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ACEI Slows Progression of Renal Dysfunction

Clinical Question:

Does benazepril improve renal outcomes for patients with a creatinine level of >3.0 mg/dL?

Bottom Line:

In a group of nondiabetic patients with serum creatinine levels between 3.0–5.0 mg/dL, benazepril slows the progression of renal disease. These patients were carefully monitored for any changes in renal function during the first eight weeks and were carefully screened and monitored to detect any early adverse effects on renal function. (LOE = 1b)

Study Design:

Randomized controlled trial (double-blinded)

Funding:

Industry + government

Setting:

Outpatient (specialty)

Allocation:

Concealed

Synopsis:

Angiotensin-converting enzyme (ACE) inhibitors are known to slow the decline in serum creatinine levels in diabetic and nondiabetic patients with mild-to-moderate renal insufficiency (serum creatinine = 1.5–3.0 mg/dL). In this study, nondiabetic Chinese patients with more severe renal dysfunction (serum creatinine = 3.1–5.0 mg/dL) were studied to determine if this renal protective effect occurs at higher levels of dysfunction. The authors identified 422 patients—141 with a serum creatinine level between 1.5 and 3.0

mg/dL (133–265 μ mol/L) and 281 with a serum creatinine level between 3.1 and 5.0 mg/dL (274–442 μ mol/L). Their mean age was 45 years, and half were women. The authors then put all of the patients through an eight-week active run-in period to test their tolerance of the study drug, benazepril. This resulted in the exclusion of 94 patients, mostly for dry cough ($n=72$) but also because of an acute increase in serum creatinine ($n=9$), hyperkalemia ($n=5$) and for poor adherence ($n=8$). This type of active run-in inflates the apparent efficacy of the study drug. All remaining patients then received drugs other than ACE inhibitors or angiotensin-receptor blockers to control their blood pressure, since the goal was to identify any potential benefit of the ACE inhibitor above and beyond that of better blood pressure control. The authors then randomized the 224 remaining patients with serum creatinine levels from 3.1–5.0 mg/dL to receive benazepril 10 mg twice daily or placebo. The 104 patients with a serum creatinine level between 1.5–3.0 mg/dL all received benazepril 10 mg twice daily. Patients were followed up for a mean of 3.4 years and told to avoid sodium and potassium in their diet. The primary outcome was a combination of doubling of the serum creatinine level, the need for dialysis or transplantation, or death. It was reached by 41% of patients in the benazepril group and 60% in the placebo group ($P=0.004$; number needed to treat = 5; 95% CI: 3–18). There was a 51% reduction in the risk of doubling the serum creatinine ($P=0.02$) and a 40% reduction in the risk of end-stage renal disease ($P=0.02$). There was only one death in the entire study population, and adverse events were similar between groups. The results seen in this study will not be replicated in clinical practice, since the initial trial therapy with benzapril eliminated patients

who responded poorly to the treatment. Interestingly, the study was cosponsored by Novartis and the People's Liberation Army of China.

REFERENCE

Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med*. 2006;354:131-140.

Barrett's Esophagus Occurs in 1.6% of Population

Clinical Question:

How common is Barrett's esophagus (BE), and what is the relationship between reflux symptoms and BE?

Bottom Line:

BE is uncommon, and a large percentage of patients with BE do not have reflux symptoms. (LOE = 1b)

Study Design:

Cross-sectional

Funding:

Industry + government

Setting:

Population-based

Synopsis:

Although approximately 0.5–1.0% of patients with BE develop adenocarcinoma of the esophagus each year, the relationship between reflux symptoms and BE is less clear. In fact, many patients with esophageal cancer have no reflux symptoms at all. In this study, researchers contacted every seventh person in two neighboring communities in northern Sweden ($n=3000$) of whom 2,860 were available at the time of the study. Of this group, 2,122 (74%) completed a validated survey of abdominal symptoms by mail. The researchers then approached those who had completed the survey to request that they come in for upper endoscopy; 73% agreed. The par-

