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ABSTRACT & COMMENTARY

Giving the Cold Shoulder to Drug Therapy for Atrial Fibrillation

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SYNOPSIS: In two randomized trials published simultaneously, cryoballoon ablation proved superior to drug therapy for prevention of arrhythmia recurrence in patients with paroxysmal atrial fibrillation.

SOURCES: Wazni OM, Dandamudi G, Sood N, et al. Cryoballoon ablation as initial therapy for atrial fibrillation. *N Engl J Med* 2020; Nov 16. doi: 10.1056/NEJMoa2029554. [Online ahead of print].

Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med* 2020; Nov 16. doi: 10.1056/NEJMoa2029980. [Online ahead of print].

Mounting evidence suggests there are better outcomes with a rhythm control strategy than a rate control strategy for many patients with atrial fibrillation (AF). An important question remains: Once selected, should clinicians attempt the rhythm control strategy first with antiarrhythmic drug (AAD) therapy, or with catheter ablation? Guidelines recommended ablation after a failed trial of at least one AAD, while gradually accepting there are circumstances in which starting with ablation might be preferred.

In STOP-AF (Wazni et al) and EARLY-AF (Andrade et al), investigators sought to compare cryoballoon ablation to AAD therapy as first-line treatment for paroxysmal AF. Wazni et al randomized 203 patients 1:1 to cryoablation or AAD (class I or III agent). Mean age was 61 years, mean ejection fraction (EF) was 61%, and mean left atrial (LA) diameter was 39 mm. Most patients recorded a CHA_2DS_2-VASc score of 1 or 2, and 27% had undergone electrical or pharmacologic cardioversion in the prior 12 months. In the ablation group, 101 of 104 patients underwent a "successful" procedure. In the AAD group, about half were treated with flecainide (100 mg to 200 mg daily), and 12 of 99 crossed over to ablation before a documented arrhythmia recurrence. The primary endpoint was freedom from atrial arrhythmia recurrence after a 90-day blanking period. Patients were monitored via ECG every

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three months, via patient-activated phone monitoring for symptoms weekly, and via 24-hour ambulatory monitoring at six and 12 months.

Andrade et al randomized 303 patients 1:1 to cryoablation or AAD. Patient profiles were similar to those in STOP-AF: mean age was 58 years, mean EF was 60%, and mean LA diameter was 39 mm. The mean CHA_2DS_2-VASc score was 1.9, and 39% had undergone prior cardioversion. In the ablation group, complete pulmonary vein isolation was confirmed in 152 of 154 patients (two patients did not undergo the procedure). In the AAD group, a prespecified protocol was used to up-titrate medications to the maximum dose associated with an "acceptable" side effect profile. Most were treated with flecainide (median dose of 200 mg daily). No patients crossed over to ablation before the occurrence of a primary endpoint event. The primary endpoint was freedom from atrial arrhythmia recurrence after a 90-day blanking period. Notably, all patients received a LINQ implantable loop recorder (ILR) for continuous cardiac monitoring, inserted no more than 24 hours after catheter ablation or initiation of AAD.

Although patient populations and treatment strategies were similar, EARLY-AF was designed with more sensitive arrhythmia monitoring via ILR. Andrade et al also used a more regimented protocol for drug titration. Flecainide was most commonly used in both trials, although at somewhat lower doses in STOP-AF.

The results of both trials also were similar. In STOP-AF, freedom from procedural failure or recurrent arrhythmia at 12 months was 75% in the ablation group and 45% in the AAD group ($P < 0.001$). There were two pericardial effusions, two phrenic nerve injuries, and a transient ischemic attack in the ablation group. Adverse events in the AAD group included four episodes of syncope in three patients, bradycardia in two patients, and a variety of drug side effects. Quality of life in the ablation group as assessed with two different measures improved significantly from baseline to 12 months. Scores were not reported for patients in the AAD group.

In EARLY-AF, freedom from recurrent arrhythmia at 12 months was 57% in the ablation group and 32% in the AAD group ($P < 0.001$). Symptomatic recurrence was documented in 11% of the ablation group and 26% of the AAD group. Overall arrhythmia burden was low. Median time in AF was 0% in the ablation group vs. 0.13% in the AAD group. There were two patients who required a pacemaker, one episode of syncope, and three persistent phrenic nerve palsies in the ablation group. Adverse events in the AAD group included one episode of tamponade (in a patient who underwent ablation after arrhythmia recurrence), two episodes of syncope and five episodes of presyncope, two wide complex tachycardia or proarrhythmic events, two patients who required a pacemaker, and one TIA event. Quality of life scores improved significantly in both groups.

