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Brain Food: It's Not About Fish Anymore

ABSTRACT & COMMENTARY

Synopsis: *High intake of vitamins C and E in food (not supplements) is associated with reduced risk of Alzheimer's disease.*

Source: Engelhart MJ, et al. *JAMA.* 2002;287:3223-3229.

THE ROTTERDAM STUDY IS A LONGITUDINAL STUDY OF HEALTHY elderly in The Netherlands. The current report is based on 5395 subjects who were recruited between 1990-1993 and followed until 1999. Engelhart and colleagues hypothesized that dietary antioxidants might reduce the risk of dementia.

The assessment of dementia occurred as follows: if a subject had a Mini-Mental State Examination (MMSE) score of 26 or less or a Geriatric Mental State Schedule (GMS) of 1 or more, he/she was administered the Cambridge Examination of Mental Disorders in the Elderly (CAMDEX) and an interview. If dementia was suspected based on the CAMDEX, the subject was evaluated by a neurologist and a neuropsychologist, and usually had magnetic resonance imaging of the brain. Dietary intake was evaluated both by checklist and by interview with a dietician. The checklist included questions about all foods and drinks consumed in the previous year, dietary supplements, and prescribed diets. The interview used an extensive, validated, semiquantitative food-frequency questionnaire. Engelhart et al were looking for intake of the following antioxidants: beta carotene, flavonoids, vitamin C, and vitamin E. Daily dietary intake of these antioxidants was calculated in mgs. Careful assessment of total and saturated fat also was done. Engelhart et al also obtained demographic, socioeconomic, and lifestyle data, as well as ultrasonography of the carotid arteries.

The mean age at baseline was 67.7 years, and 595 of the participants were women. Twenty-three percent were current smokers, 12% used antioxidative supplements, and 28% carried at least 1 APOE*4 allele.

Intake of flavonoids, but not of beta carotene, vitamin C, and vitamin E, was significantly associated with higher MMSE scores at baseline. Subjects were followed for an average of 6 years, during

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which 197 participants developed dementia (146 of these had Alzheimer's disease [AD]). After adjustment for a wide range of relevant confounders (age, gender, education, smoking, body mass intake, and carotid plaques, among others) high intake of dietary vitamin C and vitamin E were associated with reduced risk of AD. Supplements, beta carotene, and flavonoids were not related to the risk of AD at follow-up (though flavonoids intake was related to MMSE scores at baseline). For smokers, high intake of beta carotene and flavonoids was associated with reduced risk of AD. For participants with at least 1 APOE*4 allele, higher intake of all but flavonoids was associated with somewhat lower risk of AD.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

AD increases with age, and is the fourth leading cause of death in adults. It is more common in women than in men. Loss of memory, inability to reason, and gradual changes in behavior are the classic symptoms. The Alzheimer's patient will eventually die from this disease—usually within 8 years of symptom onset.[1] The emotional and fiscal toll of AD in countries with long life expectancies is staggering.

Apolipoprotein E (APOE) is a plasma protein involved in the transport of cholesterol. It is encoded by a gene on chromosome 19. Some 34-65% of individuals with AD carry the APOE *4 allele, but it is present in only approximately 24-31% of the nonaffected adult population. The risk of AD increases and the age of onset decreases with the number of APOE epsilon*4 alleles.[2] Oxidative stress has been felt to be one possible mechanism by which the genetic risk conferred by presence of the APOE allele might be potentiated. Previous work has addressed the issue of antioxidants and the risk of AD[3-5] but has produced conflicting results. In the same issue of *JAMA* as the current study, a back-to-back article found that dietary, but not supplemental vitamin E reduced the risk of AD in older adults with the APOE*4 allele,[6] and an editorial[7] pointed out that there might be a biologic difference between "nutritional phenomena" of real food vs. vitamin content alone. In other words (I think), you have to eat food (not take supplements) to have the best chance of getting the benefits of nutrients.

