This is a corrected version of the department that appeared in print.

POEMs

Patient-Oriented Evidence That Matters

Vitamin D Is Equal to Placebo for Preventing Cognitive Decline in African American Women with Low Vitamin D Levels

Clinical Question

Is vitamin D more effective than placebo in preventing cognitive decline in African American women older than 65 years who have low serum vitamin D levels at baseline?

Bottom Line

No. (Level of Evidence = 2b)

Synopsis

The authors recruited African American women from various community settings. During a preenrollment telephone interview, women were asked not to take vitamin D–containing supplements for four to six weeks before the study. The researchers then measured their plasma vitamin D levels and included those women with levels between 8 ng per mL (20 nmol per L) and 26 ng per mL (65 nmol per L). They excluded women with hip osteoporosis, Mini-Mental State Examination (MMSE) scores of less than 21, moderate to severe vertebral fractures, liver disease, or kidney stones. The researchers randomly assigned half of the women to receive daily vitamin D_3 (i.e., 2,400 IU, 3,600 IU, or 4,800 IU; n = 130) and the other half to receive matching placebo (n = 130). They used the baseline vitamin D level to determine the initial dose, then titrated the dose every three months to achieve a target level of 30 ng per mL (75 nmol per L). They also gave women in each group 1,200 mg of calcium daily. The researchers assessed the MMSE score every six months for three years and used a score of less than 27 as the cutoff for mild cognitive impairment. Seventy-four women dropped out of the study, which raises serious concerns about trusting the final results. Among the women who completed the study, the MMSE scores increased in both groups, and the degree of improvement was comparable. The authors report no vitamin D–related adverse events. The authors do not provide sample size or power estimates for the study. They properly recognize the limitations of the MMSE in detecting cognitive decline.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Population-based

Reference: *Owusu JE, Islam S, Katumuluwa SS, et al. Cognition and vitamin D in older African-American women–physical performance and osteoporosis prevention with vitamin D in older African Americans trial and dementia.* J Am Geriatr Soc. *2019;67(1):81-86.*

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In Healthy Older Adults, Low-Dose Aspirin Increases All-Cause and Cancer-Specific Mortality

Clinical Question

Does low-dose aspirin reduce all-cause mortality in generally healthy older adults?

Bottom Line

The findings are completely unexpected. Although recent studies by this group and other groups of researchers have failed to find a cardiovascular benefit, likely because of better control of other cardiovascular risk factors, this study found increased all-cause mortality, primarily due to increased cancer-related mortality. Other studies, such as the individual patient meta-analysis by Rothwell and colleagues (*Lancet.* 2011;377(9759):31-41), found the opposite. A Bayesian thinker would urge caution in interpreting these results, considering the existing body of research concluding the opposite regarding cancer-specific mortality. (Level of Evidence = 1b)

Synopsis

This is one of three reports of the same study in the same issue of the *New England Journal of Medicine*; this one focuses on all-cause mortality. The Aspirin in Reducing Events in the Elderly trial randomized 19,114 community-dwelling adults to receive 100 mg of enteric-coated aspirin or placebo. The study was conducted in the United States

and Australia, with patients recruited between 2010 and 2014. Participants were 70 years or older (65 years or older if black or Hispanic in the United States, because of their shorter average lifespan), had no serious comorbidity that would be expected to limit their life expectancy to less than five years, and no known cardiovascular or cerebrovascular disease, dementia, high bleeding risk, or contraindication to aspirin. The study included a one-month placebo run-in period to ensure at least 80% adherence to the study medication. During the run-in period, 4,049 patients were excluded, 61% because of failed adherence. Included patients were contacted every three months to further encourage adherence and to gather interim data. Outcomes were adjudicated by a committee masked to treatment assignment. The median age of participants was 74 years, 56% were women, and 8.7% were nonwhite. Most of the patients were recruited in Australia (87%), 74% had hypertension, 65% had hyperlipidemia, and only 11% had diabetes mellitus. Participants were followed up for a median of 4.8 years, and only 2.2% withdrew or were lost to follow-up. All-cause mortality was higher in the aspirin group (5.9% vs. 5.2%; hazard ratio [HR] = 1.14; 95% CI, 1.01 to 1.29; number needed to harm [NNH] = 143 over 4.8 years). The likelihood of cancer death was also higher in the aspirin group, with the increased risk beginning after approximately three years of aspirin use (3.1% vs. 2.3%; HR = 1.31; CI, 1.10 to 1.56; NNH = 125 over 4.8 years).

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Population-based

Reference: *McNeil JJ, Nelson MR, Woods RL, et al.; ASPREE Investigator Group. Effect of aspirin on all-cause mortality in the healthy elderly.* N Engl J Med. *2018;379(16):1519-1528.*

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Misoprostol Alone Is Associated with a High Rate of Successful First-Trimester Abortion

Clinical Question

Is misoprostol (Cytotec) alone associated with a high rate of success when used for first-trimester abortion of a viable pregnancy?