The authors of both studies concluded that in patients with paroxysmal AF, cryoablation was superior to AAD therapy for preventing recurrent AF.

■ COMMENTARY

To cardiologists and electrophysiologists treating paroxysmal AF, the top line results of these two trials come as little surprise: Ablation is superior to AAD therapy in preventing recurrence of atrial arrhythmias. However, there are several additional important findings, with a few caveats to remember.

First, the benefit of intensive arrhythmia monitoring for accurate reporting in AF trials is demonstrated in EARLY-AF. There were higher overall rates of documented arrhythmia recurrence compared with STOP-AF, but with outcomes that were similarly superior for catheter ablation. In other words, more sensitive monitoring detected more asymptomatic episodes but did not "falsely" improve outcomes in one arm over the other.

The restricted crossover in EARLY-AF also was notable and helps increase confidence in the results. Patients with paroxysmal AF clearly experience asymptomatic arrhythmia episodes despite ablation and/or AAD therapy, affirming the need for continuous anticoagulation when risk factors are present. On the other hand, these trial authors used cryoballoon ablation. Although similar outcomes might

be expected with radiofrequency ablation (preferred by many operators), this was not part of either trial. Procedural complications were infrequent but not absent, particularly phrenic nerve palsy, an injury that often heals with time but can be associated with uncomfortable shortness of breath. The trials likely were underpowered and follow-up too brief to detect differences in "hard" outcomes, such as stroke or death. Critics also point to the lack of a "true control" observation (and presumably risk factor modification). Nevertheless, for many patients who feel unwell with AF, in whom AF is likely to progress, and for whom recent data support earlier rhythm control to improve cardiovascular outcomes, ablation by an experienced operator after thorough discussion of risks is a reasonable first-line strategy. ■

ABSTRACT & COMMENTARY

Dairy, Bone Health, and Menopause

By Ghazaleh Barghgir, MD, and Nancy Selfridge, MD

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SYNOPSIS: An analysis of data from the Study of Women's Health Across the Nation cohort did not reveal a significant association between daily dairy intake frequency, femoral and spine bone mineral density loss, and non-traumatic fracture risk among women transitioning to menopause.

SOURCE: Wallace TC, Jun S, Zou P, et al. Dairy intake is not associated with improvements in bone mineral density or risk of fractures across the menopause transition: Data from the Study of Women's Health Across the Nation. *Menopause* 2020;27:879-886.

Osteoporosis is a disease characterized by an increase in osteoclastic bone resorption not balanced by osteoblastic bone formation, resulting in low bone mass and an increased risk of fractures. Osteoporosis often is diagnosed via dual-energy X-ray absorptiometry (DEXA) scans and defined as a bone mineral density (BMD) 2.5 standard deviations or more below the norm for healthy young women (T score of less than -2.5 standard deviations). Osteoporosis has been estimated to affect 53.6 million people, representing approximately 54% of U.S. adults age 50 years and older.[1]

Osteoporosis is more prevalent in postmenopausal women and in the United States (25% to 30% of global prevalence).[2] In 2010-2011, there were 131,443 osteoporosis-attributable fractures, resulting in 64,884 acute care admissions and 983,074 acute hospital days. Acute care costs were $1.5 billion, an 18% increase since 2008.[3] Risk factors associated with osteoporosis include age, female sex, ethnicity, family history of osteoporosis, smoking, vitamin D or calcium deficiency, high caffeine intake, immobilization, late menarche, early menopause, and being underweight.[4] Bone loss accelerates during menopause; thus, prevention tactics aimed at age-related bone loss are important potential interventions.

