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ABSTRACT & COMMENTARY

# NOACs vs. Warfarin: What Are the Data in Patients With TBI and ICH?

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

SYNOPSIS: A three-year analysis of a prospectively maintained database with traumatic brain injury patients revealed that novel oral anticoagulant use is associated with increased risk of intracranial hemorrhage progression, neurosurgical intervention, and mortality.

SOURCE: Zeeshan M, Jehan F, O'Keeffe T, et al. The novel oral anticoagulants (NOACs) have worse outcomes compared with warfarin in patients with intracranial hemorrhage after TBI. *J Trauma Acute Care Surg* 2018;85:915-920.

Despite the increasing use of novel oral anticoagulants (NOACs) within the healthcare system, emergent reversal of these agents remains a management challenge. There is little data comparing the use of NOACs to warfarin in patients with intracranial hemorrhage (ICH) after traumatic brain injury (TBI). Zeeshan and colleagues conducted a three-year analysis of their prospectively maintained database examining the outcomes after TBI in patients taking NOACs compared to those taking warfarin. Researchers analyzed all adult trauma patients admitted to a single Level I trauma center with a diagnosis of TBI. Inclusion criteria were all adult TBI patients with ICH on initial head CT scans who received anticoagulation prior to injury. Anticoagulants included warfarin or NOACs, including direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban and apixaban). Patients with documented bleeding diathesis, chronic liver disease, penetrating mechanisms of injury, or those who died within 24 hours of trauma were excluded.

The primary outcomes were ICH progression and the need for surgical intervention. Progression was defined as an increase in the size of an existing hemorrhage or development of a new hemorrhage not previously seen on CT head. The need for surgical intervention was defined as intracranial pressure monitoring, craniotomy, or craniectomy that was performed as a result of ICH progression. Secondary outcomes included complications in the

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hospital, discharge to rehabilitation hospital or skilled nursing facility (SNF), hospital and ICU length of stay, and in-hospital mortality.

From the 1,459 eligible patients, 210 matched TBI patients were identified (70 patients on NOACs and 140 patients on warfarin). The matched groups were similar in age ($P = 0.21$), Glasgow Coma Scale (GCS) score ($P = 0.54$), mechanism of injury ($P = 0.61$), Injury Severity Score ($P = 0.62$), and type and size of ICH ($P = 0.09$). Compared to patients on warfarin, patients who had been treated with NOACs prior to injury had a higher rate of progression ($P = 0.03$), neurosurgical intervention ($P = 0.04$), mortality ($P = 0.04$), and longer ICU length of stay ($P = 0.04$). There was no difference in hospital length of stay ($P = 0.22$) or SNF disposition ($P = 0.14$). A sub-analysis for severe TBI patients (defined as GCS ≤ 8) revealed no difference in rate of progression ($P = 0.59$), neurosurgical intervention ($P = 0.62$), or mortality ($P = 0.81$). NOAC use was associated with an increased risk of ICH progression, neurosurgical intervention, and mortality after mild and moderate TBI. It is important to carefully keep these risks in mind when deciding on the optimal form of anticoagulation for each individual patient.

## ■ COMMENTARY

Patients on oral antithrombotics are at increased risk of ICH after trauma.[1] Although vitamin K antagonists have been the only class of oral anticoagulants available for decades, many clinicians have substituted NOACs for warfarin because of the ease of use. NOACs have a rapid onset of action, fewer drug interactions, no dietary limitations, no laboratory monitoring requirements, and predictable pharmacokinetics.[2] The difficulty in NOAC reversal in cases of serious, life-threatening hemorrhage, especially from ICH after TBI, remains an important clinical concern in the setting of growing use of these agents. The findings of Zeeshan and colleagues underscore this problem, finding that prior NOAC use was associated with an increased risk of ICH progression, neurosurgical intervention, and mortality after a mild and moderate TBI when compared to similar patients receiving warfarin.

Previous data regarding the outcomes of TBI patients on NOACs were published by Kobayashi and colleagues and conducted by the American Association for the Surgery of Trauma.[3] Although in this study researchers found that TBI patients on NOACs were not at higher risk of ICH, ICH progression, or death, the study population was substantially different. These investigators included all trauma patients admitted to the hospital on prior dabigatran, rivaroxaban, apixaban, warfarin, aspirin, or clopidogrel. In the study by Kobayashi and colleagues, only 30% of the patients had ICH on presentation, while ICH was an inclusion criterion in the Zeeshan et al study. The Kobayashi study also included lower rates of subdural hematoma (SDH) (19% vs. 30%) and older patients with a lower Injury Severity Score. An additional limitation to the study was that only 10% of the study population was taking a NOAC.

