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ABSTRACT & COMMENTARY

Hold the Hormones — At Least for Chronic Condition Prevention

By David Fiore, MD

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

SYNOPSIS: The U.S. Preventive Services Task Force reissued a statement on hormone replacement therapy for the prevention of chronic conditions that reiterates its D recommendation from 2012. It recommends physicians do not prescribe hormone replacement therapy (HRT) to prevent medical conditions, but leave the question of using HRT for treatment of menopausal symptoms unanswered.

SOURCE: US Preventive Services Task Force, Grossman DC, Curry SJ, Owens DK, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force Recommendation statement. *JAMA* 2017;318:2224-2233.

The U.S. Preventive Services Task Force (USPSTF) released a statement on hormone replacement therapy (HRT) for the primary prevention of chronic conditions in postmenopausal women that updates its 2012 statement. Although it was released very recently, the statement already has generated significant controversy, which is especially surprising in that it is not a big change from the 2012 statement.

In 2012, the USPSTF gave HRT for the prevention of chronic conditions a D rating, meaning that the panelists recommended against it.[1] The current update was undertaken to include extended data from the Women's Health Initiative (WHI)[4,5] and an analysis of data drawn only from randomized trials, eliminating any analysis of observational trials. Essentially, the revised statement reiterates the findings from 2012, concluding that "The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal women (D recommendation). The USPSTF recommends against the use of estrogen alone for the primary

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prevention of chronic conditions in postmenopausal women who have had a hysterectomy (D recommendation)."
In an editorial entitled "Menopausal hormone therapy (MHT) for primary prevention: Why the USPSTF is wrong," an "ad hoc group of clinical scientists well published in the area of MHT" proclaims the USPSTF misinterprets the WHI (a major randomized trial that was widely publicized for finding overall harm of HRT).[2] These editorialists claim that the WHI "was not designed to evaluate mainstream use of MHT" and that the hormone preparations used are not appropriate. In conclusion, the authors stated that the current guidelines "will perpetuate egregious harm to the public health." In another editorial, Cano et al wrote that "the statement conveys the message that any MHT, at any age, may not be of benefit and could be harmful. This is simplistic and wrong."[3]

■ COMMENTARY

Given this controversy, it is important to read the findings and discussion more carefully to better understand how to incorporate this statement into clinical practice. One thing I found refreshing in this USPSTF statement is the humility of its recommendation. The recommendation is made with "moderate certainty" about the lack of benefit and likely harms. This is a nice way of saying that "we just don't know for sure." I am also impressed that the USPSTF included two tables with absolute benefit and harms, rather than just hazard ratios. This puts the likely benefit or harm for a patient in much clearer terms. For example, the hazard ratio for breast cancer found in the estrogen plus progestin WHI trial was 1.26. This can be stated as, "Women treated with estrogen and progestin were 25% more likely to develop breast cancer." That sounds pretty scary, but the absolute risk was found to be only nine more cases per 10,000 women. Many women might find that risk is something they can accept, especially when suffering from hot flashes and other menopausal symptoms. Most importantly, as the authors make clear, this statement *only* concerns the use of HRT for *prevention*, not treatment, of symptoms.

The only part of Cano et al's conclusion with which I agree is their statement that "this is simplistic and wrong," but in reference to his (and Langer et al's) rejection of the USPSTF statement. This statement summarizes thousands of women-years of data demonstrating that clinicians should not use HRT to prevent illness. It does not address the issue of using HRT to treat symptoms, but it does give us reassurance that the potential harms of doing so are rare. Therefore, I will continue to use HRT for women who report severe menopausal symptoms in as low a dose and as short a duration as works for them. ■

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ABSTRACT & COMMENTARY

CT Calcium Score vs. Stress Testing

By Michael H. Crawford, MD

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

SYNOPSIS: A subgroup analysis of the PROMISE trial showed that CT coronary calcium scores in symptomatic patients at low to intermediate risk for coronary artery disease are more sensitive but less specific for major adverse cardiac events over a two-year follow-up period than stress testing. Consequently, both approaches exhibited similar but modest discriminatory ability.