But what the heck are flavonoids? These articles leave us pretty much on our own to figure this out, so I went to the internet. According to one web site, "Both pine bark and grape seed extract are rich in a group of flavonoids called proanthocyanidins, or condensed tannins. Researchers have identified about 250 different proanthocyanidins in plants and, as a group, they constitute one of 12 subcategories of flavonoids. Some 4000 flavonoids have been identified, and they are part of an even larger class of chemicals known as polyphenols."[8] Thus, pine bark, grape seed, and green tea are 3 of the more common dietary sources of flavonoids. However, since there are more than 4000 flavonoids in plants, and only a few of them in tablets, the reason that food might confer more benefit than does taking supplements begins to become clearer. ■

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Lansoprazole for the Prevention of Recurrences of Ulcer Complications

ABSTRACT & COMMENTARY

Synopsis: *Even low-dose aspirin leads to a significant risk of recurrent ulceration and bleeding, and this risk can be lowered with concomitant lansoprazole therapy.*

Source: Lai KC, et al. *N Engl J Med.* 2002;346:2033-2038.

A GROUP OF 123 PATIENTS WITH ULCER COMPLICATIONS were on low-dose aspirin for prophylaxis of CVA or ischemic heart disease. Ulcers were healed and patients had *Helicobacter pylori* eradicated. Aspirin 100 mg/d was resumed and patients were then randomized to receive 30 mg of lansoprazole daily or placebo. Over 12 months, 9 of 61 patients on placebo had recurrent ulcer complications vs. 1 of 62 patients on lansoprazole. Although a larger study had been planned, the trial was aborted due to these findings with an adjusted hazard ratio of 9.6. The interpretation of study results were complicated by NSAID use in 2 patients and 4 recurrences of *H pylori* infection. Nevertheless, it seems clear that patients who have had ulcer complications such as bleeding or obstruction on low-dose aspirin remain at risk for recurrent complications if they continue on aspirin. This risk can be substantially eliminated by coadministration of an effective dose of a proton pump inhibitor (PPI).

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

Although it is well known that PPIs can block NSAID-related damage and that bleeding with aspirin also can be reduced with PPI therapy, some have assumed that it should be safe to resume low-dose aspirin in *H pylori*-positive patients with ulcer complications once the *H pylori* infection has been eradicated. This study from Hong Kong clearly demonstrates that patients with ulcer complications while on low-dose aspirin remain at substantial risk with resumption of aspirin, even if the *H pylori* has been eradicated and the ulcer healed. More important is the fact that this risk can be largely eliminated by the coadministration of lansoprazole 30 mg (and presumably by comparable doses of alternative PPIs). The clinician should strongly consider PPI prophylaxis of patients at high risk of ulcer complications. ■

Homocysteine and Stroke Risk: Role for Folate Therapy

ABSTRACTS & COMMENTARY

Synopsis: *Dietary folate intake has a strong influence on subsequent stroke risk.*

Sources: Bazzano LA, et al. *Stroke.* 2002;33:1183-1189; Kasner SE. *Stroke.* 2002;33:1189; Miller JW, et al. *Neurology.* 2002;58:1471-1475.

SUBSTANTIAL EVIDENCE EXISTS TO LINK HOMOCYSTEINE (Hcy) levels with atherosclerosis and cardiovascular disease. Hcy may damage arteries by promoting endothelial cell proliferation or it may produce oxidative damage to vessel walls. Alternatively, it may increase coagulation and disturb endothelium-dependent vasomotor reactivity. Because Hcy metabolism directly depends on other nutrients, such as folate and vitamin B_{12}, intake of these compounds either in the diet or as supplementation is crucial to keep Hcy levels low. An inverse relationship between blood concentrations of folate and cardiovascular disease has been strongly suggested in epidemiological studies. Similar findings occur with stroke. Bazzano and colleagues' study further strengthens these associations showing that dietary folate intake has a strong influence on subsequent stroke risk.