One potential modifiable risk factor is dietary dairy product intake, since these foods are rich in nutrients (calcium, magnesium, phosphorus, vitamin D, zinc, and protein) beneficial for bone health maintenance.[5,6] Currently, the 2015-2020 Dietary Guidelines for Americans (DGA) recommend adults consume three servings/day of fat-free or low-fat dairy, with one serving equivalent to one cup of milk (e.g., one cup of low-fat yogurt or half an ounce of hard cheese).[7] No long-term clinical data exist regarding the relationship between bone health and dairy intake for women transitioning into menopause. Wallace et al aimed to help fill this gap by examining dairy intake and bone health outcomes using publicly available data from the Study of Women's Health Across the Nation (SWAN).

SWAN data collection began in 1996 for 3,302 pre- and perimenopausal women age 42 to 53 years. Criteria for inclusion were having an intact uterus and at least one ovary and no hormone usage within the three months before screening. Five clinical sites in the United States included Oakland, CA; Los Angeles, Boston, Detroit, and Pittsburgh. Enrolled participants were followed annually to gather information on their demographics, clinical data, and anthropomorphic data. There were 2,335 women with complete baseline femoral neck and/or lumbar spine BMD data. Of these, women with osteoporosis; diabetes; unknown menopausal status; and missing information on dairy intake, physical activity, and smoking status were eliminated. Ultimately, 1,955 participants were included in this BMD and fracture analysis. Loss of femoral neck bone density mass over 10 years was calculated using the following formula: ([BMD at visit 10 - BMD at baseline] / BMD at baseline) × 100.

Menopausal status was determined on annual questionnaires and characterized as premenopause (menstrual bleeding within the past three months and no change in bleeding pattern over the last year), early perimenopause (bleeding in the past three months with decreased menstrual regularity over the past year), late perimenopause (no bleeding for the past three to 11 months), and postmenopause (no bleeding in the past 12 months).

Participants missing data on their femoral neck bone density measurement at baseline (n = 7) and for visit 10 (n = 587) and those missing a final menstrual period date (n = 252) were excluded from the analysis, leaving 1,109 women with adequate data for the study cohort analysis.

BMD of the femoral neck and spine was assessed at each annual follow-up visit using DEXA scanning. The occurrence of fractures was entirely self-reported for visits 1-7 but confirmed at visits 7-10 by a review of medical records and radiology reports. The investigators excluded face, toe, and digit fractures not typically seen in osteoporosis and fractures caused by significant trauma (fall from a height > 6 inches, motor vehicle accident, sports activity-related falls, and fractures when struck by a heavy object).

A modified block food frequency questionnaire assessing the average intake of 137 food items was administered at baseline, visit 5, and visit 9 to collect data on eating habits and dairy product consumption. In the analysis, the average number of dairy servings were used, and any missing dietary data in the questionnaires were imputed using the last observation carried forward method. Study subjects then were classified into four groups based on their cumulative average daily dairy intake: < 0.5 servings, 0.5-1.5 servings, 1.5-2.5 servings, and ≥ 2.5 servings. Linear trend estimations were used for participants in each dairy-intake group to assess differences in continuous variables, such as weight, body mass index (BMI), age, and BMD. Chi-square tests were similarly applied to the groups to analyze difference in categorical variables. The statistical significance was set at $P < 0.01$.

The association of dairy intake with 10-year BMD loss rate was analyzed using a general linear model. A Cox proportional hazard model was applied to calculate hazard ratios (HR) for non-traumatic fractures with 95% confidence intervals. Because of the small number of fractures reported in the cohort, HRs between only the < 1.5 dairy serving per day and ≥ 1.5 dairy serving per day groups were used. The authors used several different models in the analysis, adjusting for a variety of variables. The fully adjusted models controlled for race, baseline height, age, activity level, smoking status, time-varying weight, menopausal status, alcohol use, calcium supplementation, and caloric intake.

The final analysis yielded some noteworthy associations. Women consuming more dairy at baseline also were more likely to be premenopausal, heavier, taller, nonsmokers, alcohol consumers, and somewhat more physically active. Compared to Chinese, African-American, and Japanese participants, non-Hispanic white individuals were more likely to consume a higher daily intake of dairy. There were no significant differences between the dairy intake groups at baseline for age, BMI, bone density measurements of femoral neck and lumbar spine, use of calcium supplements, or history of fractures.

Despite adjustment for potential confounding variables and sensitivity analysis, the authors did not find significant differences in changes in BMD among the four dairy intake groups. The authors did not observe differences in HRs and relative risks for non-traumatic fractures based on daily dairy intake group in fully adjusted models.

