

POEMs

Patient-Oriented Evidence That Matters

LABA Plus Inhaled Corticosteroid Reduces Exacerbations, But Not Hospitalizations

Clinical Question

Is adding a long-acting beta-agonist (LABA) to an inhaled corticosteroid safe and effective for patients with persistent asthma?

Bottom Line

Adding a LABA to an inhaled corticosteroid is safe but does not reduce the likelihood of a serious exacerbation requiring hospitalization. There is a small reduction in nonsevere asthma exacerbations, with one fewer exacerbation for every 53 patients treated for six months. (Level of Evidence = 1b)

Synopsis

The use of a LABA as the sole medication to control asthma was associated with increased mortality. The U.S. Food and Drug Administration mandated that companies that make a LABA do adequately powered randomized trials to assess the safety and efficacy of adding a LABA or placebo to an inhaled corticosteroid in patients with persistent asthma. This current study is a pre-planned combined analysis of these four 26-week drug company-sponsored trials. Each study used a different LABA, but the results were consistent across trials. There were only two asthma-related deaths (both in the inhaled corticosteroid-LABA group) and three intubations (two in the inhaled

corticosteroid group, one in the inhaled corticosteroid-LABA group). In the combined analysis, there was no significant difference in the risk of hospitalization between groups (0.60% for inhaled corticosteroid vs. 0.66% for inhaled corticosteroid-LABA). The likelihood of an asthma exacerbation was lower in the inhaled corticosteroid-LABA group (9.8% vs. 11.7%; $P < .001$; number needed to treat = 53).

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Concealed

Setting: Outpatient (any)

Reference: Busse WW, Bateman ED, Caplan AL, et al. Combined analysis of asthma safety trials of long-acting β_2 -agonists. *N Engl J Med.* 2018;378(26):2497-2505.

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NPH Insulin: Fewer Episodes of Severe Hypoglycemia Than Analogs and Less Than One-Half the Cost

Clinical Question

Do long-acting insulin analogs, such as glargine (Lantus) or detemir (Levemir), reduce the risk of clinically significant hypoglycemia compared with neutral protamine Hagedorn (NPH) insulin?

Bottom Line

This study found that compared with expensive long-acting insulin analogs costing two to 10 times as much, NPH insulin results in a similar number of episodes of severe hypoglycemia (if not fewer) that result in emergency department visits and hospitalizations. NPH insulin also improves glycemic control as well as, if not better than, insulin analogs. In a previous report (Singh SR, et al. *CMAJ.* 2009;180(4):385-97), overall quality of life was also similar with NPH insulin or insulin analogs. Compared with long-acting insulin analogs, NPH insulin is as safe, if not safer, equally tolerated, equally or more effective, and at a much lower price. One in four adults

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with diabetes mellitus either stops or cuts back significantly on their insulin because they cannot afford it. (Level of Evidence = 2b-)

Synopsis

Marketing efforts have convinced most clinicians that long-acting insulin analogs, such as glargine and detemir, reduce the risk of hypoglycemia and are thus safer than traditional NPH insulin. These investigators analyzed data from 2006 and 2015 from multiple patient and prescription registries with Kaiser Permanente of Northern California. Outcomes of interest included pharmacy use; laboratory results; and outpatient, emergency department, and hospitalization diagnoses of diabetes and related complications. The inception cohort comprised 25,489 adults, 19 years or older, with type 2 diabetes who were initiating basal insulin therapy without any insulin prescription fills during the prior 12 months. Results were analyzed after controlling for multiple potential confounders, including demographics, index year, clinician specialty, comorbidity index, chronic kidney and/or liver disease, visual impairment, history of depression, glycemic control, history of severe hypoglycemia episodes requiring third-party intervention, and medication nonadherence. The risk of a subsequent severe hypoglycemic episode resulting in an emergency department visit or hospital admission was not significantly lower in patients who initiated NPH insulin at baseline compared with those initiating insulin analogs (8.8 vs. 11.9 events per 1,000 person-years, respectively). In addition, glycemic control was significantly improved in patients using NPH insulin vs. insulin analogs (difference in A1C, -0.22% ; 95% confidence interval, -0.09% to -0.37%).

Study design: Cohort (retrospective)

Funding source: Government

Setting: Population-based

Reference: Lipska KJ, Parker MM, Moffet HH, Huang ES, Karter AJ. Association of initiation of basal insulin analogs vs neutral protamine Hagedorn insulin with hypoglycemia-related emergency department visits or hospital admissions and with glycemic control in patients with type 2 diabetes. *JAMA*. 2018;320(1):53-62.