Bazzano et al studied 9764 subjects from a National Health and Nutrition Examination Survey (NHANES), aged 25-74 years who were healthy at the time of recruitment in 1971-1975. Dietary folate intake was calculated based on a 24-hour food survey. Follow-up through 1992 showed 926 stroke events and 3758 incidents of cardiac disease. Stroke was defined based on ICD-9 codes with data taken from death certificates, hospital, or nursing home records. Individuals who consumed > 300 μg of folate per day were 20% less likely to suffer stroke than those consuming < 136 μg. Higher folate intake reduced cardiovascular disease by 13%. These effects were preserved when adjusting for variables such as gender, blood pressure, cholesterol, tobacco use, diabetes, or physical activity. Benefits were similar whether folate intake was analyzed as a continuous

variable or by quartile analysis, suggesting that there was no particular threshold effect.

As observed by Bazzano et al, this study is limited by possible inaccuracies in dietary recall or variability not appreciated with a 1-day survey. Such discrepancies, however, would have skewed the study toward a negative result (Type-II error) rather than bias in favor of a folate benefit. Also, folate supplementation with vitamins was not specifically examined in the 1970s, however, typical vitamins contained only 100 µg of folate and only 12.6% of participants reported regular vitamin use.

In another study worthy of note, Miller and colleagues studied Hcy levels in patients with Alzheimer's disease (AD) and compared them to controls without AD. There was no increase in plasma Hcy levels in the AD patients. This was in contrast to several other studies that have previously associated elevated Hcy levels with AD risk. Interestingly, however, when patients in Miller's study were divided based on the presence of concomitant vascular disease, there was a significant association between vascular disease and elevated Hcy. Mean serum Hcy levels among patients with vascular disease was 12.9 compared with 10.1 among those without ($P < 0.001$). When dichotomized into groups with Hcy above or below 12, elevated Hcy showed an odds ratio of 10.0 ($P < 0.03$). Vascular disease was not restricted to stroke but, rather, was broadly defined as patients with coronary artery disease, prior TIA, or the presence of cerebral infarction on CT or MRI.

COMMENT BY ALAN Z. SEGAL, MD

As noted by Kasner in an accompanying editorial, studies of high-dose vitamin supplementation such as the Vitamin Intervention for Stroke Prevention (VISP) may provide randomized evidence to support the findings of the observational studies such as that of Bazzano et al. Such studies may be underpowered, however, since over the past few years the FDA has mandated the addition of folate to flour and other food products. The effect of additional supplementation may, therefore, be attenuated by increased background dietary intake.

It is not entirely clear what dose of folate is optimal. Typical multivitamin preparations contain 400 µg of folate that exceeds the quantity found effective in Bazzano et al's study. Intake of fortified food, for instance, highly supplemented breakfast cereals, could also match these levels. In contrast, studies such as VISP dose folate in a much higher 2.5-3.0 mg range. Folate dosing may be best guided by serum Hcy levels. However, it is equally unclear exactly how low we should go with Hcy. Hcy levels < 12 are likely optimal, but since risk related to Hcy is a continuous rather than dichotomized variable, further decreases into the 8-10 range are probably optimal. ■

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Getting High With Salmeterol

ABSTRACTS & COMMENTARY

Synopsis: *Prophylactic inhalation of salmeterol decreases the incidence of high-altitude pulmonary edema (HAPE).*

Sources: Sartori C, et al. *N Engl J Med.* 2002;346:1631-1636; Voelkel NF. *N Engl J Med.* 2002;346:1606-1607.

HAPE IS A LIFE-THREATENING EVENT. THE MECHANISMS that lead to this physiologic insult have eluded investigators for years. Among the mechanisms that predispose to this condition is the absorption of liquid driven by active alveolar transepithelial sodium transport. Sartori and colleagues postulated that a defect in this mechanism might predispose patients to HAPE. Beta-adrenergic agonists up-regulate the clearance of alveolar fluid and attenuate pulmonary edema in animals.

