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ABSTRACT & COMMENTARY

Advance Care Planning Must Advance Forward

By Seema Gupta, MD, MSPH

Clinical Assistant Professor, Department of Family and Community Health, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

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

SYNOPSIS: In a systematic review of 795,909 people in 150 studies, researchers found many Americans have not completed an advance directive.

SOURCE: Yadav KN, Gabler NB, Cooney E, et al. Approximately one in three US adults completes any type of advance directive for end-of-life care. *Health Aff (Millwood)* 2017;36:1244-1251.

Advance care planning (ACP) is a continual process of preparing for future medical care in case patients are unable to make his or her own decisions. It includes engaging patients and families to reflect on patients' personal goals, values, and belief systems, which ultimately translate into informing medical care. This process helps prepare the patient for current and future decisions regarding medical treatment. Data show that Americans have fallen behind on this process. For example, a survey revealed that although many people say they would prefer to die at home, only about one in three American adults have created an advance directive expressing their wishes for end-of-life care.[1] Only 28% of home healthcare patients, 65% of nursing home residents, and 88% of hospice care patients have created an advance directive.[2] Data show that among severely or terminally ill patients, < 50% have an advance directive. As many as three-quarters of physicians whose patients had an advance directive were not even aware that it existed.[3] In fact, studies have shown that in ICU patients, as few as 17% of patients possessed advance directives.[4] As components of ACP, advance directives such as durable power of attorney for healthcare and living will ensure patients receive the care that is consistent with their wishes while significantly improving multiple outcomes

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in patients with serious medical conditions. Additionally, ACP improves communication for shared decision-making while reducing the level of anxiety in family members during times of high stress.

Yadav et al conducted a systematic review of the data on the prevalence of advance directives among U.S. adults collected between 2011 and 2016 to determine how many Americans had advance directives, both overall and specifically among people most likely to benefit from them, and how advance directive completion rates have changed over time. Researchers included 795,909 Americans who were part of 150 different studies. Approximately 63.6% were female, 65.1% were white, 80.6% were ≥ 65 years of age, and 62.7% were in a nursing home. The meta-analyses revealed completion proportions of 29.3% (95% confidence interval [CI], 25.0-34.0%) for living wills, 33.4% (95% CI, 29.5-37.6%) for healthcare powers of attorney, and 32.2% (95% CI, 27.2-37.7%) for undefined advance directives. Patients ≥ 65 years of age exhibited a significantly greater completion percentage of any advance directive (45.6%; 95% CI, 40.6-50.8%) compared to younger adults (31.6%; 95% CI, 28.4-35.0%; $P < 0.001$). There was a significant difference in any advance directive completion by patient type ($P < 0.001$), with the highest rates among patients in hospice or palliative care (59.6%; 95% CI, 41.8-75.1%) and nursing home patients (50.1%; 95% CI, 42.1-58.2%).

■ COMMENTARY

Using advance directives to plan for the end of life is viewed as a public health issue. Not only does this prevent unnecessary suffering and anxiety among families, but it can reduce unwanted and expensive treatment. However, as the research by Yadav et al demonstrated, the prevalence of advance directives remains low and stagnant. Recognizing a challenge in the field, effective Jan. 1, 2016, Medicare made the decision to reimburse physicians for ACP counseling. As Americans continue to live longer, many more are surviving with one or more chronic diseases and experience substantial disability before dying. For instance, 70% of Americans die of a chronic disease, and about 62% of all deaths each year are caused by five chronic diseases: cancer, COPD, diabetes, heart disease, and stroke. However, to ensure that more patients are able to create updated advance directives, it is critical to reduce the barriers to ACP. This includes increasing awareness among patients and their family members, and addressing denial about death and dying where it may exist. A discussion about palliative care, which may involve end-of-life care much earlier in a person's disease process, could help avoid the confusion while maintaining quality of life at the end of life. Finally, as physicians, we must recognize the cultural differences within our patients that result in certain patients' lower usage of hospice services and ACP, with the resultant increased likelihood of dying in hospital as well as use of intensive care and life-sustaining treatments.[5] ■

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ABSTRACT & COMMENTARY

B-type Natriuretic Peptide Is Less Useful in Elderly Patients with Dyspnea

By Van Selby, MD

Assistant Professor of Medicine, University of California, San Francisco Cardiology Division, Advanced Heart Failure Section

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

SYNOPSIS: Among patients ≥ 80 years of age presenting with acute dyspnea, B-type natriuretic peptide level was not useful for differentiating cardiac vs. respiratory etiologies when added to a model of clinical predictors.

