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Update in Geriatric Medicine: Evidence Published in 2015

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Highlights of the year in geriatric medicine were the publication of several long-awaited large clinical trials, smaller clinical trials, and observational studies that addressed preventing cognitive decline, risks and treatment of common conditions in older persons, surgical versus medical treatment of knee arthritis and lumbar spinal stenosis, risks and benefits of specific medications, and the effects of exergaming on balance and falls. In aggregate, these studies address the balance between aggressively managing risk factors and diseases versus more conservative treatment, a fundamental tension in the care of older persons.

I identified the studies by hand-searching the ACP JournalWise list of top articles in 2015 in geriatrics and reviewed the content of major general journals each week.

Preventing Cognitive Decline

Polyunsaturated Fatty Acids, Antioxidants, and Zinc Supplements Do Not Slow Cognitive Decline

Chew EY, Clemons TE, Agrón E, et al; Age-Related Eye Disease Study 2 (AREDS2) Research Group. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: the AREDS2 randomized clinical trial. *JAMA*. 2015;314:791-801. [PMID: 26305649] doi:10.1001/jama.2015.9677

Background: Observational studies suggest that diets high in omega-3 long-chain polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and antioxidants, such as lutein and zeaxanthin, may protect against cognitive decline. A large randomized clinical trial intended to assess the benefit of nutritional supplements for adults with age-related macular degeneration and cataracts provided an excellent opportunity to assess the effects of these substances on cognitive outcomes.

Findings: The 5-year randomized clinical trial assigned 3741 participants (mean age, 73 years), who were at high risk for progressing to late age-related macular degeneration, to 1 of 4 groups: 1) placebo, 2) DHA/EPA, 3) lutein/zeaxanthin, or 4) DHA/EPA and lutein/zeaxanthin. Participants were also given varying combinations of vitamins C, E, and β -carotene and zinc. Outcome measures, collected by telephone, included a summary evaluation (the Telephone Interview Cognitive Status-Modified) and tests of language and executive function, memory, processing speed, and delayed recall. Neither DHA/EPA nor lutein/zeaxanthin reduced progression of cognitive decline. The yearly change in the composite cognitive function score was -0.19 (99%

CI, -0.25 to -0.13) for participants randomly assigned to receive DHA/EPA and -0.18 (99% CI, -0.24 to -0.12) for those randomly assigned to no DHA/EPA (difference in yearly change, -0.03 [99% CI, -0.20 to 0.13]; $P = 0.63$). The yearly changes in the composite cognitive function score were -0.18 (99% CI, -0.24 to -0.11) in participants assigned to lutein/zeaxanthin and -0.19 (99% CI, -0.25 to -0.13) in those assigned to no lutein/zeaxanthin (difference in yearly change, 0.03 [99% CI, -0.14 to 0.19]; $P = 0.66$). In addition, there were no statistically significant differences between groups for patients assigned to high zinc versus low zinc or β -carotene versus no β -carotene.

Cautions: Only elderly persons who were at high risk for progression of macular degeneration were studied. Most participants (97%) were white.

Implications: Dietary supplementation with long-chain polyunsaturated fatty acids, antioxidants, zinc, or β -carotene does not prevent cognitive decline and should not be recommended for this purpose.

Moderate-Intensity Physical Activity Training Program Does Not Slow Cognitive Decline

Sink KM, Espeland MA, Castro CM, et al; LIFE Study Investigators. Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults: the LIFE randomized trial. *JAMA*. 2015;314:781-90. [PMID: 26305648] doi:10.1001/jama.2015.9617

Background: Observational studies suggest associations between greater physical activity and less cognitive decline in older persons.

Findings: The Lifestyle Interventions and Independence for Elders randomized trial, which involved 1635 participants aged 70 to 89 years who were at risk for mobility disability and had no diagnosis of dementia or significant cognitive impairment, found that a structured, moderate-intensity physical activity training program reduced risk for major mobility disability. This analysis of secondary outcomes examined change in cognitive performance from baseline to 24 months on the basis of a neuropsychological battery of tests, including the Digit Symbol Coding task subtest of the Wechsler Adult Intelligence Scale, the revised Hopkins Verbal Learning Test (12-item word list recall task), and global and executive cognitive function. At 24 months, the physical activity group and a group that received only health education did not significantly differ on any cognitive measures or incidence of mild cognitive impairment, dementia, or both combined. The mean Digit Symbol Coding task scores were 46.26 points for the physical activity group and 46.28 for the health education group (mean difference, -0.01 point [95% CI,

−0.80 to 0.77 point; $P = 0.97$). The mean delayed recall scores on the revised Hopkins Verbal Learning Test were 7.22 for the physical activity group and 7.25 for the health education group (mean difference, −0.03 word [CI, −0.29 to 0.24 word]; $P = 0.84$). Subgroup analysis indicated some benefit on executive function among participants who had poorer initial physical performance ($P = 0.01$ for interaction).

