POEMs

Patient-Oriented Evidence That Matters

Improved Decongestion With the Addition of Acetazolamide to Intravenous Loop Diuretics for Acute Heart Failure

Clinical Question

Does the addition of acetazolamide to intravenous loop diuretics lead to faster decongestion in hospitalized patients with acute decompensated heart failure?

Bottom Line

For patients with chronic heart failure who are hospitalized with acute volume overload, the addition of acetazolamide to intravenous loop diuretics leads to faster decongestion. Nine patients would need to be treated with acetazolamide to have one patient achieve this outcome. The trial was initiated before the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors for the treatment of heart failure and had a predominantly White population. The results may not be generalizable to all populations. (Level of Evidence = 1b)

Synopsis

The investigators randomized hospitalized adults with acute decompensated heart failure (i.e., one clinical sign of volume overload plus elevated N-terminal pro-brain natriuretic peptide or brain natriuretic peptide) to receive intravenous acetazolamide, 500 mg daily (n = 259), or matching placebo (n = 260) for three days. All patients received standardized intravenous loop diuretic therapy at double the dose of their oral maintenance therapy. Those taking maintenance acetazolamide or SGLT-2 inhibitors were excluded. Trial participants had a mean age of 78 years, two-thirds were men, and 99% were White. Additionally, 87% were classified as New York Heart Association class III or IV. The primary outcome was successful decongestion, defined as the absence of signs of volume overload within three days of randomization without a need for escalation of decongestive therapy. More patients in the acetazolamide group than in the placebo group achieved the primary outcome (42.2% vs. 30.5%; relative risk [RR] = 1.46; 95% CI, 1.17 to 1.82). This was consistent across all subgroups except for a smaller benefit seen in patients receiving a higher dose of maintenance diuretics compared with those receiving a lower dose. The acetazolamide group had a shorter hospital stay (8.8 vs. 9.9 days; RR = 0.89; 95% CI, 0.81 to 0.98) and a higher incidence of successful decongestion at discharge (78.8% vs. 62.5%; RR = 1.27; 95% CI, 1.13 to 1.43). Adverse events were similar in the two groups, and no differences were detected in death or rehospitalization at three months.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Inpatient (any location)

Reference: *Mullens W, Dauw J, Martens P, et al.; ADVOR Study Group. Acetazolamide in acute decompensated heart failure with volume overload.* N Engl J Med. *2022;387(13):1185-1195.*

Nita Shrikant Kulkarni, MD
Assistant Professor in Hospital Medicine
Northwestern University
Chicago, Ill.

Rebound Symptoms Common With COVID-19 Even After Placebo Treatment

Clinical Question

Does symptomatic rebound occur in patients with COVID-19 who are not treated with nirmatrelvir/ritonavir (Paxlovid)?

Bottom Line

Symptomatic recurrences in patients who initially recovered from COVID-19 are common, even without nirmatrelvir/ritonavir treatment, and are generally mild. Some symptoms may represent viral recurrence, and some may represent postinflammatory symptoms or the development of long COVID. Some symptoms may be caused by different infections. (Level of Evidence = 1b)

Synopsis

Nirmatrelvir/ritonavir rebound has been widely reported by patients and in the media. It comprises recurrent symptoms of COVID-19 following a five-day course of nirmatrelvir/ritonavir in someone who initially recovered. Is this

causally related to the use of this drug, or is it part of the natural history of SARS-CoV-2 infection? The authors used data from the placebo group in the ACTIV-2 randomized trial that compared several treatments (including nirmatrelvir/ritonavir with placebo) in symptomatic outpatients with COVID-19 for 10 days or less. The current study reports only on symptom recurrence in the placebo group. The 158 participants in the placebo group completed a daily symptom diary for 28 days, tracking 13 symptoms. The participants had a median age of 47 years, 50% were women, 18% self-identified as part of a minority racial group, and 31% were Hispanic. During the 28 days of follow-up, 108 of 158 participants (68%) achieved complete resolution of all symptoms for at least two consecutive days. Of these 108 people, 48 (44%) reported at least one symptom recurring at least one day during the follow-up period. The most common recurrent symptoms were cough (44%), fatigue (35%), and headache (35%). The recurrent symptoms were mild, with no patient reporting severe recurrent symptoms, and only eight of the 48 reporting moderate-severity symptoms for at least one day. The interval between resolution of the initial symptoms and recurrence varied from one day to more than two weeks later, so some of these recurrences may represent a separate viral illness. Approximately one-half recurred in the first week after resolution.