SOURCE: Plichart M, Orvoën G, Jourdain P, et al. Brain natriuretic peptide usefulness in very elderly dyspnoeic patients: The BED study. *Eur J Heart Fail* 2017;19:540-548.

B-type natriuretic peptide (BNP) is used frequently to identify cardiac vs. respiratory etiologies in patients presenting with dyspnea. However, many factors influence BNP level, limiting its usefulness in certain populations. The diagnostic accuracy of BNP concentration in the assessment of dyspnea in very elderly (> 80 years of age) patients has not been studied adequately. The authors of the BNP Usefulness in Elderly Dyspneic Patients (BED) study enrolled 383 patients ≥ 80 years of age who were evaluated for acute dyspnea. All patients had BNP levels measured in addition to other clinical testing, including echocardiography. Independent cardiologists blinded to the BNP result evaluated each case according to standard guidelines to determine whether the cause of dyspnea was cardiac vs. respiratory.

Sixty-two percent of patients had cardiac dyspnea, and 38% had respiratory dyspnea. BNP levels were significantly higher among patients with cardiac vs. respiratory etiologies (median level 385.5 vs. 172.0 ng/L; $P < 0.001$). However, BNP was not a good test for discriminating cardiac vs. respiratory etiologies (area under the curve [AUC] = 0.68). The authors created a multivariate model of clinical predictors that discriminated cardiac vs. respiratory dyspnea with high accuracy (AUC = 0.915). When added to this model, BNP was independently associated with cardiac etiology but did not improve the AUC significantly ($P = 0.16$). No single BNP cutoff value was found that diagnosed or excluded cardiac etiologies with adequate reliability. Clinical predictors associated with a cardiac etiology included higher body mass index, history of heart failure (HF), X-ray findings consistent with pulmonary edema, and lower ejection fraction. History of chronic respiratory disease, rhonchi, and higher white blood cell count all were associated with a respiratory etiology. The authors concluded that BNP is not a useful diagnostic tool among very elderly patients with acute dyspnea, but noted that it may be of interest for prognosis in heart failure.

■ COMMENTARY

Both American and European guidelines give a class IA recommendation for the use of natriuretic peptide biomarkers such as BNP to support or exclude heart failure in patients presenting with dyspnea. A cutoff level of 100 ng/L is recommended often to rule out cardiac dyspnea, regardless of age. However, guidelines also acknowledge that comorbidities can influence BNP levels and recommend they be taken into account when interpreting a given patient's BNP. Elderly patients are more likely to present with comorbidities, and age alone can influence BNP level. Therefore, it is important to understand how this changes the utility of BNP as a diagnostic test.

The Breathing Not Properly Multinational Study was one of the first and largest to evaluate the utility of BNP measurement in patients presenting with dyspnea. A post-hoc subanalysis of this study found that BNP was a weaker predictor in subjects > 70 years of age. BNP levels tended to be higher in elderly subjects, and this decreased the specificity for any given cutpoint. Several smaller studies subsequently found that BNP remained useful in elderly patients, though higher cut-points were needed.

Plichart et al now add the largest study to date specifically evaluating the utility of BNP in elderly patients. Their primary finding is that a clinical model consisting of age, body mass index, gender, and other covariates discriminated cardiac vs. respiratory etiologies with high accuracy. Although BNP levels were higher in patients with cardiac dyspnea, adding BNP levels to their clinical model did not improve the discriminative ability of their model significantly. Although the findings of this study weaken enthusiasm for BNP use in elderly patients, there are a few important aspects to keep in mind. The baseline multivariable model already had an impressive ability to discriminate cardiac vs. respiratory dyspnea, and it would be difficult for the addition of BNP to improve

on this model significantly. The model these authors used involved many variables and was not practical for routine use in clinical settings. BNP levels clearly were higher in patients with cardiac etiologies, and perhaps if a simpler, more realistic baseline model were used, then adding BNP would improve the diagnostic accuracy. Another limitation is the lack of a "gold standard" for the diagnosis of cardiac (as opposed to respiratory) dyspnea. Instead of abandoning BNP testing in elderly patients, it may be better to continue using it to differentiate cardiac vs. respiratory causes of dyspnea while taking into consideration its limitations. Elderly patients have higher BNP levels than younger patients, and a higher BNP level cannot "rule in" cardiac dyspnea with the same accuracy as it can in younger patients. BNP levels should be used along with all other available clinical data when determining the etiology of acute dyspnea in elderly patients. ■