Cautions: Enrollment was limited to older adults who were at high risk for mobility disability. Control group participants attended weekly health education workshops that may have provided cognitive and social stimulation.

Implications: Despite the many reasons to encourage older persons to become more physically active, physicians should not tout prevention of cognitive decline as a definite benefit of exercise.

Multidomain Intervention Can Slow Cognitive Decline

Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385:2255-63. [PMID: 25771249] doi:10.1016/S0140-6736(15)60461-5

Background: Little evidence suggests that interventions focused on single domains, such as diet or exercise, prevent cognitive decline in older adults.

Findings: The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability randomly assigned 1260 participants with high cardiovascular risk factors for dementia and cognitive performance at the mean or slightly lower than expected for age to a multicomponent intervention (diet, exercise, cognitive training, and vascular risk monitoring) or health advice (control). Ninety-three percent of the intervention participants reported participating in 3 or 4 of the components. The primary outcome measure was change in performance on a neuropsychological test battery (NTB) consisting of 14 tests.

During 24 months, participants randomly assigned to the intervention had 25% overall higher scores on the NTB composite score and better executive functioning and processing speed, but not better memory. Estimated mean change ($\pm$ SE) in NTB total Z score at 2 years was 0.20 ± 0.02 (SD, 0.51) in the intervention group and 0.16 ± 0.01 (SD, 0.51) in the control group. Between-group difference in the change of NTB total score per year was 0.022 (95% CI, 0.002 to 0.042; $P = 0.030$). The odds ratios for decline in scores at 24 months in the control group compared with the intervention group were 1.31 for overall cognition ($P = 0.04$), 1.23 for memory ($P = 0.12$), 1.29 for executive function ($P = 0.04$), and 1.35 for processing speed ($P = 0.01$).

Cautions: Both groups improved their cognitive performance, suggesting a “practice effect” whereby participants learn the outcome measures. Whether any component or specific combination of components was more effective than others could not be established.

The clinical significance of the differences between groups was unclear, and memory was not affected. Prevention of dementia (an outcome to be evaluated in a longer follow-up period) was not reported.

Implications: The 4 components of this multifactorial intervention are all reasonable strategies for preventing cognitive decline that have few downsides. Whether it is cost-effective to mount specific programs that include all 4 components remains to be determined, as does whether the intervention has any effect on prevention of dementia.

Risks and Treatment of Common Medical Conditions in Older Persons

Among Older Persons With Normal Kidney Function, Mild Type 2 Diabetes Is Associated With Lower Mortality

Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;373:1720-32. [PMID: 26510021] doi:10.1056/NEJMoa1504347

Background: Large numbers of older adults with type 2 diabetes are treated with medications to decrease blood glucose, with the intent of preventing complications and reducing mortality.

Findings: This observational study conducted by using Swedish registries (435 369 persons with diabetes and 2 117 483 controls) found a 15% (adjusted hazard ratio, 1.15; 95% CI, 1.14 to 1.16) increased risk for death over 4.6 years among persons with diabetes. Mortality risk was higher with younger age, worse glycemic control, and greater severity of renal complications. Diabetic individuals aged 65 to 74 years and those 75 years of age or older who had normoalbuminuria had slightly decreased risk for death from any cause (hazard ratios, 0.96 [CI, 0.94 to 0.99] and 0.83 [CI, 0.82 to 0.84], respectively) and death from cardiovascular causes (hazard ratios, 0.95 [CI, 0.01 to 1.00] and 0.79 [CI, 0.78 to 0.81], respectively) compared with controls. Patients 75 years of age or older who had glycated hemoglobin levels less than 6.9% had a survival advantage for death from any cause and from cardiovascular causes (hazard ratios, 0.95 [CI, 0.94 to 0.96] and 0.79 [CI, 0.78 to 0.81], respectively) compared with controls. Among patients with normoalbuminuria and glycated hemoglobin level of 6.9% or less, the hazard ratios for death from any cause were 0.76 (CI, 0.75 to 0.78) for those 75 years of age or older and 0.87 (CI, 0.84 to 0.91) for those age 65 to 75 years compared with controls. Diabetic adults aged 65 years or older with an estimated glomerular filtration rate greater than 60 mL/min/1.73 m² also had lower all-cause mortality compared with controls.