Although NOACs often are favored for their attractive pharmacokinetic qualities previously discussed, the reversal strategies for these novel agents are still evolving.[4] Ideally, most forms of anticoagulation have a specific reversal agent or antidote for episodes of serious or life-threatening bleeding. Dabigatran's reversal agent is idarucizumab, but this anti-dabigatran monoclonal antibody fragment often is unavailable to many because of its cost.[5] Andexanet alfa recently was approved as a reversal agent for the oral direct factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban), but again, it is costly with limited availability. There are other promising antidotes under development, including a small molecule antidote, PER977, and a mutant form of factor Xa, FXa(I16L), but they are not currently available. As a result, clinicians often are left with less targeted interventions, such as four-factor prothrombin complex concentrate (4-factor PCC) and fresh frozen plasma in this setting.

The use of NOACs will continue to rise, and critical care providers should ensure that their hospitals have a systematic protocol available to treat patients receiving these agents who present with life-threatening or uncontrolled bleeding. Although the Zeeshan study appears to have been more deliberate in addressing the question of NOAC vs. warfarin in TBI, it also had limitations that warrant further consideration.

The study was a single-center, observational study without a true control group. Because it was an observational study, there is an

association between NOAC use and increased risk of progression of ICH, neurosurgical intervention, and mortality after mild and moderate TBI, but causation cannot be assigned. There also is concern for sampling bias, since the institution was a Level I trauma center serving as a quaternary referral hospital. Although the manuscript relays the details of the reversal agents (fresh frozen plasma, prothrombin complex concentrate, vitamin K), the results of these data points were not mentioned again throughout the manuscript. Not knowing the frequency, timing, or type of reversal agent for each case is a major limitation.

Despite these substantial limitations, this study challenges a provider to balance risks and benefits of a particular anticoagulant carefully and to be ready to intervene with rapid recognition and reversal in patients with ICH. These findings also highlight the need for future larger, multicenter studies to further explore the outcomes of patients on NOACs after traumatic brain injury. ■

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ABSTRACT & COMMENTARY

# Estrogen Replacement: Is Long Duration of Therapy Good for the Brain?


***By Jeffrey T. Jensen, MD, MPH***

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**Dr. Jensen reports that he is a consultant for Bayer, Sebela, TherapeuticsMD, and CooperSurgical; and he receives grant/research support from AbbVie, Bayer Healthcare, Merck, Estetra SPRL, Medicines360, and Daré Bioscience.**



SYNOPSIS: Longer lifetime exposure to endogenous estrogen and menopausal estrogen replacement were associated with better cognitive status in older adult women. Women who initiated estrogen therapy early (within five years of the onset of menopause) showed higher cognitive test scores than those who started later.

SOURCE: Matyi JM, Rattinger GB, Schwartz S, et al. Lifetime estrogen exposure and cognition in late life: The Cache County Study. *Menopause* 2019;26:1366-1374.


Several animal models and in vitro studies support a role for estrogen in memory.[1] Case control and other epidemiologic observational studies generally support a decrease in the risk of Alzheimer's disease (AD) associated with long duration use of postmenopausal hormone replacement therapy (HT).[2] However, the large prospective, randomized Women's Health Initiative (WHI) Memory Study found an increased risk of dementia and cognitive decline associated with oral conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (MPA).[3]

Matyi and colleagues used data from the Cache County Study on Memory in Aging (CCSMA) to study lifetime estrogen exposure and the risk of cognitive decline. The CCSMA surveyed residents of Cache County, UT, age 65 years or older, without dementia, beginning in 1995. Researchers collected demographic information, including age, education, lifestyle factors (physical activity, smoking, and drinking), diet, and family history. They performed genotyping for apolipoprotein E (APOE) and cognitive and dementia screening. Reproductive health questions included age at menarche and menopause, number of pregnancies and live births, breastfeeding duration, and use of hormonal therapy. The authors used the 100-point modified Mini-Mental State Examination (3MS) to assess the outcome of dementia. To assess exposure to estrogen, they calculated lifetime: 1) endogenous estrogen exposure (EEE) as the reproductive window (menopausal age minus age of menarche), minus total duration of breastfeeding; and 2) exogenous estrogen exposure as the duration of hormone therapy used, type (none, estrogen only, estrogen/progestogen), and timing (no HT; within one year of menopause; between one and five years; six years or more).