ABSTRACT & COMMENTARY

Omega-3 Polyunsaturated Fatty Acid Supplementation and Cognitive Decline

By Makoto Ishii, MD, PhD

Assistant Professor of Neuroscience and Neurology, Feil Family Brain and Mind Research Institute, Department of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In a randomized, placebo-controlled trial of 1,680 participants ≥ 70 years of age, there was no significant difference in cognitive decline between any of the intervention groups taking omega-3 polyunsaturated fatty acid supplementation and/or multidomain intervention (physical activity, cognitive training, and nutritional advice) compared to the placebo group. However, exploratory post hoc analyses showed some promise for a protective effect with intervention in certain at-risk subgroups.

SOURCE: Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. *Lancet Neurol* 2017;16:377-389.

As Alzheimer's disease and related dementia remain incurable, there is significant interest in identifying effective prevention strategies. Previous single-domain intervention trials (e.g., nutritional supplements, cognitive training, physical activity) have found protective effects on cognitive decline, but they remain controversial because of a lack of large-scale, randomized, controlled studies. The Multidomain Alzheimer Preventive Trial (MAPT) is a pioneering large multicenter, randomized, placebo-controlled trial testing whether multidomain lifestyle intervention and polyunsaturated fatty acids, either alone or in combination, could prevent cognitive decline over 36 months.

Between 2008 and 2011, study authors enrolled 1,680 participants from 13 memory centers in France and Monaco. Participants were non-demented, ≥ 70 years of age, community dwelling, and met at least one of three criteria: spontaneous memory complaint, limitation in one instrumental activity of daily living, or slow gait speed. Exclusion criteria included Mini Mental State Examination (MMSE) < 24, any difficulty in basic activities of living, and taking polyunsaturated fatty acids supplementation at baseline. Subjects were randomly allocated (1:1:1:1) to the combined intervention with multidomain intervention plus polyunsaturated fatty acids supplementation (total daily dose of 800 mg docosahexaenoic acid [DHA] and 225 mg of eicosapentaenoic acid [EPA]), multidomain intervention plus placebo, polyunsaturated fatty acids only, or placebo only. The multidomain intervention consisted of small group sessions focused on three domains (cognitive stimulation, physical activity, and nutrition) and preventive consultation sessions with a physician to optimize cardiovascular risk factors and detect any functional impairment. The primary outcome of the study was change from baseline to 36 months in a composite Z score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding Test, 10 MMSE orientation items, the Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale-Revised, and the Category Naming Test). Secondary outcomes were the individual components of the composite score, scores on other cognitive tests, and scores on the Short Physical Performance Battery and the Alzheimer's Disease Cooperative Study – Activities of Daily Living Prevention Instrument, Clinical Dementia Rating (CDR), Fried's frailty criteria, and the Geriatric Depression Scale. One hundred fifty-four participants were excluded because of lack of follow-up cognitive assessments, and one participant withdrew consent. Adherence was lower for the multidomain intervention groups with polyunsaturated fatty acids (55%) or with placebo (53%) compared to the polyunsaturated fatty acid (79%) or placebo-alone groups (85%). In

the primary efficacy analyses, there were no significant differences in three-year cognitive decline between any of the three intervention groups and placebo group. In a post hoc analysis, pooled analyses of all participants who received the multidomain intervention demonstrated significantly less cognitive decline compared to those who did not ($P = 0.015$), while the cognitive decline was similar between all participants who received the polyunsaturated fatty acids compared to those who did not. For secondary outcomes, the combined intervention group exhibited less of a decline in the 10 MMSE orientation items compared to the placebo group. No differences were seen in the other secondary outcome measures.

