabapentin. It will be marketed by Pfizer as Lyrica™.

Indications

Pregabalin is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.

Dosage

The initial dose is 150 mg daily (in 2 to 3 divided daily doses) and may be increased after 3 to 7 days to 300 mg and to 600 mg after 7 days. The dose should be reduced in patients with renal impairment.

Pregabalin is expected to be available as 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg capsules.

Potential Advantages

Pregabalin is the first drug to be approved for both diabetic neuropathy and postherpetic neuralgia. In randomized, placebo-controlled studies, pregabalin provided significant improvement in pain relief, reduction in sleep interference, and various other secondary measures.[1-5]

Potential Disadvantages

The most common side effects include dizziness, somnolence, dry mouth, peripheral edema, blurred vision, weight gain, and difficulty concentrating. Peripheral edema is the third most common dose-related adverse event usually beginning within 2-4 weeks after drug initiation.[4,5] This event does not appear to be associated with worsening of underlying cardiovascular condition. Pregabalin requires dosing 2 to 3 times daily.

Comments

Pregabalin is a 3-substituted analog of gamma-amino butyric acid similar to gabapentin. It is believed be similar to gabapentin in pharmacological action.[1,2] Randomized, placebo-controlled studies in both postherpetic neuralgia and peripheral diabetic neuropathy were of very similar design. Primary end points were pain reduction based on an 11-point scale. Secondary end points included daily sleep interference score and various other measures that may differ among studies. These included quality-of-life surveys, patient and clinical global impression of change. Effective doses of pregabalin were 150 mg to 600 mg/d. Patients were excluded if they had previously not responded to doses of gabapentin ≥ 1200 mg/d. The percentage of patients with = 50% reduction in mean daily pain scores ranged from 26-50% for pregabalin 150 to 600 mg, compared to 10-20% for placebo. Significant improvements were also observed in weekly mean sleep interference scores, patient and clinician global impression and various quality-of-life surveys. Significant improvement was observed at week one. The most common side effects were dizziness (10-39% vs 2-15% for placebo), somnolence (5-27% vs 3-7%), and peripheral edema (3-19% vs 1-5%).[1,2] Side effects were dose dependent. The median onset of dizziness or somnolence was 2 to 3 days.[5] Discontinuation of therapy also appeared to be dose dependent, 32% (600 mg/d), 16% (300 mg), 11% (150 mg), 10% (placebo).[1] There are currently no published comparative trials with gabapentin, lidocaine patch, duloxetine, or tricyclic antidepressants (eg, nortriptyline). Studies with similar design have reported a similar magnitude of pain reduction with gabapentin relative to placebo.[6,7] Pregabalin is not yet available pending its classification as a controlled medication. Cost is also not available.

Clinical Implications

Neuropathic pain can be a debilitating form of pain. In the United States, about 1 million people may be affected by postherpetic neuralgia and another 3 million affected by painful diabetic neuropathy.[1,2] Pregabalin is the first drug to be approved for both diabetic peripheral neuropathy and postherpetic neuralgia. Due to the lack of comparative studies it's not known if it offers any clear clinical advantages over other drugs including its predecessor, gabapentin, which is available generically. ■

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CME Questions

12. Which one of the following statements is true?

a. All patients with sub-clinical hyperthyroidism should be treated.
b. A therapeutic trial of treatment for patients with sub-clinical hypothyroidism may be useful.
c. Sub-clinical thyroid disease is not common in clinical practice.

13. For patients with diabetes and sleep apnea:

a. CPAP use has no effect on diabetes control.
b. CPAP use improves diabetic control, regardless of hours of use
c. CPAP use worsens diabetic control.
d. CPAP use improves glucose control, and improvement correlates with compliance.
e. CPAP worsens diabetic control, particularly in those patients who use oral agents.

14. Amlodipine is:

a. much more effective then enalapril in lowering blood pressure.
b. not as effective as is enalapril in lowering blood pressure.
c. essentially equally effective as is enalapril in lowering blood pressure.
d. highly effective in reducing systolic blood pressure in the CAMELOT study.

15. The absolute risk for coronary artery disease death in 50-59-year-old patients:

a. bears no relationship to the systolic blood pressure
b. is 20 times higher for patients with a systolic BP over 180 mm Hg compared to patients with a systolic BP of 120 mm Hg.
c. is 10 times higher for patients with a systolic BP over 180 mm Hg compared to patients with a systolic BP of 120 mmHg.
d. is not continuous for systolic blood pressures > 115 mm Hg.