SOURCES: Budoff MJ, Mayrhofer T, Ferencik M, et al. Prognostic value of coronary artery calcium in the PROMISE Study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation* 2017;136:1993-2005.

Newby DE. Computed tomography or functional stress testing for the prediction of risk: Can I have my cake and eat it? *Circulation* 2017;136:2006-2008.

The diagnostic accuracy of stress testing for detecting significant coronary artery disease (CAD) in low-risk patients that clinicians encounter frequently is reduced compared to that in intermediate-risk patients. Thus, investigators from the PROMISE trial (Prospective Multicenter Imaging Study for the Evaluation of Chest Pain) hypothesized that CT coronary artery calcium score (CAC) would be superior to stress testing for predicting major adverse cardiac events (MACE) in symptomatic but low to intermediate risk patients. Among the more than 10,000 patients enrolled in PROMISE at 193 North American medical centers, 4,209 received CAC as their first test and 4,602 received stress testing first, as randomized. Stress testing included exercise or pharmacologic stress plus either ECG alone, nuclear myocardial perfusion imaging, or echocardiography. CAC was determined on at least a 64-slice multidetector CT machine. Studies were classified as normal (CAC = 0), mildly abnormal (CAC = 1-99), moderately abnormal (CAC = 100-400), and severely abnormal (CAC > 400). The stress tests were rated similarly based on the perceived extent of ischemia. There were no clinically meaningful differences in baseline characteristics between the patients in each group. The average age was 61 years, slightly more than half were women, and about half were low risk. Median follow-up was 26 months. Moderate or severely abnormal results in both tests robustly predicted MACE (moderate CAC = hazard ratio, 3.14; 95% confidence interval, 1.81-5.44, and stress test 2.65 [1.46-4.83]; severe CAC = 3.56; 1.99-6.36 and stress test, 3.88 [2.58-5.85]). Any CAC abnormality detected 84% of the patients experiencing a MACE, whereas a positive stress test only detected 43%. However, an abnormal stress test was significantly more specific in predicting MACE (78.6% vs. 35.2%; $P < 0.001$). Thus, overall discriminatory ability was similar and modest for both tests (C statistic for CAC = 0.67 and for stress testing = 0.64). In a separate analysis of those in the CAC group who also underwent CT angiography (CTA), CTA demonstrated better discriminatory ability (C = 0.72). The authors concluded that in symptomatic outpatients at low to intermediate risk of CAD, most with subsequent events registered a CAC > 0, but only less than half exhibited an abnormal stress test. On the other hand, an abnormal stress test was much more specific for predicting events. Consequently, both tests demonstrated a similar but modest discriminatory ability.

■ COMMENTARY

This post-hoc subgroup analysis of the PROMISE trial, which compared CTA to stress testing, is really an apple-oranges comparison. CAC detects the presence of advanced atherosclerosis (young plaques are not detected) and is not directly related to luminal stenosis or plaque status. In fact, the presence of calcium may be a stabilizing event in atherosclerosis. So, it is not surprising that CAC > 0 detects 84% of patients who experience a MACE over two years. Presumably, the other 16% exhibited non-calcified plaques, which could be detected by CTA. However, CTA is not perfect, as it cannot image the vessel lumen through heavy calcification and there are contradictions to its use, such as advanced kidney disease and tachycardia, that cannot be eliminated safely. CAC imaging has no contraindications, but it carries a low specificity for predicting MACE, especially if the CAC value of > 0 is used (35%). Specificity increased with higher cutoff values (> 100, 67%; > 400, 85%) but at the expense of sensitivity (61% and 31%, respectively). Stress testing detects the functional consequences of atherosclerosis but does not diagnose atherosclerosis because myocardial ischemia can be caused by other conditions such as microvascular disease or left ventricular hypertrophy. Also, it cannot detect non-flow-limiting plaques. Most cardiac events occur with the disruption of such plaques. However, stress testing is superior