To evaluate the relationship between estrogen exposure and 3MS score, the researchers created a series of linear mixed effects models and adjusted the results for additional covariates of interest guided by prior studies,

including age, level of formal education, APOE genotype (number of E4 alleles), body mass index (BMI), physical activity, overall health, and depression status.

The first model examined only EEE; the second model examined EEE and duration of exogenous HT exposure (time varying); the third model examined EEE and type of HT (none, unopposed, opposed); and the fourth model examined EEE and timing of HT initiation relative to menopause. They also evaluated the effects of HT discontinuation.

A total of 2,147 women without dementia at the baseline visit comprised the study cohort for this paper. The women in the overall study sample had a mean age of 75 years and an average of almost 13 years of education. Almost all of the women were white and Mormon. The mean EEE was 33 years. Participants who reported ever using HT at baseline were significantly younger and better educated, and more physically active than never-users, and had higher baseline 3MS scores.

In the analysis evaluating the effect of EEE on cognition, the unadjusted model found that each additional year of EEE was associated with a 0.05-point higher score on the 3MS ($P = 0.008$). However, this result did not remain statistically significant in the fully adjusted mixed model. The researchers found a similar effect with respect to hormone therapy duration (each additional year was associated with a 0.02-point higher score). Both combined and estrogen-only therapies increased the 3MS scores. However, none of these relationships remained statistically significant after full adjustment.

All of the women who reported use of HT had higher 3MS scores than nonusers. However, in the fully adjusted model, women who used estrogen continuously or within five years of menopause scored significantly higher than those who initiated HT six or more years after menopause.

## ■ COMMENTARY

This study provides some additional evidence that menopausal hormone therapy may reduce the risk of cognitive decline. The results must be viewed with caution, as they represent a highly selected sample of older white women living in Utah. All of the effects are modest, and many of the outcomes lose statistical significance with adjustment. Despite those limitations, the results provide additional support for the timing hypothesis, and add to the body of work that refutes the WHI evidence suggesting cognitive risks associated with hormone therapy.

The Cache County study began in 1995. Zandi and colleagues published the first results from this cohort in the *Journal of the American Medical Association* in 2002.[2] I suspect most of you have seen the figures from this publication that show a dramatic difference between men and women in the risk of AD. The risk for women sharply increases beginning around age 80. Zandi and colleagues found a dose response for a reduction in the risk of AD associated with the duration of HT use. The risk associated with greater than 10 years of HT use approached the baseline risk observed in men. While these observations are consistent with the biologic mechanism of estrogen-induced synaptic connections, limitations of the Cache County study design deserve mention. The biggest concern is the healthy user effect. Women using HT had better 3MS scores at baseline, and as health declines (including mental health), many women may discontinue HT. Another problem is the effect of the WHI results in 2002 that led to a tremendous overall decline in HT use in the cohort.

Given that these limitations also apply to the new study by Matyi et al, how should clinicians use this information in counseling? The most interesting new results include the protective effect of EEE on cognitive decline. A late menopause is good for cognitive health, and early menopause is bad. Women who undergo premature ovarian failure or surgical menopause at a young age are at high risk for cognitive decline. I worry about these women, particularly if they receive care from a primary care clinician stuck in the post-WHI mindset of recommending HT at the "lowest dose" and for the "shortest duration." The Matyi paper also supports that early initiation of HT may result in the best protection.

While attractive, randomized trials have not confirmed the "timing hypothesis." The Elite-Cog[4] and KEEPS-Cog[5] studies explored the hypothesis of a critical window for HT initiation and found no treatment-related benefit of HT with respect to overall cognitive function. Although the outcome of these studies did not support the use of estrogen therapy to prevent subtle cognitive decline in postmenopausal women, this does not rule out a potential protective effect on the subsequent development of AD. In 2017, Finnish investigators published results from the Kuopio Osteoporosis Risk Factor and Prevention cohort, a population-based cohort followed for 20 years. They reported that a history of HT use did not change the risk of AD, but that a trend toward protection emerged with longer duration of self-reported use, with an approximately 50% reduction in risk seen in women reporting greater than 10 years of HT.[6] To restate, the consistent finding from both the Cache County and the Kuopio studies is that duration of treatment seems to matter for prevention of AD. At least 10 years of use represents an important goal of therapy. Current use of shorter duration may not reduce risk.