In a double-blind, randomized, placebo-controlled study, Sartori et al assessed the effect of prophylactic inhalation of the beta-agonist salmeterol on the incidence of pulmonary edema during exposure to high altitudes (4559 m reached in less than 22 hours) in 37 subjects who were susceptible to HAPE. (Salmeterol, 125 µg, was started the morning of the day before the climb and every 12 hours thereafter.) They also measured the nasal transepithelial sodium and water transport in the distal airways, in 33 mountaineers who were prone to HAPE and 33 mountaineers who were resistant to this condition.

Prophylactic inhalation of salmeterol decreased the incidence of HAPE in susceptible subjects by more than 50%, from 74% in placebo to 33% in salmeterol-treated climbers. The nasal potential difference value under low altitude conditions was more than 30% lower in subjects who were susceptible to HAPE than in those who were not ($P < 0.001$).

Sartori et al concluded that inhalation of salmeterol reduces the risk of HAPE. Sodium-dependent absorption of liquid from the airways may be defective in patients susceptible to HAPE. Sodium driven clearance of alveolar fluid may have a pathogenic role in pulmonary edema in humans and, therefore, represents an

appropriate target for therapy.

COMMENT BY RALPH R. HALL, MD, FACP, FACSM

In 1991 in Summit County, Colorado, where Keystone Ski Resort is located and nearby Leadville, Colo, the incidence of acute mountain sickness was 22% at 7000-9000 ft and 42% at 10,000 ft.[1] People living at these altitudes develop mountain sickness if they leave these altitudes for a few days and then return. High-altitude illness is a common problem in these and similarly located mountain areas.

In an editorial, Hackett and Roach beautifully describe the huge support needed to carry out this research.[1] "It was carried out at the Capanna Regina Margherita, perched on the Punta Gnifetti (4559 m), one of the summits of Monte Rosa on the Italian-Swiss border. The mountain hut where this was done has a distinguished record in the annals of high altitude research. The great Italian physiologist Angelo Mosso (1846-1910) made Turin a center for exercise physiologist at the end of the 19th century." Most of the early studies on high altitude illness were accomplished there.

Salmeterol is now added to our tools for the prevention of HAPE. Since these climbers were susceptible to HAPE, the reduction in risk may be greater than with nifedipine or acetazolamide. It will be interesting to see if this can be confirmed when salmeterol is compared with other drugs used to treat high-altitude illness.

As pointed out by Voelkel in the accompanying editorial, it was noted that the placebo and the salmeterol groups had similar degrees of pulmonary hypertension after treatment. There are no data, however, regarding whether there were effects on pulmonary microvascular pressure.

It is interesting that Roncin et al, in a well-conducted study, found that a carefully compounded preparation of *Ginkgo biloba* markedly reduced the incidence of mountain sickness during ascent to 5000 m.[2] This study noted that there was an improvement in pulmonary function that was not found with salmeterol or other preparations. Maakestad et al confirmed these observations in a subsequent study.[3]

The risk of HAPE is increased with rapid ascent, individual susceptibility, and the level of exertion. It was interesting to see in the log, kept near the top of Mt Kilimanjaro, that Sir Edmond Hillary was unable to reach the top of Kilimanjaro on his first attempt because he tried to summit in 1 day.[4]

For those interested in a recent review, including current treatments and prevention of high altitude illness, I recommend the review by Hackett and Roach.[1] ■

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Changing Patterns of New Tuberculosis Infections

ABSTRACT & COMMENTARY

Synopsis: *Although the incidence of tuberculosis has declined in the United States in the last decade, new cases have actually risen among foreign-born residents. Molecular and epidemiological analyses of tuberculosis case isolates in New York City suggest that reactivation of latent infection is responsible for the rise, while declining rates of acute transmission account for most new cases in US-born residents.*

Source: Geng E, et al. *N Engl J Med.* 2002;346:1453-1458.

Starting with 812 new cases of tuberculosis (TB) diagnosed between 1990-1999 at Columbia Presbyterian Medical Center in northern Manhattan, and eliminating 29 who were not local residents, 575 (77%) were able to be "DNA fingerprinted" using restriction-fragment-length polymorphism. This enabled clusters of cases from recent transmission to be distinguished from unique cases, and further information on clinical, social, and demographic variables could then be linked from records at the Tuberculosis Control Program in the New York City Department of Health.