Study design: Cohort (prospective)

Funding source: Government

Setting: Outpatient (any)

Reference: *Smith DM, Li JZ, Moser C, et al.; ACTIV-2/A5401 Study Team. Recurrence of symptoms following a 2-day symptom free period in patients with COVID-19.* JAMA Netw Open. *2022;5(10):e2238867.*

Mark H. Ebell, MD, MS
Professor
University of Georgia
Athens, Ga.

Invitation to a Single Colonoscopy Has Only Modest Impact on Colorectal Cancer Incidence

Clinical Question

Does an invitation to receive a colonoscopy reduce the incidence and mortality of colorectal cancer (CRC) compared with usual care?

Bottom Line

In the first randomized trial of CRC screening using colonoscopy, a smaller than expected reduction in CRC incidence was seen in the intention-to-treat (absolute risk reduction [ARR] = −0.22% over 10 years; number needed to invite = 455) and adjusted per-protocol analyses (ARR = −0.38%; $P < .05$; number needed to screen = 263). The same was true for reduction in CRC mortality in the intention-to-treat (ARR = −0.03%; P = not significant) and per-protocol analyses (ARR = −0.15%; $P < .05$). The lower than expected mortality reduction may be explained in part by improvements in treatment and the modest duration of follow-up. The authors were careful to adjust for differences between invitees who accepted colonoscopy and those who did not (to avoid the healthy volunteer bias), although unmeasured confounding is still possible. Trials comparing fecal immunochemical tests with colonoscopy are nearing their conclusion, and the results may add further clarity. (Level of Evidence = 1b)

Synopsis

Despite widespread use as a screening test for CRC in the United States, colonoscopy has never been subjected to a randomized trial. The authors identified 94,959 healthy men and women, 55 to 64 years of age, from the Netherlands, Norway, Sweden, and Poland who had not been screened for CRC in the past. The regions from which the participants were recruited did not have organized programs for CRC screening using colonoscopy. Follow-up data for 10,374 Dutch participants could not be included because of changes in European data protection laws that made it impossible to obtain data for uninvited people from the general population. The remaining 84,585 participants were randomized in a 1:2 ratio to receive an invitation for a single screening colonoscopy or usual care. The median age at enrollment was 59 years, one-half of the participants were women, and most came from Poland or Norway. Colonoscopy was performed at dedicated centers with training and quality assurance programs.

Only 11,843 (42%) of the 28,220 people invited to screening underwent colonoscopy. The median follow-up was 10 years, 91% had a good or very good bowel preparation, 97% achieved intubation of the cecum, and 30.7% had an adenoma detected. The risk of CRC was higher in the screened group for the first five years after colonoscopy, presumably because of cancer diagnoses during the examinations and heightened surveillance for precancerous lesions, but was less likely thereafter. In the intention-to-treat analysis, the incidence of CRC was significantly lower in the screened group (0.98% vs. 1.20%; relative risk [RR] = 0.82; 95% CI, 0.70 to 0.93; number needed to invite = 455 over 10 years). CRC mortality was not significantly lower in the screened group (0.28% vs. 0.31%; RR = 0.9; 95% CI, 0.64 to 1.16). There was no difference in all-cause mortality (11.03% vs. 11.04%). The authors performed a separate per-protocol analysis to estimate the benefits if everyone that was invited to receive a colonoscopy had been screened, adjusting for baseline differences between those accepting the invitation and those who ignored it (it is important to at least partially adjust for the healthy volunteer bias). They estimated a lower incidence of CRC (0.84% vs. 1.22%; RR = 0.69; 95% CI, 0.55

to 0.83; number needed to screen = 263) and a greater reduction in CRC mortality (0.15% vs. 0.30%; RR = 0.50; 95% CI, 0.27 to 0.77; number needed to screen = 667). Complications were rare; there were 15 episodes of major bleeding (0.13%; none were fatal) and no perforations.