While most women remain interested in cognitive benefits, these are not approved indications for HT. Clinicians should always discuss the limitations of the data and the

potential risks and benefits of treatment. However, I do not believe that HT increases the risk of dementia. While estrogen is not a panacea for age-related memory loss, a reduction in risk of AD development in women using HT for at least 10 years may come to pass as a hidden additional benefit. ■


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ABSTRACT & COMMENTARY

# Bright Light Therapy in Depression and Insomnia Associated With Parkinson's


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



SYNOPSIS: Bright light therapy (10,000 lux intensity for 30 minutes twice daily) and a low intensity control light showed similar efficacy in treatment of depression associated with Parkinson's disease; the bright light therapy showed some advantages in improving subjective quality of sleep.

SOURCE: Rutten S, Vriend C, Smit JH, et al. Bright light therapy for depression in Parkinson disease: A randomized controlled trial. *Neurology* 2019;92:e1145-e1156.


The pivotal work of Kleitman in the 1950s and his discovery of rapid eye movement (REM) sleep sparked renewed interest in the essential role of sleep in health.[1] Sleep medicine, a new branch of medicine devoted to the study and treatment of sleep disorders, emerged from Kleitman's work and other related work of the time. With advances in technology, a new understanding of the electrical activity of the brain during wake and sleep cycles propelled investigation of the science behind the link between sleep and mental health disorders.[1,2]

Over the last 20 years, a growing recognition of a bidirectional relationship (think chicken and egg) between sleep and disorders of mood led to a focus on improving sleep in treatment and prevention of mood disorders.[3] Rutten et al designed a randomized controlled trial investigating bright light therapy (BLT) to treat depression in Parkinson's disease (PD). The researchers noted the high prevalence of both depression (17%) and insomnia (30%) in this population, as well as the significant functional impairment associated with each of these states. The group also noted the likelihood that disruptions in circadian rhythm (known to be associated with PD) may be a key factor in the development of both of these states. The researchers postulated that BLT would be more effective than a control light in treating patients with depression associated with PD. Secondary outcomes in the study included measuring markers of circadian rhythm (including cortisol) and sleep quality. Previous studies have shown a positive impact of BLT on sleep, mood, and motor improvement in PD, but this is the first known randomized controlled trial to review the effects on depression in PD with the use of BLT.

To be included in this Norwegian study, patients needed to have a diagnosis of idiopathic PD and major depressive disorder (MDD) and be stable on medications used for these conditions. Exclusion criteria revolved around comorbid medical factors that could contraindicate use of BLT (such as photosensitivity from medication and bipolar disorder) or instability of PD or MDD. The study was controlled to account for the impact of seasonal changes on ambient light.

There were significant difficulties recruiting and retaining participants for the study. Out of 389 volunteers over a five-year period (between 2012 and 2017), only 83 met the inclusion criteria. Of those 83 volunteers, 11 withdrew before the end of the first week of the study, resulting in only 72 participants. After randomizing into

two groups, all participants received a light box and were instructed to use it for 30 minutes twice daily at specified times. Light boxes for the intervention arm emitted daylight spectrum light at 10,000 lux; a filter placed in the boxes for those in the control arm lowered the light intensity to 200 lux. In addition, members of both groups were asked to keep a sleep diary and collect and submit saliva samples periodically during the study.

Severity of depression as measured by the Hamilton Depression Rating Scale (HDRS) and several other measurements of secondary outcomes were assessed at baseline, midway, and at the conclusion of the three-month study. After the study period, patients were encouraged to assume care as usual, and researchers continued to follow up for six months, with assessments at months one, three, and six.

### PRIMARY OUTCOME MEASURES

Scores on the HDRS are one way to measure and follow the severity or intensity of symptoms of MDD. Individuals with scores under 10 are generally not reporting depressive symptoms; scores between 10 and 13 represent mild distress; scores between 14 and 17 represent mild to moderate distress; and scores above 17 represent moderate to severe distress. In this study, mean HDRS at baseline was 14.5 for the control group and 14.7 for the BLT group. At the three-month endpoint of the active intervention, both groups showed a decrease in HDRS, to 8.3 for the control group and 7.6 for the BLT group. These values were not significantly different, but both were under the threshold measurement for the diagnosis of MDD. At the conclusion of the six-month follow-up period, the mean HDRS in the control group had dropped to 5.9, while the mean HDRS in the BLT group remained close to the last measured value at 8.5. This difference was significant with a $P = 0.03$.