In post hoc analyses, participants in the placebo group with low baseline concentrations of DHA and EPA in red blood cells demonstrated a significant cognitive decline compared to those in the placebo group with high concentrations of DHA and EPA, whose cognitive performances remained stable, but the interventions did not alter cognitive decline in this subgroup. Additional post hoc subgroup analyses found participants with a positive amyloid PET scan receiving combined intervention or multidomain intervention plus placebo demonstrated less cognitive decline compared to those with a positive amyloid PET scan receiving placebo alone ($P < 0.0001$, $P = 0.003$, respectively).

■ COMMENTARY

As the first large randomized, placebo-controlled trial studying the efficacy of a lifestyle intervention with a nutraceutical compound (polyunsaturated fatty acid), MAPT is a landmark study. The negative results from the primary outcome at first may be seen as a disappointing failure for prevention intervention in dementia; however, the results from this study have yielded important information for designing future prevention trials. Results from recent Alzheimer's disease clinical trials suggest that intervening as early as possible, such as during the pre-symptomatic or preclinical stage may be critical. In MAPT, a significant portion of the study population (~40%) had a CDR of 0.5, which may be too late for preventive intervention. Additionally, exploratory analyses found specific subgroups that exhibited decreased cognitive decline with multidomain intervention, including those individuals with positive amyloid PET scans and those with CAIDE dementia risk score of ≥ 6. Collectively, this suggests that preventive interventions may be most efficacious by targeting those with the highest risk of developing dementia as early as possible. ■

PHARMACOLOGY UPDATE

Betrixaban Capsules (Bevyxxa)

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

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

The FDA has approved an oral factor Xa inhibitor for the prophylaxis of venous thromboembolism in hospitalized patients suffering from an acute illness. Betrixaban was granted a priority review and fast-track designation, and is the fourth oral factor Xa inhibitor to be approved and the first with this specific indication. Currently marketed oral factor Xa inhibitors are rivaroxaban, apixaban, and edoxaban. Betrixaban is marketed as Bevyxxa.

INDICATIONS

Betrixaban is indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications because of moderate or severe restricted mobility and other risk factors for VTE.[1]

DOSAGE

Clinicians should administer an initial dose of 160 mg, followed by 80 mg once daily for 35 to 42 days.[1] In patients with severe renal impairment (CrCl ≥ 15 to < 30 mL/min) or taking a P-glycoprotein (P-gp) inhibitor (e.g., amiodarone, verapamil), the dose should be 80 mg initially, followed by 40 mg daily. Betrixaban should be taken at the same time each day with food. Betrixaban is available as 40 mg and 80 mg capsules.

POTENTIAL ADVANTAGES

Extended duration betrixaban has been shown to be more effective than short duration enoxaparin, with comparable rates of major bleeding.[1,2] Betrixaban is the only member of the class to be approved for VTE prophylaxis in the hospitalized, acutely ill patient. In contrast, extended treatment with apixaban and rivaroxaban has been associated with increased risk of major bleeding.[3-5]

POTENTIAL DISADVANTAGES

Treatment discontinuation because of bleeding was more likely with betrixaban compared to enoxaparin

(2.4% vs. 1.2%).[1] Betrixaban carries the black box warning for epidural or spinal hematoma in patients receiving neuraxial anesthesia or undergoing spinal puncture.