■ COMMENTARY

This analysis contributes to the current body of knowledge concerning dairy food intake associations with bone density and fracture risk or prevention. A significant strength of this study was the SWAN cohort data collection was designed to assess changes in BMD and occurrence of fractures and also included data for many potential confounding variables that strengthened the ultimate data analyses. A major weakness of the study was the fact the cohort did not include any Hispanic women.

A significant factor to consider while interpreting results of this study is that dairy intake was low overall among SWAN participants, with 65% of participants consuming < 1.5 servings per day (well below the three servings/day recommended in the DGA) and was notably lower for ethnic groups other than non-Hispanic whites. In fact, only 7% of the SWAN cohort met the DGA dairy intake recommendations. This low overall dairy consumption in the cohort may have been insufficient to affect BMD loss and fracture outcomes. Further, the study did not explore associations according to different types of dairy food consumption (e.g., yogurt vs. cheese vs. milk), only focusing on a derived composite of total dairy intake. This is noteworthy given the varying nutritional content and inflammatory potential in different dairy products.[8] Potential bias in data collection would be present in all self-reported data, including food and supplement intake and fracture occurrence before visit 5. Although the investigators adjusted all analyses for confounding variables, residual confounding remains a source of potential bias.

Although the authors found no association between higher dairy intake and reduced risk of bone mineral loss and fracture occurrence in perimenopausal women, physicians can and should continue to recommend adequate dietary calcium intake, which can be

accomplished through consumption of green leafy vegetables (spinach, collard greens, and kale), canned fish with bones (salmon, sardines), tofu, edamame, beans, lentils, and, only if their patients can tolerate them, dairy products (milk, fortified soy milk, etc.). Additional high-quality research is needed, assessing larger cohorts with higher daily dairy intake, accounting for early life nutritional and dairy intake adequacy, differentiating types of dairy products consumed (fermented vs. non-fermented), including data on exercise volume/type, and extending investigation into the post-menopausal period to determine the best evidence-based recommendations for optimizing bone density before menopause, preserving bone density, and reducing fracture risk thereafter. ■

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ABSTRACT & COMMENTARY

Vitamin D and COVID-19

By Philip R. Fischer, MD, DTM&H

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SYNOPSIS: Low levels of vitamin D are associated with in-hospital mortality in patients with COVID-19, but causality is unknown.

SOURCE: Angelidi AM, Belanger MJ, Lorinsky MK, et al. Vitamin D status is associated with in-hospital mortality and mechanical ventilation: A cohort of COVID-19 hospitalized patients. *Mayo Clin Proc* 2021;96:875-886.

Vitamin D features immunomodulatory properties and produces anti-inflammatory activity. In fact, vitamin D deficiency has been associated with both an elevated risk of acute respiratory infection and worse clinical outcomes following critical illnesses. Vitamin D deficiency is associated with problems, such as obesity, older age, and cardiac disease, that are risk factors for bad outcomes with COVID-19. Investigators have wondered if vitamin D deficiency (and potential treatment) might influence the clinical course of COVID-19.

Angelidi et al performed a retrospective study of adults who were hospitalized at one of two hospitals (one in Boston and one in New York) with COVID-19 from February to mid-May 2020. They reviewed records and compared patient data to 25-hydroxyvitamin D levels determined either at the time of hospital admission or within the preceding six months.

A total of 144 patients were included in the study: 79 with vitamin D levels of less than 30 ng/mL and 65 with levels of 30 ng/mL or higher. The median age was 66 years. Overall, 44% of subjects were male, and 42% were non-Hispanic Blacks. The median body mass index was 29 kg/m^2. More than 90% of included individuals presented with at least one significant medical comorbidity; hypertension (74%), hyperlipidemia (55%), and diabetes (44%) were especially common. Cough, dyspnea, fever, and/or malaise were presenting symptoms in most patients. Steroids were used in the management of 24% of patients, antivirals were used in 10%, an antibiotic (usually azithromycin) was used in 72%, and hydroxychloroquine was used in 44%. Treatment included oxygen in 64% of patients and mechanical ventilation in 27%; 39% of patients required intensive care. In-hospital mortality was 18%.