### SECONDARY OUTCOME MEASURES

**Geriatric Depression Rating Scale:** There were decreases in both groups without significant difference between the two groups.

**Subjective quality of sleep (measured with the Scales for Outcomes in Parkinson's Disease — Sleep):** After correcting for confounders at the end of the three-month study period, scores improved in both groups but improved more significantly in the BLT arm ($P < 0.05$). This difference was no longer significant at the conclusion of the six-month follow-up period.

**Circadian rhythm markers:** Measurements reflected estimates of total cortisol secretion and of cortisol level on awakening. Cortisol has a complex relationship to sleep and depression; in general, sleep disruption is associated with elevated levels of cortisol, as are some forms of depression.[5] Estimated total cortisol levels decreased in the intervention arm and increased in the control arm during the study period, with the BLT group having a significant decrease at the end of the intervention period ($P = 0.04$). This difference was no longer significant at the end of the six-month follow-up period, with both arms showing an increase in cortisol levels from baseline. Adverse effects were mild and occurred less in the control group than the intervention group. These included mild nausea, dizziness, and transient photophobia.

## ■ COMMENTARY

This Rutten et al randomized controlled trial not only provides Class I evidence that BLT is not more effective than control light in treatment of depression associated with PD, but also gives rise to other thought-provoking results.

It is interesting to consider the results in a different "light." Although there was no significant difference, results from both the control and BLT arms showed a reduction in mean HDRS values to non-depressed levels at the end of the three-month intervention period. While the low light intensity of the control group (200 lux) is thought to be too low to impact circadian rhythm, it certainly is possible that the use of the light box itself was helpful in addressing symptoms of depression. Rutten et al note that proper use of the box required a participant to structure their day, and that the schedule imposed at least an outline of a daily routine. A regular sleep and wake time can be helpful in re-establishing circadian rhythms and is an established adjunct tool for treating depression. The group recommends that future work incorporate a control arm without a scheduled time for the light box as well as another arm with scheduled sleep and wake times without use of the box. Such a study will help distinguish the actual active intervention.

It is useful to note that the improvement in HDRS scales occurred in both arms, but the sleep quality measures were significantly improved in the BLT arm only. It makes sense that this improvement in sleep is linked with the decrease in cortisol levels seen in the BLT arm as well. However, it does give rise to question how the control arm patients noted a decrease in depressive symptoms without an improvement in sleep and if depressive disorder linked to PD is unique in this regard. Again, this clearly is an area for future investigation.

Finally, it is notable that at the six-month follow-up point, the HDRS scores in the control group were significantly lower than the comparable scores for the intervention group. As there was no control in place regarding treatment during the six-month period, it is difficult to know how to interpret this finding. Again, future studies with long-term follow-up and active intervention during a longer period could be very useful. It is important to keep in mind that the mean HDRS of patients in both

groups at baseline indicated a mild to moderate severity of depression. Therefore, findings from this study cannot be generalized to those with more severe depressive disorder. Given that this is a Norwegian study, it is worth considering that geographic factors (long winters with short daylight hours) affected results. Replication of this work in diverse locations and latitudes will help clarify this possibility.

Obtaining a light box may be a challenge for some patients. Guidelines can be found online, and many online vendors have a range of devices with prices well under the $100 mark.[7] There may be some insurances that will reimburse for the boxes with a prescription indicating that 10,000 lux is to be used up to 40 minutes daily.

What is the take-home message from this study? It appears that in patients with PD who have mild to moderate MDD, use of any intensity light in the morning and evening may be associated with lowering depressive symptom intensity. Additionally, use of BLT at 10,000 lux for 30 minutes, twice daily may have the added advantage of improving subjective quality of sleep. With a relatively low cost and few adverse effects, the risk of recommending such a treatment is quite low and seems well worth the potential benefit. The results remind providers to be attentive to the role that depression and insomnia play in functional impairment in PD, and to consider the potential for functional improvement by addressing the symptoms of these states. ■


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SHORT REPORT

# Vegetarians and Stroke


***By Eric Neilson, MD***

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



SYNOPSIS: A prospective cohort study in the United Kingdom demonstrated that vegetarians have a 22% lower incidence of ischemic heart disease, but a 20% increased incidence of total stroke, mostly related to hemorrhagic stroke, when compared to meat eaters. No difference in ischemic stroke or acute myocardial infarction was found.