Bottom Line

Misoprostol alone was associated with a nearly 80% success rate in the first trimester of pregnancy on meta-analysis. The best associations were with 800-mcg dosing, three or more doses, non-oral route of administration, moistening of tablets before vaginal insertion, and a delay of three to seven days after completion of the misoprostol regimen before the decision to surgically evacuate. The safety of misoprostol alone was demonstrated by a rate of hospitalization and/or transfusion of less than 1%. (Level of Evidence = 2a)

Synopsis

This is an updated meta-analysis of misoprostol alone for abortion in the first trimester of pregnancy. Selected studies included women with viable pregnancies of variable gestational age limit, ranging from 42 to 98 days, nearly universally determined by ultrasonography. The meta-analysis included 42 studies with 53 study groups and 13,573 women. A total of 12,829 women were included in the analysis after the exclusion of 744 who were lost before outcomes were known (5%). There were multiple regimens, with dosing from 200 mcg to 800 mcg. The most common dose was 800 mcg (n = 40 groups, 92% of women); the most common route of administration was vaginal (n = 38 groups, 81% of women). Most women were instructed to take no more than three doses within 48 hours. After one or more required doses, women in 35 groups (38% of women) could use additional doses, up to a maximum of six doses over 14 days. Across all studies, the meta-analytic estimate of the rate of women who underwent subsequent surgical evacuation was 22.0% (95% CI, 18.8% to 25.5%). The authors analyzed heterogeneity across studies and identified several factors associated with higher risk of surgical evacuation. They demonstrated a linear trend ($P < .001$) with the 800-mcg dosing being approximately one-fourth the risk of the 200-mcg dosing. Oral administration was associated with a threefold higher risk compared with vaginal, buccal, or sublingual administration. Surgery was less common when tablets were moistened before vaginal insertion (odds ratio = 0.46; 0.35 to 0.60). Surgery also declined with allowed number of doses, duration of dosing (linear trend $P \leq .01$ in each case). It was also less frequent when the decision to perform surgery was delayed three to seven days after treatment (odds ratio = 0.55; 0.31 to 0.96). Safety was demonstrated by the rare need for hospitalization (n = 14 women) or transfusion (n = 12). The meta-analytic estimate for either was 0.7% (0.4% to 1.0%). No women died.

Study design: Meta-analysis (other)

Funding source: Government

Allocation: Concealed

Setting: Various (meta-analysis)

Reference: *Raymond EG, Harrison MS, Weaver MA. Efficacy of misoprostol alone for first-trimester medical abortion: a systematic review.* Obstet Gynecol. *2019;133(1):137-147.*

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Omega-3 Oil Does Not Reduce Serious Cardiovascular Events for Patients with Diabetes Mellitus

Clinical Question

In patients with diabetes mellitus, what is the safety and efficacy of daily supplementation with omega-3 fatty acids for the prevention of cardiovascular events?

Bottom Line

In this study, there was no significant difference in the likelihood of a composite vascular outcome or all-cause mortality in patients given an omega-3 fatty acid supplement compared with those given an olive oil placebo. Although olive oil has been associated with better cardiovascular outcome in studies of the Mediterranean diet, those studies used approximately 1 liter per week compared with only 7 grams per week in the current trial. The reduction in vascular deaths is intriguing, but the authors urge caution given multiple comparisons. (Level of Evidence = 1b)

Synopsis

This study recruited adults 40 years and older with diabetes, no known cardiovascular disease, no contraindications to aspirin, and no major comorbidity that would keep them from participating in the study for at least five years. After a placebo run-in period to assure adherence, 15,480 participants were randomized to receive omega-3 fatty acids or placebo (olive oil) in identical 1-gram capsules. This was a factorial design study with patients also randomized to receive aspirin; those results are reported separately. The groups were balanced at the start of the study. The patients had a mean age of 63 years, 63% were men, and 96% were white. Almost all (94%) had type 2 diabetes. A validated risk score determined that approximately 40% of participants were at low risk of vascular events (less than 5% at five years), 40% had a five-year risk of 5% to 10%, and the remainder were at high risk. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke (excluding hemorrhagic stroke), vascular death, or transient ischemic attack. Transient ischemic attack was added after recruitment had begun, and the length of the trial was increased after lower-than-expected rates of the composite outcome were observed. Although the authors do not specifically state that the analysis was by intention to treat, for all practical purposes it was, because 99.1% of patients had completed follow-up. After a mean of 7.4 years of follow-up, there was no difference between groups for the primary composite outcome (8.9% in the omega-3 group and 9.2% in the placebo group; hazard ratio [HR] = 0.97; 95% CI, 0.87 to 1.08). There were no differences for any of the individual components of the composite, with the exception of vascular deaths (2.4% for omega-3 vs. 2.9% for placebo; HR = 0.81; CI, 0.67 to 0.99; number needed to treat = 200 for 7.4 years). All-cause mortality did not differ significantly between the groups, although the absolute difference of 0.5% mirrored that for the subset of vascular deaths.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry and foundation

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Bowman L, Mafham M, Wallendszus K, et al.; ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus.* N Engl J Med. *2018;379(16):1540-1550.*

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Editor's Note: Dr. Ebell is Deputy Editor for Evidence-Based Medicine for *AFP* and cofounder and Editor-in-Chief of Essential Evidence Plus. ■