POEMs

Patient-Oriented Evidence That Matters

Small Reduction in Cardiovascular Outcome After Ischemic Stroke with Lower LDL Target, but also Harms; No Change in All-Cause Mortality

Clinical Question

Does a lower low-density lipoprotein (LDL) target following ischemic stroke reduce the likelihood of major adverse cardiovascular events?

Bottom Line

A lower LDL target slightly reduced the likelihood of a broad composite outcome (number needed to treat [NNT] = 43 over 3.5 years), largely by reducing nonfatal strokes (NNT = 77; statistical significance not reported). The benefit was seen only in patients whose index event was a stroke; risk may be increased in those with transient ischemic attack (TIA). (Level of Evidence = 1b)

Synopsis

The study identified adults with a recent ischemic stroke or TIA of at least 10 minutes duration in France or South Korea who had a modified Rankin score of 0 to 3 (functionally independent or largely so). All patients underwent imaging and had stenosis of a cerebral artery or known coronary artery disease. They also had an LDL level greater than 100 mg per dL (2.59 mmol per L) if not taking a statin or greater than 70 mg per dL (1.81 mmol per L) if already taking a statin. The 2,860 patients were then randomized to an LDL target of 70 mg per dL or an LDL target of 90 to 110 mg per dL (2.33 to 2.85 mmol per L) using any type or dose of statin preferred by their physicians (plus ezetimibe [Zetia], if needed). The total number of patients recruited was less than the authors' stated target of 3,786. The included patients were followed for a median of 5.3 years in France but only 2.0 years in South Korea. The mean age of participants was 67 years, 67% were men, 64% had hypertension, and their baseline LDL level was 135 mg per dL (3.50 mmol per L) with approximately one-half already taking a statin. Groups were balanced, and analysis was by intention to treat. The patients hit their mean LDL targets: 65 mg per dL (1.68 mmol per L) in the low target group and 96 mg per dL (2.49 mmol per L) in the higher target group. The authors had a broad primary composite outcome of cardiovascular death, nonfatal stroke, acute coronary syndrome, or urgent coronary or carotid revascularization, which was lower in the low LDL target group (8.5% vs. 10.9%; $P = .04$; NNT = 42 over 3.5 years to prevent one event). Approximately one-half of the events prevented in the composite outcome were nonfatal ischemic strokes. The authors do not report statistical significance testing for any of the individual outcomes, although they say that none of the individual outcome differences were statistically significant. All-cause mortality was similar between groups (6.2% vs. 6.5%). There was a significant increase in the likelihood of the primary composite outcome in patients whose index event was a TIA rather than an ischemic stroke (11.7% vs. 6.0%; $P < .05$), but the confidence interval was wide for this outcome. Intracerebral hemorrhage and newly diagnosed diabetes mellitus were more common in the lower target group, but these differences were not statistically significant.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Setting: Inpatient (any location) with outpatient follow-up

Reference: *Amarenco P, Kim JS, Labreuche J, et al.; Treat Stroke to Target Investigators. A comparison of two LDL cholesterol targets after ischemic stroke.* N Engl J Med. *2020;382(1):9-19.*

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Daily Colchicine Post-MI Reduces Strokes and Recurrent Hospitalizations for Angina

Clinical Question

Does treatment with colchicine after myocardial infarction (MI) prevent recurrent cardiovascular events?

Bottom Line

Daily colchicine after MI reduces cardiovascular events, specifically strokes and hospitalizations for angina. It is inexpensive and well-tolerated and should be considered for patients with recent MIs who are already using guideline-directed therapy. (Level of Evidence = 1b)

Synopsis

Post-MI inflammation may play a role in atherosclerosis and lead to an increased risk of recurrent cardiovascular events. In this trial, investigators evaluated the role of colchicine, an inexpensive anti-inflammatory medication, in lowering the risk of ischemic cardiovascular events in patients with recent MIs. Adults who had an MI within the past 30 days and had completed any planned revascularization procedures were randomized, using concealed allocation, to receive colchicine 0.5 mg daily (n = 2,366) or placebo (n = 2,379). Those with severe heart failure, severe hepatic or renal disease, recent stroke, or recent coronary bypass surgery were excluded. The primary end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization. The two groups were similar at baseline. The mean age was 61 years, 19% were women, 30% were smokers, 20% had diabetes mellitus, and almost all were treated with dual antiplatelet therapy and a statin. Median follow-up was 23 months, and patients received the trial drug for a median of 19 months. Overall, 5.5% of patients in the colchicine group had a primary end point event compared with 7.1% in the placebo group (hazard ratio [HR] = 0.77; 95% CI, 0.61 to 0.96; $P = .02$; number needed to treat [NNT] = 63). This result was primarily driven by a decrease in stroke (HR = 0.26; 95% CI, 0.10 to 0.70; NNT = 167) and a decrease in urgent hospitalizations for angina leading to revascularization (HR = 0.50; 95% CI, 0.31 to 0.81; NNT = 100). As far as adverse events, the colchicine group reported more nausea and flatulence than the control group. The colchicine group had a slightly higher rate of pneumonia, although the incidence was low (0.9% vs. 0.4%; $P = .03$).

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Inpatient (any location) with outpatient follow-up

Reference: *Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction.* N Engl J Med. *2019;381(26):2497-2505.*

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Oseltamivir of Uncertain Benefit in Patients with Flulike Symptoms

Clinical Question

Is oseltamivir (Tamiflu) better than usual care in shortening the duration of symptoms in patients with flulike symptoms in primary care settings?

Bottom Line

Although the authors report that compared with usual care oseltamivir shortens the duration of symptoms, the methodologic biases in this study make their conclusions suspect. (Level of Evidence = 2b)

Synopsis

The authors recruited patients from primary care settings who were at least one year of age and had flulike symptoms lasting no more than three days. The study took place during three consecutive winters. In a pragmatic open-label design, patients were assigned using a response adaptive randomization system to receive five days of oseltamivir (n = 1,629) or their primary care clinician's usual care (n = 1,637). Each patient was formally tested for influenza. Each patient or their caregiver was asked to keep a daily symptom

diary for the two weeks following enrollment. The researchers adapted the diaries for children (e.g., clinginess for nonverbal children became a proxy for headache and myalgias). At the end of the study period, 91 of the patients (6%) assigned to oseltamivir dropped out or discontinued medication and 104 patients in the usual care group (7%) dropped out or discontinued treatment. The authors did not include these patients in their analysis, so it was not really an intention-to-treat analysis. At baseline, the patients in each group were comparable, including the severity and duration of their symptoms. Only 10% of the patients had received influenza vaccinations. Approximately one-half of the patients had a positive test result for influenza—close to evenly split between types A and B. At the end of the evaluation period for every age stratum, regardless of symptom severity and duration and whether or not the patient had a comorbid condition, the patients who received oseltamivir experienced faster recovery than those who received usual care. The average duration was one day less for patients taking oseltamivir. Older patients, those with comorbidities, and those with longer symptom duration at baseline tended to recover two to three days faster if they took oseltamivir.

Study design: Randomized controlled trial (nonblinded)

Funding source: Government

Allocation: Uncertain

Setting: Outpatient (primary care)

Reference: *Butler CC, van der Velden AW, Bongard E, et al. Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial.* Lancet. *2020; 395(10217):42-52.*

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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, published by Wiley-Blackwell. ■