COMMENTS

The approval of betrixaban was based on reanalysis of data from a randomized, double-blind, double-dummy trial that compared extended-duration betrixaban to short-duration enoxaparin in acutely medically ill hospitalized subjects at risk for VTE.[1] Subjects were ≥ 40 years of age and had been hospitalized for < 96 hours for specified acute medical illnesses (heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke) and reduced mobility.[2] Subjects (n = 7,513) were randomized to betrixaban (80 mg daily for 35 to 42 days following a 160 mg loading dose) along with placebo injection for six to 14 days or subcutaneous enoxaparin (40 mg once daily) for six to 14 days and placebo for 35 to 42 days. Subjects with renal impairment or with concomitant use of a P-gp inhibitor received a reduced dose (80 mg followed by 40 mg daily). The primary efficacy outcome was a composite of asymptomatic proximal deep vein thrombosis between day 32 and day 47, symptomatic proximal or distal deep vein thrombosis, symptomatic nonfatal pulmonary embolism, or death from VTE between day one and 42. The primary safety outcome was the occurrence of major bleeding at any point until seven days after the discontinuation of all study medications. This was based on the criteria of the International Society on Thrombosis and Haemostasis. A total of 7,441 subjects met the criteria of efficacy analyses (3,721 for betrixaban, and 3,720 for enoxaparin).[1] The primary outcome occurred in 165 subjects who received betrixaban (4.4%) and 223 (6.0%) in the enoxaparin arm (25% risk reduction). Subjects randomized to the reduced dose showed no difference in efficacy outcome (6.9% vs. 6.7%, respectively) and corresponding 42% lower median drug plasma levels.[6] Results from a retrospective substudy suggest betrixaban also reduced all-cause stroke and ischemic stroke compared to enoxaparin through 77 days of follow-up.[7] Major bleeding occurred in 0.67% of the betrixaban subjects compared to 0.57% for enoxaparin ($P = 0.55$). However, clinically relevant non-major (CRNM) bleeding was significantly higher with betrixaban (2.45% vs. 1.02 %; $P < 0.001$). CRNM bleeding was defined as overt bleeding not meeting criteria for major bleeding (e.g., ≥ 2 g/dL drop in hemoglobin, need for transfusion ≥ 2 units) but associated with medical intervention, unscheduled contact with a physician, temporary or permanent cessation of study treatment, or associated with discomfort (e.g., pain or impairment of activities of daily life).

CLINICAL IMPLICATIONS

VTE is a common cause of morbidity and mortality in patients hospitalized with acute medical illness. The American College of Chest Physicians recommends that nonsurgical acutely ill hospitalized medical patients at increased risk of thrombosis should receive thromboprophylaxis with low-molecular weight heparin, low-dose unfractionated heparin, or fondaparinux, and suggests against extending the duration of prophylaxis beyond the period of patient immobilization or hospital stay.[8] However, most VTE episodes occur after discharge, with 67% reported to occur within one month after discharge.[9] This suggests extended-duration thromboprophylaxis as a potential unmet need.[10] A systematic review and meta-analysis suggest that extended treatment with apixaban, rivaroxaban, and enoxaparin reduces the risk of VTE but was associated with increased risk of major bleeding.[6] Betrixaban, the first anticoagulant to be approved for extended duration use, was more effective than short duration enoxaparin but was not associated with increased risk of major bleeding. However, it was associated with increased risk of CRNM bleeding. The cost for betrixaban was not available at the time of this review. The drug is expected to launch between August and November 2018. ■

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Clinical Briefs

By Louis Kuritzky, MD

The Best BP for High-risk Hypertension Patients

SOURCE: Böhm M, Schumacher H, Teo KK, et al. *Lancet* 2017;389:2226-2237.

The authors of the Systolic Blood Pressure Intervention Trial (SPRINT) randomized almost 10,000 high-risk, non-diabetic patients to intensive treatment (systolic blood pressure [SBP] goal: < 120 mmHg) vs. "standard" treatment (SBP goal: < 140 mmHg) and demonstrated that the group assigned to intensive treatment experienced a statistically significant reduction in both cardiovascular (CV) and all-cause mortality. Although the "costs" of intensive treatment were not trivial (more medications, more cost, more serious and non-serious adverse events), the lesson for many clinicians was that striving for SBP control better than < 120 mmHg was of merit in patients willing to shoulder the increased complexity and potential adverse effect profile of intensive treatment. But this may not be the end of the story.

Böhm et al analyzed the outcomes of two large, previously published CV trials: ONTARGET (n = 25,127) and TRANSCEND (n = 5,810). They chose to examine CV outcomes within these two trials for patients similar to the SPRINT population (high-risk adults) in relation to on-treatment BP. According to their analysis, achieving an SBP < 120 mmHg was associated with a 14% increase in composite CV outcomes compared to an SBP 120-140 mmHg. Similarly, hazard ratios for all-cause mortality and CV mortality were approximately 30% higher in persons who achieved the lower BP threshold (< 120 mmHg).