Cautions: The study design was observational, and many subgroup analyses were performed.

Implications: This evidence supports the lack of need to aggressively treat diabetes among elderly patients with normal kidney function, particularly those who have mild elevation of glycated hemoglobin.

Achieving Lower Blood Pressure Targets in Persons Age 75 Years and Older Reduces Cardiovascular Outcomes and Cardiovascular Death

Wright JT Jr, Williamson JD, Whelton PK, et al; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103-16. [PMID: 26551272] doi:10.1056/NEJMoa1511939

Background: Although current Joint National Committee 8 guidelines recommend a blood pressure target of less than 150/90 mm Hg for persons 60 years of age and older, the optimal target systolic blood pressure for patients with cardiovascular risk factors but without diabetes is unknown.

Findings: The Systolic Blood Pressure Intervention Trial was a large randomized clinical trial (9361 participants) of target goals for patients who were at least 50 years of age, had systolic blood pressure of 130 to 180 mm Hg, and were at increased risk for cardiovascular events, as defined by one or more of the following: medical or subclinical cardiovascular disease other than stroke, chronic kidney disease, 10-year risk for cardiovascular disease of 15% or greater, or age 75 years or older. The primary outcome was a composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular causes. Among the 2636 participants aged 75 years or older, the primary outcome was reduced by 33% (hazard ratio, 0.67 [CI, 0.51 to 0.81]). Hypotension, syncope, electrolyte abnormalities, acute kidney injury, hyponatremia, and hypokalemia were more common with intensive treatment; however, each of these adverse effects occurred in fewer than 5% of participants.

Cautions: The many exclusion criteria included diabetes mellitus, previous stroke, end-stage renal disease, cardiovascular event or procedure or hospitalization for unstable angina within the last 3 months, symptomatic heart failure within the past 6 months, or left ventricular ejection fraction less than 35%, a medical condition likely to limit survival to <3 years, residence in a nursing home, dementia, and being cognitively unable to follow the protocol.

Implications: Treatment of hypertension to lower targets appears beneficial for some older persons. Findings may not apply to patients with common comorbid conditions or groups most likely to experience adverse effects of medicines.

Surgical Versus Medical Treatment of Knee Arthritis and Lumbar Spinal Stenosis

Total Knee Replacement Reduces Pain and Improves Function and Quality of Life But Has More Adverse Effects Than Nonsurgical Treatment

Skou ST, Roos EM, Laursen MB, et al. A randomized, controlled trial of total knee replacement. *N Engl J*

Med. 2015;373:1597-606. [PMID: 26488691] doi:10.1056/NEJMoa1505467

Background: Although hundreds of thousands of total knee replacements are performed each year, the evidence underlying the effectiveness of this procedure is inconclusive.

Findings: This randomized, controlled trial assigned 100 patients with moderate to severe knee arthritis to total knee replacement followed by 12 weeks of non-surgical treatment (including exercise, education, dietary advice, use of insoles, and pain medication) or to 12 weeks of nonsurgical treatment only. The primary outcome measure was change from baseline to 12 months in the mean score on 4 Knee Injury and Osteoarthritis Outcome Score subscales covering pain, symptoms, activities of daily living, and quality of life. By 12 months, 26% of patients who were assigned to receive nonsurgical treatment alone had total knee replacement (crossover). Both groups had substantial improvement on most outcomes. In the intention-to-treat analysis, the total knee replacement group had greater improvement on the Knee Injury and Osteoarthritis Outcome Score than did the nonsurgical treatment group (32.5 vs. 16.0; adjusted mean difference, 15.8 [CI, 10.0 to 21.5]). Those who had undergone total knee replacement also had greater improvement on the timed up-and-go test and 20-meter walk tests. The number needed to treat for a 15% improvement in the outcome measure was 5.7. Serious adverse events were more common (24 vs. 6; $P = 0.005$) in the total knee replacement group, especially deep venous thrombosis and stiffness requiring brisement force.

Cautions: The study was small (only 50 patients per group). Patients were relatively young (average age, late 60s) and those with severe pain were excluded. Only about half of those randomly assigned to either group adhered to the assigned treatment and could be included in the per protocol analysis.

Implications: The decision to have a total knee replacement versus waiting needs to be made individually by patients. When clinicians advise patients, they should mention possible benefits of surgery on pain, function, and quality of life, as well as the increased risk for adverse events.

