POEMs

Patient-Oriented Evidence That Matters

Chlorthalidone No Better Than Hydrochlorothiazide for Hypertension

Clinical Question

Is chlorthalidone or hydrochlorothiazide (HCTZ) associated with a difference in the rate of major adverse cardiovascular events when used to treat hypertension?

Bottom Line

There is no difference in cardiovascular outcomes when HCTZ is compared with chlorthalidone. There is a slightly higher risk of hypokalemia with chlorthalidone. (Level of Evidence = 1b)

Synopsis

There has been mixed evidence that chlorthalidone may do a better job at reducing cardiovascular events than HCTZ. Chlorthalidone has been associated with a higher likelihood of adverse events. The pragmatic trial used the U.S. Department of Veterans Affairs electronic health records to identify eligible patients 65 years and older who were currently taking HCTZ at a dosage of 25 or 50 mg daily. If participation was approved by their primary care physician, patients were randomized to continue taking HCTZ or switch to chlorthalidone. Patients in the HCTZ group continued their usual dose, and those randomized to receive chlorthalidone received a dose at one-half of their usual HCTZ dose (e.g., if they usually took 25 mg of HCTZ, they received 12.5 mg of chlorthalidone). Most patients in the HCTZ group were taking 25 mg. This was an open-label trial, although outcome assessors were masked for some outcomes. At baseline, the mean age of the 13,523 participants was 72 years, 97% were men, 15% were Black, and 44% had comorbid type 2 diabetes mellitus.

After a median of 2.4 years, blood pressure and medication adherence (79%) were similar between groups. The primary outcome was a composite of nonfatal myocardial infarction, stroke, hospitalization for heart failure, urgent revascularization, or noncancer-related death. There was no difference between groups for this primary outcome (10.4% for chlorthalidone and 10.0% for HCTZ) and no difference for any of the individual elements of the composite. When the analysis was stratified by history of myocardial infarction or stroke at baseline, patients with this history had fewer primary outcome events with chlorthalidone (14.3% vs. 19.4%; hazard ratio [HR] = 0.73; 95% CI, 0.57 to 0.94; number needed to treat = 20), whereas those without this history had a slightly higher likelihood of the primary outcome with chlorthalidone (9.9% vs. 8.9%; HR = 1.12; 95% CI, 1.0 to 1.26). The authors note that they believe this difference was most likely a chance finding. Chlorthalidone use was associated with a slightly higher risk of hypokalemia (6.0% vs. 4.4%; HR = 1.38; 95% CI, 1.19 to 1.60; number needed to harm = 62), with a potassium level of less than 3.10 mEq per L (3.1 mmol per L; 5.0% vs. 3.6%; HR = 1.39; 95% CI, 1.18 to 1.64; number needed to harm = 71). Although 15.4% of patients in the chlorthalidone group were switched back to HCTZ at some point, this kind of crossover only occurred for 3.8% in the HCTZ group.

Study design: Randomized controlled trial (nonblinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Ishani A, Cushman WC, Leatherman SM, et al.; Diuretic Comparison Project Writing Group. Chlorthalidone vs. hydrochlorothiazide for hypertension–cardiovascular events.* N Engl J Med. *2022;387(26):2401-2410.*

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Treat-to-Target LDL Strategy of Statin Dosing Is Noninferior to High-Intensity Dosing

Clinical Question

Is a strategy of treat-to-target statin dosing noninferior to high-intensity dosing for adults with coronary artery disease (CAD)?

Bottom Line

The study found that statin dosing based on a treat-to-target low-density lipoprotein (LDL) level of 50 to 70 mg per dL (1.29 to 1.81 mmol per L) is noninferior to a high-intensity

strategy to reduce adverse events in adults with established CAD. Although the authors see this as an advantage that allows a tailored approach for individual dosing variability, it also serves as some of the best evidence yet that CAD can be managed with a high-intensity strategy and patients can avoid the costs and burdens of repeated LDL testing. (Level of Evidence = 1b)

Synopsis

There is minimal evidence supporting the superiority or noninferiority of a high-intensity strategy of statin dosing vs. treating to a target LDL level. The investigators identified 4,400 adults with CAD, including stable ischemic heart disease and acute coronary syndrome. Eligible patients randomly received (concealed allocation assignment) a statin using either a strategy of a treat-to-target LDL level between 50 and 70 mg per dL or a strategy of high-intensity therapy (20 mg of rosuvastatin or 40 mg of atorvastatin daily) without a dose adjustment based on follow-up testing of LDL levels. An independent committee masked to treatment group assignment assessed outcomes. Complete follow-up occurred for 98.7% of participants at three years.

Using intention-to-treat and per-protocol analysis, the primary end point (a composite of all-cause death, myocardial infarction, stroke, and any coronary revascularization) occurred in 8.1% of the treat-to-target group and 8.7% in the high-intensity statin therapy group (nonsignificant difference, meeting the significance for noninferiority). No significant group differences occurred for multiple prespecified secondary end points, including new-onset diabetes mellitus, elevated liver enzymes, hospitalizations, end-stage renal disease, and study drug discontinuation due to intolerance.

Study design: Randomized controlled trial (single-blinded)

Funding source: Industry

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Hong SJ, Lee YJ, Lee SJ, et al.; LODESTAR Investigators. Treat-to-target or high-intensity statin in patients with coronary artery disease: a randomized clinical trial.* JAMA. *2023;329(13):1078-1087.*

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Augmentation With Aripiprazole or Bupropion, or a Switch to Nortriptyline, Effective for Treatment-Resistant Depression in Older Adults

Clinical Question

What is the best pharmacologic approach in adults 60 years and older with treatment-resistant depression?