Study design: Randomized controlled trial (single-blinded)

Funding source: Government

Allocation: Concealed

Setting: Population-based

Reference: *Bretthauer M, Løberg M, Wieszczy P, et al.; NordICC Study Group. Effect of colonoscopy screening on risks of colorectal cancer and related death.* N Engl J Med. *2022;387(17):1547-1556.*

Mark H. Ebell, MD, MS
Professor
University of Georgia
Athens, Ga.

Liraglutide Is Probably the Best Second Drug to Prevent Cardiovascular Events in Patients With Type 2 Diabetes Mellitus Who Take Metformin

Clinical Question

Which additional drug is most effective at reducing microvascular and macrovascular cardiovascular events in patients with type 2 diabetes mellitus who take metformin?

Bottom Line

Although absolute event numbers are small and not always statistically significant, liraglutide (Victoza) is consistently the best second drug to prevent cardiovascular events in patients with type 2 diabetes who take metformin. A study that reported glycemic control favored sitagliptin (Januvia), but liraglutide was significantly better at preventing cardiovascular events. A limitation was that there were no sodium-glucose cotransporter-2 (SGLT-2) inhibitors in the study because they were not approved by the U.S. Food and Drug Administration for use with metformin in 2013 when the study began. A follow-up study comparing SGLT-2 inhibitors with glucagon-like peptide-1 (GLP-1) agonists as a second drug is needed. (Level of Evidence = 1b)

Synopsis

The authors recruited 5,047 participants who had type 2 diabetes for less than 10 years and were diagnosed after the patient was 30 years of age. All participants were taking metformin. The authors included an active run-in period to try to titrate metformin to a target dosage of 2,000 mg per day. At the end of the run-in period, eligible participants had to have an A1C level between 6.8% and 8.5%. Those participants were randomly assigned to one of four therapies: (1) insulin glargine at an initial dosage of 20 units daily and adjusted upward, as needed; (2) the sulfonylurea glimepiride beginning at 1 to 2 mg per day to a maximum of 8 mg per day in divided doses; (3) liraglutide, a GLP-1 agonist, starting at 0.6 mg per day and titrating to 1.8 mg per day, as tolerated; or (4) the dipeptidyl-peptidase-4 inhibitor sitagliptin, 100 mg per day, with the dosage adjusted on the basis of renal function. At baseline, the participants' mean age was 57 years, 20% were Black, and most were being treated for comorbid hypertension and hyperlipidemia. After a mean of five years of follow-up, there was no significant difference among groups in microvascular outcomes such as albuminuria, peripheral neuropathy, and renal impairment (defined as a glomerular filtration rate of less than 60 mL per minute per 1.73 m^2). The primary cardiovascular outcome was the likelihood of any cardiovascular event, including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina warranting hospitalization, hospitalization for heart failure, or any need for revascularization. These occurred significantly less often in the liraglutide group (6.6% vs. 9.0% to 9.6% for the other groups; hazard ratio is significantly lower for liraglutide vs. sitagliptin comparison 0.68; 95% CI, 0.51 to 0.90). Liraglutide had the lowest rate of major adverse cardiovascular events (3.8% vs. 4.7% to 5.5%), hospitalizations for heart failure (1.1% vs. 2.1% to 2.4%), cardiovascular death (0.7% vs. 1.3% to 1.7%), and all-cause mortality (2.1% vs. 3.2% to 3.4%).

Study design: Randomized controlled trial (single-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Nathan DM, Lachin JM, Bebu I, et al.; GRADE Study Research Group. Glycemia reduction in type 2 diabetes - microvascular and cardiovascular outcomes.* N Engl J Med. *2022;387(12):1075-1088.*

Mark H. Ebell, MD, MS
Professor
University of Georgia
Athens, Ga.

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. ■