While these results might dampen enthusiasm for those who endorse the above-mentioned results of SPRINT, differences between the data sets, as well as the fact that this report relies on post-hoc analysis, include a substantial proportion of diabetics and post-stroke patients in the analysis of ONTARGET/TRANSCEND, both of whom had been excluded from SPRINT, and may have made an important difference in outcomes. ■

Dietary Omega-3 Fatty Acids Inversely Associated with Diabetic Retinopathy

SOURCE: Chew EY. *JAMA* 2017;317:2226-2227.

In the spirit of full disclosure, with rare exception (folate for reproductive age women), I am not an advocate for supplements. I want to make sure readers can clearly identify the difference between omega-3 fatty acid supplements and omega-3 fatty acids as provided by fish in the diet. The use of supplements by Americans has been fairly stable over the past decade at about 50%, despite little in the way of substantive scientific evidence support their use. However, let's not confuse the difference between the potential benefits of enhancement of diet with enhancement of intake through supplements. For instance, data from the Women's Health Initiative suggest that the cardiovascular effects of calcium intake through dietary enhancement differ from those of calcium supplements.

The PREDIMED clinical trial was a prospective investigation that compared a Mediterranean diet augmented with extra virgin olive oil and nuts with a control (n = 7,447). Approximately half of the PREDIMED participants were diabetic. After a follow-up of six years, the hazard ratio for new retinopathy requiring intervention was approximately half that for the Mediterranean diet group compared to the control group. Although it may be tempting to extrapolate these observations to simply take an omega-3 fatty acid supplement of comparable quantity, it remains to be determined whether this isolated ingredient from fish, when taken as a single-entity intervention, will provide similar benefits. ■

The Potential Long-term Payoff of Good Initial Diabetes Control

SOURCE: Svensson E, Baggesen LM, Johnsen SP, et al. *Diabetes Care* 2017;40:800-807.

Experts often opine that treatment of diabetes is "a marathon, not a sprint," suggesting that careful, slow steps are wise. In reference to risk for hypoglycemia, this philosophy is likely to be particularly apt, and yet some data suggest that prompt control of type 2 diabetes (T2DM), with strong early reductions in A1c, may produce long-term benefits.

Svensson et al reported on a large population of T2DM patients (n = 24,752) in Denmark among whom baseline A1c and degree of A1c reduction within the first six months could be correlated with outcomes over the next 2.6 years (mean follow-up). The group was restricted to only those patients whose initial treatment had been metformin.

The authors found that both the lowest six-month achieved A1c level and greatest absolute degree of A1c correlated with greatest risk reduction for cardiovascular outcomes.

Although the window of observation of these patients is only modest (< 3 years), these results encourage clinicians to pursue the best control of T2DM we can attain without incurring significant adverse events, such as hypoglycemia. ■

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CME QUESTIONS

1. **Based on the study by Yadav et al, which of the following statements is *false* regarding U.S. adults?**
   a. Only 29% had completed a living will that contained specific end-of-life care wishes.
   b. Only 33% had designated a healthcare power of attorney.
   c. For patients in hospice or palliative care, 59% had completed advance directives.
   d. Patients ≥ 65 years of age had a significantly greater completion proportion of any advance directive at 70%.

2. **B-type natriuretic peptide levels are of less use for diagnosing cardiac dyspnea in patients:**
   a. < age 40 years.
   b. age 40-60 years.
   c. age 60-80 years.
   d. > age 80 years.

3. **Which of the following was *not* a finding from the Multidomain Alzheimer Preventive Trial?**
   a. In the intention-to-treat population, there was no significant difference in three-year cognitive decline between any of the intervention groups and the placebo group.
   b. In a post hoc analysis, pooled analyses of all multidomain intervention subjects revealed less cognitive decline than for those who received conventional care.
   c. There was a significant three-year cognitive decline for participants with low baseline concentrations of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in red blood cells compared to stable cognitive performances for participants with high baseline concentrations of DHA and EPA.
   d. In participants identified as amyloid-positive by PET scan, there was no significant difference in three-year cognitive decline between any of the intervention groups and the placebo group.

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]

Glucose Self-monitoring Is Not Helpful In Non-insulin-treated Type 2 Diabetes Mellitus

Chondroitin Is as Effective as Celecoxib for Knee Arthritis