Most Patients With Lumbar Spinal Stenosis Who Are Candidates for Surgery Will Have Surgery, Although Outcomes Are Similar With a Physical Therapy Intervention

Delitto A, Piva SR, Moore CG, Welch WC. Surgery versus non-surgical treatment of lumbar spinal stenosis [Letter]. *Ann Intern Med*. 2015;163:397-8. [PMID: 26322703] doi:10.7326/L15-5129-4

Background: Lumbar spinal stenosis is the most often cited reason for lumbar surgery in the United States. Although some studies have compared surgical and nonsurgical treatment options, nonsurgical approaches have not been standardized, and there have been high rates of crossover to surgical intervention among participants assigned to nonsurgical treatment.

Findings: This randomized clinical trial studied 169 patients with a diagnosis of lumbar spinal stenosis identified by computed tomography or magnetic resonance imaging who were considered candidates for surgical decompression. Patients also had to have neurogenic claudication, have consented to being randomly assigned to surgery or nonsurgical treatment, and have had no previous surgery for lumbar spinal stenosis at the level being considered for decompression. Participants were randomly assigned to surgery or physical therapy for twice-weekly exercise sessions. The primary outcome was the physical function score on the Short Form-36 Health Survey. At 24 months, mean changes in physical function did not differ between groups. Mean improvement in physical function for the surgery and physical therapy groups was 22.4 (CI, 16.9 to 27.9) and 19.2 (CI, 13.6 to 24.8), respectively. Intention-to-treat analyses revealed no statistically significant differences between groups (24-month difference, 0.9 [CI, -7.9 to 9.6]). Successful outcomes (defined as an improvement of more than 0.5 SD at 24-month follow-up relative to baseline) were similar across groups (61% among those assigned to surgery, 55% among those who crossed over from physical therapy to surgery, and 52% among those assigned to physical therapy and did not cross over). One quarter (33 of 132) of patients who underwent surgery had complications, most commonly reoperation and surgical site infection.

Cautions: Participants were relatively young (average age, late 60s), and 57% of participants in the physical therapy group crossed over to surgery during the 2-year period.

Implications: Some patients with lumbar spinal stenosis who are surgical candidates can be managed successfully with physical therapy alone, with similar outcomes. However, most patients eligible for surgery will end up having surgical management.

Risks and Benefits of Medications

Older Persons May Have More Gastrointestinal Bleeding With Novel Anticoagulants Than With Warfarin

Abraham NS, Singh S, Alexander GC, et al. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. *BMJ*. 2015;350:h1857. [PMID: 25910928] doi:10.1136/bmj.h1857

Background: The novel oral anticoagulants are a breakthrough in prevention of stroke due to atrial fibrillation, with effectiveness at least as good as that of warfarin, less risk for intracerebral hemorrhage, and no need for monitoring and adjusting dosage. However, some studies have shown increased risk for gastrointestinal bleeding.

Findings: This retrospective, propensity-matched cohort study used a large database of administrative claims data on 92 826 privately insured and Medicare Advantage enrollees to examine the rates of gastroin-

testinal bleeding associated with the novel oral anticoagulants dabigatran and rivaroxaban compared with warfarin. Although patients younger than 65 years had fewer events with novel oral anticoagulants, the risk increased after age 65 years; by age 76 years, the risk exceeded that of warfarin among patients with atrial fibrillation taking dabigatran (hazard ratio, 2.49 [CI, 1.61 to 3.83]) and patients with and without atrial fibrillation taking rivaroxaban (hazard ratios, 2.91 [CI, 1.65 to 4.81] and 4.58 [CI, 2.40 to 8.72], respectively).

Cautions: The study considered only 2 novel oral anticoagulants, both of which may have higher risks for gastrointestinal bleeding than other novel oral anticoagulants. Despite higher rates of bleeding associated with novel anticoagulants in the older population, the confidence intervals overlapped, indicating that the differences in rates were not statistically significant (between novel anticoagulants and warfarin).

Implications: In planning anticoagulation among older persons, consider warfarin, apixaban, or edoxaban.

Discontinuing Statins in Patients With Advanced Illness Is Safe and Improves Quality of Life

Kutner JS, Blatchford PJ, Taylor DH Jr, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med*. 2015;175:691-700. [PMID: 25798575] doi:10.1001/jamainternmed.2015.0289

Background: Because of greater disease burden, older persons tend to accumulate medications for chronic diseases, some of which are maintained beyond the time of anticipated benefit. Few studies have evaluated the harm or benefit of discontinuing therapy with medications that are aimed at having long-term benefit in patients with limited life expectancy.