Bottom Line

There are several takeaways from the trial. Aripiprazole and bupropion augmentation produce similar modest improvements, and both are a reasonable option. Although injurious falls appear to be more common with bupropion, the authors did not report weight gain and hyperglycemia, which are both known adverse effects of aripiprazole. In the second comparison, a switch to nortriptyline seems preferable to lithium augmentation based on the simplicity of dosing and a lower risk of injurious falls. (Level of Evidence = 1b–)

Synopsis

Researchers in the Patient-Centered Outcomes Research Institute–sponsored trial identified adults 60 years and older who had not achieved remission of their depressive symptoms after trials of at least two antidepressants and had a Patient Health Questionnaire-9 (PHQ-9) score of 10 or more (range = 0 to 27). At baseline, patients had a mean age of 69 years, 67% were women, and the mean PHQ-9 score was 16. The primary outcome was patient-reported symptoms based on the Positive Affect and General Life Satisfaction subscales of the National Institutes of Health Toolbox Emotion Battery. Remission was defined as a score of 10 or lower on the Montgomery-Åsberg Depression Rating Scale (MADRS; range = 0 to 60). It was an open-label randomized trial with two phases.

In the first phase, 618 participants were randomized into one of three groups for 10 weeks: (1) aripiprazole augmentation (starting at 2.5 mg once daily up to a maximum of 15 mg once daily, (2) bupropion augmentation (starting at 150 mg once daily up to a maximum of 450 mg once daily), or (3) switching from their current medication to bupropion, 150 to 450 mg daily. At baseline, self-reported symptom scores were 33.2 to 33.7 points. At 10 weeks, the improvement in symptom scores was 4.83 points for aripiprazole augmentation, 4.33 points for bupropion augmentation, and 2.0 points for switching to bupropion. Rates of remission were 28.9%, 28.2%, and 19.3%, respectively. Improvement in the MADRS scores followed a similar pattern. The authors make much of the fact that the difference between aripiprazole augmentation and the switch to bupropion was statistically significant, whereas the difference between bupropion augmentation and the switch to bupropion was not, although numerically and clinically, the results were similar for both kinds of augmentation. Injurious falls were numerically more common with bupropion augmentation (25% vs. 17% for aripiprazole and 19% for switching to bupropion, significance not reported).

In phase 2, patients who did not achieve remission (plus 248 people who did not qualify for phase 1 because of previous use of the assigned therapies) were randomized to 10 weeks of lithium augmentation (starting at 150 to 300 mg, with a maximum of 1,200 mg per day and a target drug level of 0.6 mmol per L) or switched to nortriptyline (starting at

25 mg per day, increasing by 1 mg per kg and 80 to 120 ng per mL drug level). The improvement in the MADRS score was 4.6 points with lithium augmentation and 5.3 points with the switch to nortriptyline ($P = .57$), whereas remission rates were 18.9% and 21.5%, respectively (risk ratio = 0.84; 95% CI, 0.53 to 1.36). Injurious falls were more common with lithium (21.2% vs. 13.2%). The cost of aripiprazole varied wildly, from $2.54 at Walmart to $238 at Walgreens (https://www.goodrx.com, accessed March 27, 2023), therefore patients should shop around. Bupropion costs ranged from $5 to $30.

Study design: Randomized controlled trial (nonblinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Lenze EJ, Mulsant BH, Roose SP, et al. Antidepressant augmentation versus switch in treatment-resistant geriatric depression.* N Engl J Med. *2023;388(12):1067-1079.*

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Tailored Exercise Program Improves Function and Reduces Pain Due to Knee Osteoarthritis

Clinical Question

In patients with pain and function loss due to knee osteoarthritis, does high-dose medical exercise therapy improve pain and function scores more than low-dose exercise?

Bottom Line

Tailored exercise therapy, at least 20 to 30 minutes three times per week, improves pain and function scores in approximately one-half of patients with painful knee osteoarthritis. For patients interested in sports and recreation, high-dose, longer exercise (70 to 90 minutes) produces better results. (Level of Evidence = 1b–)

Synopsis

The study was conducted in Norway and Sweden, and the researchers enrolled 189 patients, 45 to 85 years of age, with knee osteoarthritis and a history of pain and decreased knee function. The patients did not have previous therapy. Using concealed allocation, the authors assigned participants to 20 to 30 minutes of low-dose exercise therapy (two sets of 10 repetitions) or 70 to 90 minutes of high-dose exercise therapy (three sets of 30 repetitions) that was tailored to their specific needs by a physical therapist. Both groups were given instructions on how to perform the exercises and adjust the weight to perform them without pain. The participants were asked to perform the exercises on their own three times per week for 12 weeks. Both groups improved over time to a similar extent for most outcomes of pain and function using the Knee Injury and Osteoarthritis Outcome Score, with approximately one-half of participants experiencing a clinically meaningful improvement in all outcome categories. High-dose exercise was associated with approximately 20% more participants achieving a clinically important improvement on the Function in Sport and Recreation score, which lasted for three months after the end of the study. The study may have been underpowered to find the minimal clinically important difference between treatments. About 23% of participants dropped out during the study. There may have been a possible placebo response in this unmasked study, and a usual care group as a third comparator may have been helpful.

Study design: Randomized controlled trial (single-blinded)

Funding source: Foundation

Setting: Outpatient (primary care)

Reference: *Torstensen TA, Østerås H, LoMartire R, et al. High- versus low-dose exercise therapy for knee osteoarthritis: a randomized controlled multicenter trial.* Ann Intern Med. *2023;176(2):154-165.*

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