SOURCE: Tong TYN, Appleby PN, Bradbury KE, et al. Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: Results from the prospective EPIC-Oxford study. *BMJ* 2019;366:l4897.

Published dietary recommendations often are confusing, controversial, or contradictory. This is especially true for vegetarian diets and red meat consumption, wherein current recommendations vary widely. The *Annals of Internal Medicine* recently published, with low-certainty evidence, a weak recommendation for adults to continue current processed and unprocessed red meat consumption.[1] The World Health Organization's International Agency for Research on Cancer lists processed meat in the Group 1, carcinogenic to humans, classification.[2] American College of Cardiology (ACC)/American Heart Association (AHA) guidelines strongly recommend (Class I, Level A evidence) a diet high in vegetables, fruits, and whole grains, including low-fat dairy, poultry, and fish, with limited red meat.[3] Providing patients with clear, unambiguous dietary advice seems to be an impossible mission. Tong et al in *BMJ* offer evidence that further complicates this conversation. These authors followed nearly 50,000 vegetarians, red meat eaters, and pescatarians over the course of 18 years to monitor stroke and ischemic heart disease outcomes.

Using proportional hazards regression models for associations between diet groups, results indicated that compared to a diet inclusive of red meat, a pescatarian or vegetarian diet is associated with a decreased risk of ischemic heart disease. However, when compared to a diet including red meat, a vegetarian diet is associated with

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increased risk of total and hemorrhagic stroke. This risk reduction translates to four and 10 fewer incidents of ischemic heart disease per 1,000 persons over 10 years for pescatarians and vegetarians, respectively, compared to red meat eaters (predicted incidents per 1,000 population: 40.4 pescatarians and 36.2 vegetarians vs. 46.2 meat eaters; 95% confidence interval [CI] and *P* heterogeneity value < 0.001). Vegetarians had three more cases of total stoke per 1,000 persons over 10 years compared to red meat eaters (18.3 vs. 15.4; 95% CI and *P* heterogeneity value = 0.04). Data indicated that there was no statistically significant increase in stroke incidence for pescatarians. Continued research on larger and more diverse groups of participants and considerations of the effects of specific nutrients associated with variations in diet (e.g., cholesterol, fatty acids, vitamin B12), are critical to determine the underlying mechanisms for the results found in this study. This nutritional study also is complicated by self-reporting, exclusion of high calorie intake, and changes in diet over time, which must be a component in future research. The study supports general ACC/AHA guidelines and indicates the need for physicians to have discussions with patients regarding the risks and benefits of individual dietary considerations. ■

## REFERENCES

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## CME QUESTIONS

1. **A vegetarian diet as compared to a diet inclusive of red meat increases risk for which of the following?**
   a. Ischemic stroke
   b. Acute myocardial infarction
   c. Ischemic heart disease
   d. Hemorrhagic stroke
2. **Bright light therapy (BLT) may be helpful in Parkinson's disease in the treatment of:**
   a. Depression: Although it does not appear more useful than lower intensity light therapy, in this study both the intervention and control groups were associated with lower scores on the Hamilton Depression Rating Scale.
   b. Sleep quality: Although it does not appear more useful than lower intensity light therapy, in this study both the intervention and control groups were associated with better subjective sleep quality.
   c. Movement: Although it does not appear more useful than lower light therapy, in this study both the intervention and control groups were associated with increased mobility and flexibility.
   d. Speech: Although it does not appear more useful than lower light therapy, in this study both the intervention and control groups were associated with better articulation and expressive speech.
3. **The relationship between hormonal therapy and Alzheimer's disease (AD) that appears most consistent across studies is that:**
   a. a short duration of therapy (< 3 years) provides the maximum protection against development of AD.
   b. a long duration of therapy (> 10 years) provides the maximum protection against development of AD.
   c. a short duration of therapy (< 3 years) increases the risk of development of AD.
   d. a long duration of therapy (> 10 years) increases the risk of development of AD.

## [IN FUTURE ISSUES]

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