Unique TB isolates were found in 52% of the cases, while the remaining 48% had "clustered" isolates which matched at least one other in the cohort, implying they were caused by recent transmission. However, this pattern changed with time over the 10-year study period, such that clustered isolates were high initially at 63% and declined to 31% by 1999. By the end of the decade, most new cases of TB in this area were caused by unique strains.

Population characteristics associated with recent clustered transmission were (in descending order) injection-drug use, homelessness, black race, pulmonary source of isolate, HIV infection, and male sex. For unique isolates presumably from latent reactivation, the most likely

characteristics were Hispanic ethnic background, diagnosis after 1993, non-US birth, white race, age older than 60 years, and Asian race.

Using a multivariate analysis, the strongest independent association for reactivation of latent infection was non-US birth with Hispanic ethnic background, diagnosis after 1993, age > 60 years, and other non-US births. The other characteristics found associated with recent transmission did not identify any greater risks in the non-US-born group, except for HIV infection that increased the risk of a clustered or recently transmitted infection rather than a latent reactivation.

COMMENT BY MARY ELINA FERRIS, MD

These results have important implications for TB control programs in areas of recent immigration. The extremely high rate of new TB cases in this New York City neighborhood at > 125 cases/100,000 persons was far higher than the city-wide rate of 50/100,000, and much higher than the US overall rate of 10.5/100,000 in 1992. With one of the highest concentrations of recent immigrants in Manhattan (40% non-US born, mostly from the Dominican Republic), Geng and colleagues hypothesized that this foreign-born population was either not being reached by TB control efforts or else had different sources of infection. The hospital also served an adjacent area of US-born African-Americans that could be used as a comparison group.

Control of TB in New York City was remarkably successful from 1992-2000, resulting in a decline of 65% in new cases and estimated to cost more than $1 billion. Improvements were attributed to directly observed therapy, infection control, and standardization of initial drug treatment regimens.[1] However, it soon became apparent that new cases at the end of the decade were predominantly in non-US born residents. This study shows that most of these more recent infections resulted from reactivation of latent TB, which would not necessarily be affected by the measures that reduced new acute transmissions of TB.

New immigrants to the United States are required to be free of active TB on chest x-ray, but there are currently no specific requirements for skin testing that could detect latent disease. Worldwide TB remains a serious problem, accounting for 2-3 million deaths annually, and in countries with limited health facilities, up to a 36% infection rate. The Institute of Medicine recommended intensified interest in latent TB 2 years ago,[2] predicting that soon the majority of new cases of TB in the United States would occur in foreign-born persons coming from nations with high rates of the disease. Mexican immigrants, for example, currently account for nearly 25% of all new cases in the United States

Clinicians should be aware that the risk of reactivating latent TB for immigrants is highest during the first 5 years after arrival; of those who develop the disease, a third do so within 1 year. Current guidelines from the CDC and others encourage skin testing of recent immigrants, and 9 months of isoniazid treatment for latent infection, for persons from countries of high tuberculosis prevalence.[3,4] Until Immigration regulations and public health efforts change to target these populations, the burden for detection of these new tuberculosis cases remains in our own primary care offices. ■

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Pharmacology Update

Adderall XR—A New Long-Acting Drug for ADHD

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

SHIRE US INC. HAS RECEIVED FDA APPROVAL TO MARket a once-daily extended-release form of mixed amphetamines (Adderall) for the treatment of attention deficit hyperactivity disorder (ADHD). Mixed amphetamines combine the neutral salts of dextroamphetamine and amphetamine, with the dextro isomers of amphetamine saccharate and d,l-amphetamine aspartate monohydrate at a 75:25% dextro to levoamphetamine. The mixture was first introduced 20 years ago as a diet drug, and has since been used extensively for ADHD. The extended-release capsules contain 50% of mixed amphetamines as immediate-release beads and 50% as extended-release beads. The product is marketed as Adderall XR.