for detecting those at the highest risk and those who may benefit from revascularization. CAC scores > 400 are associated with a yearly MACE rate of 6% vs. 10% with a markedly positive stress test. Also, a positive stress test is more specific (79% vs. 35%) and a normal stress test is associated with a MACE rate of < 1% per year. So, how should cardiologists deploy these tests in a low- to intermediate-risk patient with symptoms suggestive of CAD? The authors noted that CAC is a rapid test that can be performed on any CT scanner with low radiation exposure. Also, it is relatively inexpensive and produces no real contraindications. Additionally, studies have shown that knowledge of the presence of calcium can motivate patients to improve their risk profile. So CAC may represent an ideal first screening test, which then could be followed by a second test if CAC crosses some threshold. Traditionally, the second test has been stress testing, but the results of the main PROMISE study suggest it could be CTA, since compared to stress testing it was better at predicting future MACE. CTA may perform better at the lower CAC score range (1-400), but a CAC score > 400 will make lumen visualization by CTA problematic. Perhaps stress testing would be better if a CAC score is > 400. We will need further studies to sort this out. ■

ABSTRACT & COMMENTARY

The Incidence of Dementia May Be Declining

By Makoto Ishii, MD, PhD

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

SYNOPSIS: In community-dwelling people from Bronx County, New York, there was a sharp decrease in dementia incidence in those born after mid-1929, which could not be readily explained by changes in the prevalence of cardiovascular diseases, higher education, or increased racial/ethnic diversity.

SOURCE: Derby CA, Katz MJ, Lipton RB, Hall CB. Trends in dementia incidence in a birth cohort analysis of the Einstein Aging Study. *JAMA Neurol* 2017;74:1345-1351.

With an increasingly aging population and no cure or vaccine for Alzheimer's disease (AD) or age-related dementias, dementia is poised to become a medical epidemic. Surprisingly, investigators recently have found that for unclear reasons, there may be a decrease in dementia incidence. Identifying the underlying causes for any such decrease would be critical for developing effective dementia prevention strategies. In this study, investigators from the Einstein Aging Study sought to determine whether there was evidence of a decrease in dementia incidence across sequential birth cohorts. As evidence mounts supporting the role of cardiovascular disease as a significant contributor to dementia, Derby et al also sought to determine whether trends in cardiovascular disease could explain any observed dementia trends.

The Einstein Aging Study is an ongoing study that has been recruiting noninstitutionalized individuals from Bronx County, New York, since 1993. Eligibility criteria were ≥ 70 years of age, fluent in English, and no dementia at study entry. Each study participant underwent an annual follow-up assessment that included a clinical neurological examination, comprehensive neuropsychological assessments, medical history, blood pressure, anthropometrics, and psychosocial assessments. Self-report of physician diagnosis was used to determine the prevalence of myocardial infarction, stroke, or diabetes. Global cognitive performance was assessed using the Blessed Information Memory Concentration (BIMC) test, while depression was assessed using the Geriatric Depression Scale. Diagnosis of dementia was based on standardized clinical criteria from DSM-IV and assigned at consensus case conference. There were 1,348 participants in the study after excluding those who died or were unavailable for follow-up before their first annual visit.

Using crude dementia incidence rates as a function of age and dates of birth, the overall trend of increasing dementia incidence with increasing age was seen as expected. When the investigators fit locally weighted scatter plot smoothing functions using generalized additive models, there was a consistent pattern within each age range of decreasing incidence with sequential birth years and an accelerated decrease in those born in the middle to late 1920s. Investigators next identified birth years when there was a significant change in incidence rates by fitting Poisson regression models with change points. After adjusting for age, sex, race, and education level, a significant change point was found for individuals born after July 1929. Investigators then examined whether decreasing rates of cardiovascular disease affected the dementia

incidence rates. While the age-specific prevalence of myocardial infarction and stroke decreased in the cohort across sequential birth cohorts, there was an increase in diabetes prevalence in later birth cohorts. However, adjusting for changes in prevalence of cardiovascular diseases did not change the results. Additionally, in the more recent birth cohort, there was a higher proportion of African-American and Hispanic individuals, as well as higher years of education and baseline cognitive status. None of these changes explained the decreased dementia incidence.