Findings: This multicenter trial randomly assigned 381 adults who had life expectancy between 1 month and 1 year to withdraw or maintain statin therapy. The study's outcomes were death within 60 days and total score on the McGill Quality of Life questionnaire, reflected by a single-item overall quality-of-life score and selected subscales (physical symptoms, psychological symptoms, existential well-being, and support). The proportion of participants in the discontinuation versus continuation groups who died within 60 days did not statistically significantly differ (23.8% vs. 20.3%; 90% CI, -3.5% to 10.5%). Total quality of life was better for the group that discontinued statin therapy (mean McGill Quality of Life score, 7.11 vs. 6.85). Few participants experienced cardiovascular events (13 in the discontinuation group vs. 11 in the continuation group).

Cautions: The sample size was relatively small. This pragmatic trial did not include blinding. The primary outcome of survival was revised because of longer than expected survival of study participants.

Implications: Statin therapy can be safely discontinued among patients who have life expectancy less than 1 year without increasing the risk for early death and perhaps with increasing quality of life.

Discontinuing Antihypertensive Agents in Persons With Cognitive Impairment Does Not Improve Cognitive Function

Moonen JE, Foster-Dingley JC, de Ruijter W, et al. Effect of discontinuation of antihypertensive treatment in elderly people on cognitive functioning—the DANTE Study Leiden: a randomized clinical trial. *JAMA Intern Med.* 2015;175:1622-30. [PMID: 26301603] doi:10.1001/jamainternmed.2015.4103

Background: Observational studies suggest that lower blood pressure is associated with cognitive decline. Whether discontinuing antihypertensive agents reduces cognitive decline or improves cognition is not known.

Findings: This community-based trial enrolled 385 participants aged 75 years or older who were receiving antihypertensive treatment and had mild cognitive deficits but no serious cardiovascular disease. Participants were randomly assigned to continuing medication or withdrawing medication until a maximum increase in systolic blood pressure of 20 mm Hg was reached. At 16 weeks, change in the overall cognition composite score did not differ between intervention and control groups (0.01 [CI, −0.14 to 0.16] vs. −0.01 [CI, −0.16 to 0.14]; difference, 0.02 [CI, −0.19 to 0.23]). Secondary outcomes did not differ between groups for scores on executive function (−0.07 [CI, −0.29 to 0.15]), memory (0.08 [CI, −0.12 to 0.29]), psychomotor speed (−0.85 [95% CI, −1.72 to 0.02]), symptoms of apathy (0.17 [CI, −0.65 to 0.99]), depression (0.14 [CI, −0.20 to 0.48]), functional status (−0.72 [CI, −1.52 to 0.09]), and quality of life (−0.09 [CI, −0.34 to 0.16]). Adverse events were similar between groups. A substudy using magnetic resonance imaging did not find differences in white-matter hyperintensities, micro bleeds, lacunar infarcts, or cerebral blood flow.

Cautions: Older persons with serious cardiovascular disease who might be more likely to have impaired cerebral autoregulation were excluded. The study was relatively small and of short duration.

Implications: It seems inappropriate to reduce blood pressure medicines to improve cognitive status. However, some individual patients may not cognitively function well with low blood pressure. For these patients, a trial of discontinuing antihypertensive medication and reassessing cognition might be worthwhile.

in frail older adults with a history of falls. *Arch Phys Med Rehabil.* 2015;96:2096-102. [PMID: 26360975] doi:10.1016/j.apmr.2015.08.427

Background: Although a variety of community-based exercise programs may reduce risk for falling, logistic considerations, expense, and patient reluctance have limited the uptake of such approaches. In contrast, virtual reality and exergaming technologies that can be done alone are appealing to some patients because of the game-like aspects.

Findings: This randomized clinical trial enrolled 60 participants (mean age, 82 years) living in a nursing home and assigned them to 6 weeks of a conventional balance training group or a Wii Fit balance training program consisting of Soccer Heading, Table Tilt, and Balance Bubble. Participants in the Wii Fit balance group achieved statistically significantly greater muscle strength ($P < 0.001$), faster reaction times ($P < 0.001$), less body sway ($P = 0.013$), and better score on a composite measure of risk for falls ($P = 0.004$) than those who underwent conventional balance training. The incidence of falls, when adjusted for age, sex, and previous falls, was 69% lower during a 1-year period ($P < 0.001$).

Cautions: The study was small (30 participants in each group) and was restricted to nursing home residents.

Implications: The findings need replication in other populations with larger sample sizes. Nevertheless, they suggest that new approaches to balance training that rely on exergaming techniques may be more valuable than conventional balance training.

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The Effects of Exergaming on Balance and Falls

Wii Fit Exergaming May Be Superior to Conventional Balance Training in Nursing Home Residents

Fu AS, Gao KL, Tung AK, Tsang WW, Kwan MM. Effectiveness of exergaming training in reducing risk and incidence of falls