Indications

Adderall XR is indicated for the treatment of ADHD.[1]

Dosage

The recommended starting dose for those being treated for the first time or those being switched to Adderall

is 10 mg once daily in the morning. Those switching from Adderall should be started at the same daily dose administered once daily. The dose may be titrated in 5 mg or 10 mg increments weekly guided by efficacy and tolerability. The maximum dose is 30 mg daily.[1] Dosage should be individualized. The capsules should be taken whole but the contents may be sprinkled on applesauce. High-fat meals delay the rate of absorption by about 2.5 hours compared to Adderall XR but does not affect extent of absorption.[1]

Adderall XR is available as 5-mg, 10-mg, 15-mg, 20-mg, 25-mg, and 30-mg capsules. Adderall XR is schedule C-II.

Potential Advantages

A single dose of Adderall XR provides plasma levels comparable to Adderall administered twice daily 4 hours apart.[1] This provides a more convenient regimen avoiding the need for dosing at school or work.

Potential Disadvantages

The extended levels of amphetamines may extend the duration of side effects. The frequency (vs placebo) of the most common side effects is loss of appetite (22% vs 2%), insomnia (17% vs 2%), emotional lability (9% vs 2%), and nervousness (6% vs 2%).[1] Patients with ADHD symptoms associated with acute stress should avoid amphetamines.

Comments

The efficacy of Adderall XR was established in 2 placebo-controlled, 3-week, parallel-group studies in children 6-12 years of age (n = 635). Patients were randomized to a fixed-dose of 10 mg, 20 mg, 30 mg, or placebo and extrapolated from immediate form of Adderall.[1] In the studies, efficacy was based on teachers rating of attention and hyperactivity or behavior and performance. In general, mixed amphetamines have been shown to be comparable to methylphenidate in the management of ADHD.[2,3] Mixed amphetamine salts have also been shown to be effective in adults. A 7-week, randomized, double-blind, placebo-controlled crossover study in 27 subjects reported a reduction in the ADHD rating scale of 30% or greater in 70% compared to 7% for placebo.[4] At the same dose on mg/kg bases, children have a 30% less systemic exposure than adults.[1] The clinical relevance of this phenomena is not clear. Adderall XR costs about $2/d regardless of the strength.

Clinical Implications

ADHD is often regarded as a disease of children and adolescents. However, it is often a lifelong condition and can affect adults who were diagnosed at childhood and has been an increasingly recognized disorder in adults.[5,6] Psychostimulants and antidepressants are the primary treatment options.[5,7,8] Adderall XR provides a once-daily formulation of mixed amphetamines. ■

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CME Questions

3. Antioxidants:
a. prevent dementia when taken as supplements.
b. include flavonoids, proteins, and melatonin.
c. are found in pine bark, grape seeds, and citrus foods.
d. in diet probably are not associated with cognitive function in aging.

4. Low-dose aspirin can be expected to produce ulcer complications in a significant number of patients, but this can be largely eliminated by:
a. coadministered standard doses of H2 receptor antagonists.
b. coadministered high doses of PPIs.
c. a standard dose of a PPI such as lansoprazole 30 mg given with the aspirin.
d. proved eradication of *H pylori* in these patients.
e. *H pylori* eradication followed by the coadministration of lansoprazole 30 mg daily.

5. Which one of the following statements is *false*?
a. The nasal transepitelial sodium and water transport was 30% less in those subjects susceptible to HAPE.
b. Salmeterol decreases pulmonary artery pressure.
c. *Ginkgo biloba* decreases the incidence of high-altitude illness.
d. Some individuals seem to be more susceptible to high-altitude illness.