■ COMMENTARY

Although earlier studies found no significant changes in dementia incidence for cohorts followed before 1990, the major findings from this study are consistent with more recent studies that also found decreased dementia incidence, particularly in the United States and Western Europe. Of note, the analytic approach of this study differs from other recent studies by examining incidence of dementia according to year of birth, as opposed to dementia rates in specified age brackets enrolled during different periods. This should allow for more precise separation of age and cohort effects. Another strength of this study is the use of standardized diagnostic criteria applied to all participants across the study period in a community-based sample. Also, there was a high concordance with the clinical diagnosis and pathological changes found in the subset of subjects who received autopsy, giving confidence to the accuracy of the clinical diagnosis. A significant limitation is the small number of dementia cases for the more recent birth cohorts. This is important as the largest effect in decreased dementia incidence was seen in this cohort. In addition, Derby et al could not distinguish between Alzheimer's disease and other age-related dementias. Furthermore, while the authors attempted to address whether improved cardiovascular risk factors contributed to the decreased dementia incidence, they used self-reported diagnosis as opposed to more direct measures such as hemoglobin A1c levels, which may lead to errors or bias in the data. The authors also did not address other factors that may be important in more recent birth cohorts, such as improved infection control and treatment, better nutrition, and other societal changes.

Additional studies clearly are needed to replicate these findings and, importantly, to identify any potential factors that contribute to decreasing dementia incidence. Moreover, it is unknown if this trend will continue, as a significant increase in the prevalence of obesity and related cardiovascular diseases in more recent birth cohorts may reverse any gains made. Although this study shows promise that dementia incidence may be decreasing, caution should be exercised before declaring any victory against the still rising tide of a dementia epidemic. ■

PHARMACOLOGY UPDATE

Ertugliflozin Tablets (Steglatro)

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

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

The FDA has approved a fourth sodium-glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes mellitus. These drugs block the transporter that mainly is involved in the reabsorption of glucose from kidneys back into the systemic circulation, which results in increased glucose excretion in the urine. Ertugliflozin joins the previously approved SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin. Ertugliflozin is marketed as Steglatro. It also is approved as a fixed combination with sitagliptin (Steglujan) and metformin (Segluromet).

INDICATIONS

Ertugliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] The fixed combinations are indicated when both ertugliflozin and sitagliptin or ertugliflozin and metformin are appropriate.[1]

DOSAGE

The recommended starting dose is 5 mg once daily in the morning with or without food.[1] Clinicians may increase the dose up to a maximum dose of 15 mg once daily if adequate glycemic control has not been achieved and the dose is tolerated.[1] Renal function should be assessed before starting ertugliflozin and periodically thereafter. Ertugliflozin should not be started or continued in patients with an estimated glomerular filtration rate between 30 and < 60 mL/min/1.73m^2. Ertugliflozin is available as 5 mg and 15 mg tablets. It also is available in combinations with

sitagliptin (5 mg/100 mg and 15 mg/100 mg), and with metformin (2.5 mg/500 mg, 2.5 mg/1,000 mg, 7.5 mg/500 mg, 7.5 mg/1,000 mg).

POTENTIAL ADVANTAGES

Ertugliflozin provides another competitor in the SGLT2 inhibitor market.

POTENTIAL DISADVANTAGES

The most frequent adverse event is female genital mycotic infections (9-12% vs. 3% for placebo).[1] Other adverse events associated with SGLT2 inhibitors are increase in low-density lipoprotein cholesterol, dehydration/hypotension, urosepsis and pyelonephritis, renal impairment, and diabetic ketoacidosis.[1,3] Increased risk of lower limb amputation has been reported for another SGLT2 inhibitor (canagliflozin). In Phase III studies, the frequency of similar events was 0.2% in the 5 mg group and 0.5% in the 15 mg group compared to 0.1% in the comparator group.[1] Long-term safety has not been established with ertugliflozin, including effects on cardiovascular risk or outcomes.