Mortality was higher (25% vs. 9%) in patients with low (< 30 ng/mL) vs. higher 25-hydroxyvitamin D levels. The timing (during the six months before admission vs. during the hospitalization) of vitamin D testing was not related to mortality. Of dozens of variables, only vitamin D level, age, malignancy, and chronic obstructive pulmonary disease were

associated with an increased risk of in-hospital death with COVID-19. After conducting a careful statistical analysis, researchers found hypovitaminosis D was strongly associated with in-hospital mortality, even independent of medical comorbidities. The inverse association between vitamin D level and mortality was present whether 20 ng/mL or 30 ng/mL was used as the cut-off (i.e., whether there was vitamin D deficiency or insufficiency).

■ COMMENTARY

Angelidi et al carefully and convincingly showed low vitamin D levels are associated with mortality in patients hospitalized with COVID-19. Of course, this association does not necessarily imply causality, and it does not prove that either preventive or therapeutic vitamin D administration would alter mortality.

Low vitamin D levels have been associated with other factors that give risk for poor outcomes with COVID-19, including obesity and diabetes. However, in this analysis, low vitamin D levels were independently associated with in-hospital mortality from COVID-19. There likely is either a causal effect of hypovitaminosis on the course of COVID-19 or there are other unmeasured variables, such as outdoor activity, that link both hypovitaminosis D and death from COVID-19 without the vitamin D level directly affecting the course of COVID-19.

Hypovitaminosis D does seem causally related to other respiratory infections, even if a causal link has yet to be proven for COVID-19. Low vitamin D levels are seen more commonly in patients with acute respiratory infection than in healthy controls, and vitamin D does affect immune functioning.[1] However, studies of vitamin D supplementation to prevent respiratory infections have yielded mixed results.[1] A new meta-analysis of studies of vitamin D as prevention for acute respiratory infection in children age 1 to 15 years showed a significant (P = 0.018) but modest (odds ratio, 0.92, with 95% confidence interval, 0.86-0.99) effect when supplements of 400 IU/day to 1,000 IU/day were administered for up to 12 months.[1]

It is important to consider the timing of effects of intervention. Whether vitamin D provides protection against acquiring SARS-CoV-2 or other respiratory pathogens, different mechanisms of action could be necessary for vitamin D to be effective therapeutically. Griffin et al recently summarized the various stages of COVID-19 and eloquently reviewed potential effects of various interventions at different times before, during, and after the actual infection.[2]

A recent placebo-controlled study of high-dose vitamin D as treatment of established COVID-19 infection included 236 hospitalized adults in multiple centers in Brazil (mean age 56 years, mean 25-hydroxyvitamin D level 21 ng/mL at entry into the study, with 20 ng/mL considered the upper limit of "deficiency").[3] Vitamin D levels increased significantly with treatment, and no significant adverse events were noted.[3] However, hospital length of stay, need for intensive care, need for mechanical ventilation, and mortality were not altered by vitamin D treatment.[3]

Thus, these new data remind us hypovitaminosis D is at least associated with respiratory infections, but that preventive supplementation only modestly reduces the risk of acquiring infection (in children for non-COVID-19 infection), and therapeutic administration of vitamin D does not alter the course of disease in adults hospitalized with COVID-19. Vitamin D generally is safe in the preventive and therapeutic doses used, but further convincing data will be required before vitamin D is recommended to either prevent or treat COVID-19.

Two years ago, Hu et al reported patients with chronic hepatitis B recorded lower vitamin D levels than healthy controls. Among hepatitis B patients, viral loads were inversely correlated with vitamin D level.[4] Vitamin D also has been proposed for the prevention and treatment of a variety of other conditions, including diabetes, multiple sclerosis, and cognitive decline. Observational studies are supportive, but systematic reviews and randomized, controlled trials are lacking.[5] Although it seems reasonable to supplement individuals with or at risk of hypovitaminosis D to maintain a "normal" vitamin D level, definitive studies do not yet support widespread recommendations to use vitamin D specifically to prevent or treat other conditions.[5,6] ■

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PHARMACOLOGY UPDATE

Drospirenone and Estetrol Tablets (Nextstellis)

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

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The FDA has approved the first combination oral contraceptive containing a naturally occurring estrogen. Estetrol (E4) is produced during human pregnancy and is synthesized from plant-derived estrone for clinical use. E4 is selective for nuclear estrogen receptor alpha and beta, with greater affinity for the receptor alpha.[1,2] It is categorized as a native estrogen, with selective action in tissues (NEST). E4 is combined with a commonly used progestin, drospirenone (DRSP), with antimineralocorticoid and antiandrogen properties. This combination is manufactured in Germany and distributed as Nextstellis.