6. Which group currently accounts for the largest number of new tuberculosis cases in the United States?
a. African-American males
b. Recent immigrants from Mexico
c. Recent immigrants from Russia
d. American citizens aged 65 and older
e. Intravenous drug-users

By Louis Kuritzky, MD

Efficacy of Angiotensin II Receptor Antagonists in Preventing Headache

HEADACHE IS AMONG THE MOST commonly reported events in placebo-controlled trials of pharmaceutical agents, usually occurring in both the recipients of active drug and placebo. It has not gone unnoticed that, in contrast to some other antihypertensive agents which have been associated with increases in headache, angiotensin II receptor antagonists (ARBs) have often demonstrated reduced headache incidence when compared to placebo.

To clarify whether this favorable effect of ARB upon headache was consistent, Etminan and colleagues analyzed 27 studies, including more than 12,000 patients, who had received ARB treatment in placebo-controlled trials. In addition, trial data had to include headache either as a primary outcome or as one of the listed adverse effects.

Overall, the risk of headache in recipients of ARBs was reduced about one third compared to placebo. This compares favorably with the headache reduction seen in migraine prophylaxis trials using ACE inhibitors (22% reduction).

Although headache was not further delineated in this report by subtype (eg, migraine, tension, cluster), this report suggests that there has been good consistency between studies. To date, there has not been a comparison trial between ACE inhibitors and ARBs. ■

Etminan M, et al. Am J Med. 2002; 112:642-646.

Effect of Lower Doses of HRT on Bone in Early Postmenopausal Women

IN ADDITION TO RELIEF OF VASOMOtor symptoms, postmenopausal hormone replacement therapy (HRT) has been shown to improve bone mineral density (BMD). Traditionally, 0.625 mg of conjugated equine estrogen (CEE) daily, or the equivalent, has been viewed as "standard" dosing. Nonetheless, substantially lower doses (eg, 0.3 mg/d CEE) have been shown to provide relief for vasomotor symptoms, as well as enhance BMD when combined with calcium supplementation. Combined HRT (estrogen + progestogen) studies have suggested that CEE + medroxyprogesterone acetate (MPA), is either neutral, or possibly beneficial for BMD.

In this report, Lindsay and colleagues examined the effects of various doses of CEE (0.3-0.625 mg/d) and MPA (1.5-2.5 mg/d) in healthy postmenopausal women. End points included BMD (spine and hip) and markers of bone turnover (eg, osteocalcin, urinary telopeptides).

All treatments were superior to placebo for BMD in spine and hip, as well as markers of bone turnover. 'Standard' dose CEE (0.625 mg/d) alone was superior to CEE 0.3mg/d alone. The addition of MPA had no effect, positive or negative, on BMD except in women using higher dose CEE (0.625 mg/d), in whom the effect was favorable. Lindsay et al conclude that lower dose CEE-MPA does reduce bone loss in postmenopausal women. ■

Lindsay R, et al. JAMA. 2002;287: 2668-2676.

Pulse Pressure and Cardiovascular Disease-Related Mortality

THE POPULATION OF MEN screened for participation in the Multiple Risk Factor Intervention Trial (MRFIT) has provided a large population (n = 342,815) from which to derive important observational epidemiologic data. Men were screened from 1973 until 1975, and followed for cardiovascular mortality until 1996.

Pulse pressure (= SBP-DBP) has been increasingly recognized as a predictive factor for cardiovascular morbidity and mortality. Pulse pressure rises as large artery elasticity is lost. Hence, an increased pulse pressure reflects increasing arterial rigidity.

In the MRFIT screenees, the SBP and DBP showed a stronger association with cardiovascular mortality than pulse pressure. Using any 2 of the 3 variables (DBP, SBP, pulse pressure) was superior to any one individual variable for predicting adverse cardiovascular outcome. Intuitively, it can be recognized that at lower levels of blood pressure (eg, 120/50), the pulse pressure alone (= 70), even though the same as that seen at 160/90 (= 70) would not likely reflect cardiovascular risk. However, in support of the predictive role of pulse pressure, in this population the men suffering elevated SBP with the LOWEST DBP (thus, with the highest pulse pressure), experienced the highest cardiovascular mortality rates. ■

Domanski M, et al. JAMA. 2002;287: 2677-2683.

In Future Issues: **The Long-Term Effects of Intimate Partner Violence**