COMMENTS

The efficacy and safety for FDA approval was based on seven randomized, double-blind, placebo- or active comparator-controlled clinical studies involving 4,863 subjects with type 2 diabetes. In the placebo-controlled study, ertugliflozin 5 mg and 15 mg were compared to placebo in a 26-week study. Subjects were treatment-naïve or on no antihyperglycemic treatment ≥ 8 weeks before the run-in period. Mean baseline HbA1c levels were 8.2%, 8.4%, and 8.1%, and mean baseline fasting plasma glucose were 181 mg/dL, 179 mg/dL, and 180 mg/dL, respectively. At week 26, mean differences from placebo were -0.6% and -31 mg/dL for 5 mg patients and -0.7% and -36 mg/dL for 15 mg patients, respectively. In addition, there was a mean 2 kg loss in body weight between ertugliflozin and placebo. When ertugliflozin was added to metformin monotherapy (≥ 1,500 mg/day), similar magnitudes of change in HbA1c and fasting plasma glucose were observed. In an active-controlled, 52-week study, ertugliflozin was noninferior to glimepiride as an add-on to metformin.

In other studies, ertugliflozin plus sitagliptin added to metformin produced greater HbA1c reduction than either alone plus metformin. Additionally, ertugliflozin added to sitagliptin and metformin was more effective than placebo plus sitagliptin and metformin. Similar to other SGLT2 inhibitors, the glucose-lowering effect declines with declining renal function. Currently, there are no published direct comparisons among the SGLT2 inhibitors. However, the results of placebo-controlled studies indicate the lowering effect on HbA1c is similar to that reported in two large placebo-controlled studies with canagliflozin and empagliflozin.[2,5]

CLINICAL IMPLICATIONS

SGLT2 inhibitors are the newest class of antihyperglycemic drugs. In 2008, the FDA issued a guidance directing new therapies for diabetes to undergo assessments for cardiovascular outcomes.[4] So far, two glucagon-like peptide agonists (liraglutide and semaglutide) and two SGLT2 inhibitors (canagliflozin and empagliflozin) have been reported to reduce the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.[3] Both liraglutide and empagliflozin are FDA approved to reduce the risk of cardiovascular events in patients with established cardiovascular disease. In the same study, canagliflozin was associated with lower limb (primarily toe or metatarsal) amputations, resulting in a boxed warning.[2,6] The cardiovascular safety and outcome trial for dapagliflozin and ertugliflozin is expected to be completed in 2019. The American Association of Clinical Endocrinologists/American College of Endocrinology guideline lists SGLT2 drugs as potential alternatives to metformin as monotherapy, in combination with metformin as dual therapy and triple therapy.[7] Because of limited clinical experience, the role of ertugliflozin remains to be determined, as current clinical evidence seems to favor empagliflozin. The daily cost is $8.94 for ertugliflozin, $17,45 for ertugliflozin/sitagliptin, and $8.94 for ertugliflozin/metformin. Availability is expected in February 2018. ■

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Clinical Briefs

By Louis Kuritzky, MD

The Ever-elusive Prescription for the Optimum Diet

SOURCE: Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): A prospective cohort study. *Lancet* 2017;390:2050-2062.

Opinions about how to best structure optimum dietary constituents have gone through multiple dramatic changes in the last three decades, with little consistency. Remember when eggs were bad because of cholesterol, and margarine was preferred to butter because of calories and fat, and fat, generally, was regarded as an anathema?

The Prospective Urban Rural Epidemiology study was an observational cohort (n = 135,335) of adults aged 35-70 years, followed for 7.4 years, representing 18 different countries, selected to represent the three tiers of low-, middle-, and high-income nations.

During the follow-up interval, 5,796 deaths and 4,784 nonfatal cardiovascular events occurred. Overall for carbohydrates, comparing the highest quintile of intake to the lowest (quintile 5 vs. quintile 1), the hazard ratio for mortality was 1.28. Perhaps surprisingly, carbohydrate levels were *not* associated with mortality from cardiovascular disease or with cardiovascular events. Additionally, somewhat contrary to the prevailing wisdom, intake of total fat was *inversely* associated with total mortality (hazard ratio, 0.77). Even the much-maligned saturated fat in the diet was associated with a reduced hazard ratio for total mortality (0.86). Each of these outcomes was statistically significant.