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Lower Systolic BP During Antihypertensive Treatment Associated with More Deaths in Older Adults

Clinical Question

Is lower systolic blood pressure associated with better outcomes in older patients who take antihypertension medications?

Bottom Line

In this small cohort study of patients older than 85 years, lower systolic blood pressure during treatment with antihypertensive medications is associated with higher death rates and greater cognitive decline. (Level of Evidence = 1b-)

Synopsis

These researchers assembled a cohort of 570 residents of Leiden in the Netherlands who turned 85 years of age between 1997 and 1999. They excluded people who died within three months of enrollment and those who had no blood pressure measurement at baseline. At baseline, and periodically over the course of five years of follow-up, the researchers collected all kinds of information: sociodemographics, medical diagnoses, medications, mental status, grip strength (as a proxy for frailty), blood pressure, and so forth. They assessed the main outcome—death from any cause—by using municipal records. Slightly fewer than one-half of the residents (44%) took antihypertensive medications at baseline; these patients were more likely to have other cardiovascular disorders than those not taking antihypertensive medications (62% vs. 36%). During the five years of follow-up, 263 participants (46%) died. For those taking antihypertensive medications, all-cause mortality was significantly higher with decreasing systolic blood pressure (hazard ratio = 1.29 per 10 mm Hg lower systolic blood pressure; 95% confidence interval, 1.15 to 1.46). For the residents who were not taking antihypertensive medications, there was no significant correlation between systolic blood pressure and all-cause mortality. The patients taking antihypertensives had more rapid cognitive decline with lower systolic blood pressure. Although many explanations for the differences in treatment thresholds are given by the various guidelines, one is how we value clinical trial vs. observational data. The guidelines that promulgate lower blood pressure targets are more likely to value observational data. The data from this study are subject to many

of the biases inherent in cohort studies, but they should moderate the enthusiasm for lower blood pressure targets.

Study design: Cohort (prospective)

Funding source: Government

Setting: Population-based

Reference: *Streit S, Poortvliet RK, Gussekloo J. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old data from the Leiden 85-plus study. Age Ageing. 2018;47(4):545-550.*

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Oral Contraceptives and Antiandrogens Most Effective for Hirsutism Pharmacotherapy

Clinical Question

What are the most effective drug therapies for hirsutism?

Bottom Line

Combination oral contraceptive pills (OCPs) are an excellent treatment option for women desiring medical therapy for hirsutism. Based on this meta-analysis, an accompanying practice guideline recommends adding an antiandrogen, such as finasteride (Propecia), if there is an inadequate response within six months. The guideline also recommends avoiding monotherapy with an antiandrogen and avoiding the use of insulin sensitizers such as metformin because of the inconsistency of the evidence (*J Clin Endocrinol Metab.* 2018;103(4):1233-1257). (Level of Evidence = 1a-)

Synopsis

This is a network meta-analysis from the Mayo Clinic Evidence-Based Practice Center. It was methodologically sound, although the risks of comparing apples to bananas, and oranges to bananas, and using the results to extrapolate

about apples to oranges has inherent limitations. After a search of three databases, the authors found 43 randomized trials that evaluated a treatment for hirsutism compared with either placebo or another active treatment. Eight studies compared different OCPs with one another and three studies provided qualitative data, leaving 32 for the network meta-analysis. The median age of participants was approximately 25 years, and the studies included women with a fairly wide range of hirsutism severity. Most trials were believed to be at high risk of bias due to inadequate allocation concealment during randomization, a failure to mask participants and/or outcome assessors, and financial conflicts of interest of the investigators. The strongest evidence comes from direct comparisons. Regarding comparisons with placebo, metformin was studied in nine trials (albeit with heterogeneity); finasteride in three trials; flutamide (Eulexin) in two; and OCPs, spironolactone, troglitazone, and OCP plus flutamide in one each. The network meta-analysis concluded that there was the strongest evidence for efficacy of combination estrogen-progestin OCPs, antiandrogens (primarily for women who are using long-acting contraception or who have been sterilized), and metformin. All OCPs appeared to be similarly effective.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Foundation

Setting: Various (meta-analysis)

Reference: *Barrionuevo P, Nabhan M, Altayar O, et al. Treatment options for hirsutism: a systematic review and network meta-analysis. J Clin Endocrinol Metab. 2018;103(4):1258-1264.*

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