16. Intravascular ultrasound (IVUS) data:

a. is of no value in following the progression of coronary atherosclerosis.
b. revealed a trend toward less progression of atherosclerosis in the amlodipine treated group versus the placebo group.
c. Demonstrated significant progression of coronary atherosclerosis in the amlodipine treated group.
d. demonstrated minimal progression of coronary atherosclerosis in the placebo group.

17. Low-to-moderate alcohol use in women has been linked to which of the following health outcomes?

a. Increased risk of coronary heart disease
b. Increased risk of thyroid disease
c. Increased risk of liver disease
d. Decreased risk of cognitive decline
e. Decreased risk of diabetes

Answers: 12 (b); 13 (d); 14 (c); 15 (c); 16 (b); 17 (d)

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By Louis Kuritzky, MD

Risk Factors and Diabetic Neuropathy

ALTHOUGH WE HAVE RECENTLY enjoyed the FDA approval of two agents for treatment of diabetic peripheral neuropathic pain (duloxetine [Cymbalta], pregabalin [Lyrica]), as yet we have no treatment for diabetic peripheral neuropathy (DPN) itself. Trials in both type 1 and type 2 diabetes have shown that tight glycemic control reduces the incidence of DPN; additionally, tight blood pressure control has been shown to reduce the incidence of DPN in type 2 DM. Identification of potentially modifiable risk factors for development of DPN might aid clinicians in its prevention.

Studying subjects from the European Diabetes Prospective Complications Study (n = 3250), Chaturvedi and colleagues identified 276 cases of new onset neuropathy during an observation period of approximately 10 years. Multivariate analysis indicated that the greatest odds ratios for development of DNP were seen with duration of diabetes, A1C, BMI, and smoking.

Good glucose control is already a target to reduce incident DPN. When controlling for A1C and duration of diabetes, other prominent risk factors emerged. For instance elevated levels of LDL showed a 22-26% increase in odds ratio for DPN. Ultimately, the 2 factors with greatest increase in odds ratio for development of DPN were cardiovascular disease at the time of enrollment (ie, at baseline), in which case the odds ratio was almost triple, and microalbuminuria, which was associated with greater than a 2-fold increase. ■

Chaturvedi N, et al. N Eng J Med. 2005;352:341-350.

Stress Reduction in African Americans Treated for HBP

CARDIOVASCULAR DISEASE REMAINS the number one cause of mortality in America. The African American population shoulders a disproportionate burden of this mortality, likely due to a correspondingly increased incidence, severity, and prevalence of hypertension, and a greater degree of manifest target organ damage.

A diversity of available antihypertensive agents notwithstanding, only a fraction of hypertensive patients have reached and maintain currently identified blood pressure goals. Lifestyle modification may provide substantial reductions in blood pressure, but clinicians may commonly include only diet, exercise, and salt modulation as typical components. Schneider and colleagues evaluated whether stress reduction through Transcendental Medication might result in meaningful impact upon BP in African American men.

Study subjects (n = 150) were randomized to either Transcendental Meditation (TM) 20 minutes twice daily, progressive muscle relaxation, or health education classes, and were followed for 12 months. Compared to health education classes, the TM group enjoyed a significant reduction in antihypertensive medication. Although SBP did not differ significantly between treatment groups, diastolic BP was 2.7 mm Hg lower in the TM group. Looking just at the female subjects, TM impact was much more substantial, resulting in a BP change of -7.3/-6.9 vs -0.7/-3.0 BP change in subjects allocated to education classes. Transcendental Meditation is a specific meditation technique requiring specific, personal instruction. Whether other relaxation or meditation techniques might also be efficacious is unknown. ■

Schneider RH, et al. Am J Hypertens. 2005;18:88-98.

Folate Intake and the Risk of Hypertension

THERE ARE SEVERAL WAYS IN WHICH folate could play a vital role in the maintenance of vascular health. Folate treatment lowers homocysteine, an acknowledged cardiovascular risk factor. Folate supplementation has also been shown to lower blood pressure and improve endothelial cell function on a short-term basis. Whether long-term dietary and supplemental intake of folate is ultimately related to development of hypertension (HTN) has not been studied.

The Nurses Health Study I and Nurses Health Study II comprise more than 150,000 individuals who have been studied observationally since the early 1990s; they are considered separate studies because the former is comprised of younger women (age, 27-44 at enrollment vs age 43-70). Amongst this population, during the observation period 7,373 persons developed new-onset HTN.

In younger women, those who consumed 1 mg or more of folate daily enjoyed half the relative risk of developing HTN compared to women who consumed 0.2 mg or less. In older women, the results were similarly favorable, but less dramatic (RR = 0.82).

The evidence base linking folate intake with vascular health is plausible. These observational data strengthen the association between folate nutriture and maintenance of normotension. ■

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In Future Issues: Vitamin E Supplementation May Increase All-Cause Mortality