The authors' interpretation of their results, as quoted, is appropriate: "Global dietary guidelines should be reconsidered in light of these findings." ■

Dealing With Severe Acute Pain in the ED

SOURCE: Chang AK, Bijur PE, Esses D, et al. Effect of a single dose of oral opioid and nonopioid analgesics on acute extremity pain in the emergency department: A randomized clinical trial. *JAMA* 2017;318:1661-1667.

The desire to provide meaningful pain relief for patients with acute severe pain is complicated by concerns about potential overuse of opioids, sometimes leading to misuse, diversion, dependency, and addiction. Despite the commonplace nature of acute pain syndromes (e.g., acute fracture), the literature base comparing different analgesic strategies is modest.

Chang et al performed a randomized, controlled trial among adults (n = 411) presenting with severe acute pain to EDs in the Bronx. The authors compared four different pain regimens, with the specific outcome of change in pain at two hours post-analgesic as measured on a 10-point (0-10) numeric pain rating scale. At baseline, the mean pain scale score was 8.7, indicative of moderately severe to severe pain.

The four regimens (each given as a single dose) were ibuprofen 400 mg/acetaminophen 1,000 mg, oxycodone 325 mg/acetaminophen 325 mg, hydrocodone 5 mg/acetaminophen 300 mg, and codeine 30 mg/acetaminophen 300 mg. At two hours, there was no statistically significant difference in pain reduction between the four different treatment arms. The success of a non-opioid treatment arm in direct comparison with three opioid treatment arms should justify greater consideration of non-opioid treatment for acute severe pain. ■

Reducing Falls Among Older Adults

SOURCE: Tricco AC, Thomas SM, Veroniki AA, et al. Comparisons of interventions for preventing falls in older adults: A systematic review and meta-analysis. *JAMA* 2017;318:1687-1699.

Most clinicians recognize the serious burden resulting from falls in senior citizens. Even when falls do not result in serious injury, fear of falls may be quite compromising. Seniors may be reluctant to report postural instability to their families, caregivers, or clinicians, lest their disclosure result in loss of autonomy, nursing home placement, or other restrictions.

Fortunately, as reported in this systematic review, a substantial number of randomized, controlled trials (n = 283 trials, which included 159,910 participants) provide convincing evidence that interventions are remarkably beneficial. Exercise, correction of impaired vision, supplemental calcium/vitamin D, and environmental interventions reduce falls. The interventions that were multimodal appear to produce additive benefits.

Although these results are encouraging, it is noted that there is some signal for an increase in falls when patients become more mobile subsequent to strength and exercise training. Clinicians are advised to caution patients to be cognizant of the risks of greater levels of activity while enjoying greater mobility. ■

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CME QUESTIONS

1. **The new U.S. Preventive Services Task Force statement says:**
   a. premenopausal women should not be prescribed hormone replacement therapy (HRT).
   b. premenopausal women sonly should be prescribed HRT for treatment of symptoms.
   c. postmenopausal women should not be prescribed HRT for prevention of medical conditions.
   d. postmenopausal women should not be prescribed HRT for any reason.

2. **In patients with low to intermediate risk of coronary artery disease and chest pain, coronary calcium score vs. stress testing for predicting major cardiac adverse events (MACE) showed:**
   a. more robust discriminatory ability.
   b. a high sensitivity for MACE.
   c. a high specificity for MACE.
   d. that only patients with scores > 400 experienced MACE.

3. **In the study population from the Einstein Aging Study, which of the following was associated with a significant decrease in the incidence of dementia?**
   a. Higher mean years of education
   b. Lower prevalence of myocardial infarction and stroke
   c. Change in racial/ethnic diversity
   d. Birth after mid-1929

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.

[IN FUTURE ISSUES]

Obesity Is a Hormonal Illness

Blockade of CGRP for Migraine Prevention: Promising, but Not a Cure