INDICATIONS

E4/DRSP can be prescribed to women of reproductive potential to prevent pregnancy.[1]

DOSAGE

The recommended dose is one tablet taken orally at the same time every day.[1] The E4/DRSP pill pack contains 24 active pink pills (E4 14.2 mg and DRSP 3 mg), followed by four "inactive" white inert pills.

POTENTIAL ADVANTAGES

E4 may produce a limited effect on various endocrine and metabolic parameters (e.g., gonadotropins, cortisol, angiotensinogen, cortisol-binding globulin, sex hormone-binding globulin, lipid profile, and carbohydrate parameters) compared to ethinyl estradiol (EE).[3] The lower hepatic and vascular estrogenicity compared to EE/DRSP may lower the risk of venous thromboembolic events.[4] E4 has 1/100 the stimulation on breast proliferation compared to natural estrogen and actually antagonizes estradiol-dependent mammary gland proliferation.[2]

POTENTIAL DISADVANTAGES

A body mass index (BMI) ≥ 30 kg/m^2 may make the drug less effective.[1]

COMMENTS

E4/DRSP showed comparable complete ovulation inhibition compared to EE/DRSP.[5] This was based on an assessment of follicular development and double-layer endometrial thickness. The efficacy of E4/DRSP was evaluated in a prospective, open-label, single-arm, one-year study that included 1,674 women age 16 to 35 years.[1] There were 26 on-treatment pregnancies (1,524 women and 12,763 at-risk cycles).

The overall Pearl Index was 2.65 pregnancies per 100 women-years of use. The Pearl Index was higher in those with BMI ≥ 30 kg/m^2 to < 35 kg/m^2 (2.94; 95% CI, 1.08-6.41) compared to those < 30 kg/m^2 (2.57; 95% CI, 1.57-3.97).

CLINICAL IMPLICATIONS

E4/DRSP is the first E4 containing combined oral contraceptive (COC) to be approved. While some evidence may suggest a more favorable and attractive safety profile for E4 compared to the commonly used EE, this needs to be confirmed with clinical evidence. The FDA labeling still carries the same box warning and precaution as other COCs.

There are no clinical comparisons to the corresponding EE equivalent (i.e., EE/DRSP) in terms of cycle control or safety profile, but that combination has a Pearl Index of 1.41 and no limitation based on BMI.[6] Still, some women may prefer a "natural" estrogen product and the potential of less endocrine and metabolic side effects. The cost for a 28-day cycle is $190, which is more than 10 times the cost for a typical generic EE/DRSP. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. In two recent studies of patients with paroxysmal atrial fibrillation comparing cryoablation to antiarrhythmic drug therapy, which serious adverse effect was most common with cryoablation?
a. Phrenic nerve injury
b. Pericardial tamponade
c. Stroke/transient ischemic attack
d. Pacemaker requirement

2. Based on the results of the analysis by Wallace et al, which statement about the effect of daily dairy consumption on non-traumatic fractures and bone mineral density (BMD) in perimenopausal women is correct?
a. No significant difference was found between any of the four dairy intake groups (between < 0.5 servings to ≥ 2.5 servings per day) for either non-traumatic fractures or BMD.
b. Perimenopausal women consuming more than ≥ 2.5 servings per day recorded a significantly lower hazard ratio and risk ratio for non-traumatic fractures and change in BMD.
c. The risk reduction for non-traumatic fractures was significant only in the ≥ 2.5 servings per day dairy intake group.
d. BMD was preserved in the > 2.5 servings per day dairy intake group, although fracture risk was not affected.

3. Vitamin D administration has proven effective at:
a. preventing respiratory infections in children.
b. treating COVID-19 in adults.
c. treating chronic hepatitis B.
d. preventing multiple sclerosis.

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]

Overdiagnosis of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents

Antibiotic Therapy: How Long Is Long Enough?

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