ticipants were similar to the overall population, with the exception that they were a mean of 3.7 years older (because of lower participation among symptom-free younger patients). In this way, a group of 1,000 patients who were fairly representative of the general population were assembled to undergo upper endoscopy. Their mean age was 53.5 years, and 51% were female. BE was found in 1.6% of the population, including 2.3% of those with reflux symptoms and 1.2% of those without symptoms ($P=0.18$). Since more patients did not have reflux than had reflux in the population, only 56% of patients with BE complained of reflux symptoms. The prevalence was 2.6% in those patients with esophagitis seen on endoscopy and 1.4% in those without objective evidence of esophagitis ($P=0.32$); only 25% with BE also had esophagitis. BE was more common in patients who smoked, drank alcohol or had a hiatal hernia.

REFERENCE

Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology*. 2005;129:1825-1831.

Diet High in Beta Carotene, Vitamins C and E, and Zinc May Reduce Risk of Macular Degeneration

Clinical Question:

Is a high dietary intake of beta carotene, vitamins C and E, and zinc associated with a reduced risk of age-related macular degeneration (AMD)?

Bottom Line:

A high dietary intake of beta carotene, vitamins C and E, and zinc reduces the risk of AMD. (LOE = 2b-)

Study Design:

Cohort (prospective)

Funding:

Government

Setting:

Population-based

Synopsis:

High-dose supplementation with beta carotene, vitamins C and E, and zinc slows the progression of AMD. It remains uncertain, however, whether regular dietary intake from normal daily foods is similarly effective. The investigators assessed dietary intake of all 10,275 residents aged ≥ 55 , of Rotterdam, the Netherlands. Of these, 6,780 (66%) took part in the ophthalmologic evaluation. Dietary intake was assessed by a questionnaire that was further validated with two-week food diaries. From a baseline cohort of 5,836 patients with no AMD in either eye, 4,170 (71%) were available for full follow-up at eight years. Of these, 560 persons (13.4%) were found to have incident AMD. Individuals blinded to dietary intake status performed all outcome assessments. An above-median intake of all four nutrients—beta carotene, vitamins C and E, and zinc—was associated with a 35% reduced risk (hazard ratio: 0.65; 95% CI: 0.46–0.92) of AMD. Statistical adjustments for potential confounders (e.g., smoking, serum lipid levels, blood pressure) did not change the results.

REFERENCE

van Leeuwen R, Boekhoorn S, Vingerling JR, et al. Dietary intake of antioxidants and risk of age-related macular degeneration. *JAMA*. 2005;294:3101-107.

Glucose Intolerance Predicts Mortality in Nondiabetics

Clinical Question:

Does a higher fasting glucose level or a higher two-hour postprandial glucose level in men predict mortality?

Bottom Line:

Higher fasting blood glucose lev-

els or two-hour postprandial blood glucose levels in middle-aged men are predictive of subsequent mortality. However, that doesn't necessarily mean that lowering their blood glucose with therapy reduces that mortality; this was not demonstrated in the U.K. Prospective Diabetes Study (UKPDS Group). *Lancet*. 1998; 352:837-853). (LOE = 1b)

Study Design:

Cohort (prospective)

Funding:

Government

Setting:

Population-based

Synopsis:

The researchers, starting back in 1963, enrolled 1,236 men in a longitudinal study of aging. None of the men had diabetes at the time of enrollment. At enrollment, the men were tested for fasting blood glucose levels and, later, also for two-hour postprandial glucose levels. They were followed up for an average of 13.4 years; follow-up was almost 100%. The mean age of the men at enrollment was 53 years, and 35% died during their follow-up period. Risk of mortality increased with a fasting glucose level of >110 mg/dL (6.1 mmol/l). At a glucose level of 110–125 mg/dL (6.1–6.9 mmol/l), the relative risk was 1.41 (95% CI: 1.01–1.97); at a glucose level of 126–139 mg/dL (7.0–7.7 mmol/l), the relative risk was 2.02 (1.09–3.73). Similarly, a two-hour postprandial glucose of >140 mg/dL (7.8 mmol/L) also predicted mortality.

One important caveat: this type of study shows a relationship that may or not be a cause. In other words, even though higher glucose levels were associated with higher mortality, it doesn't necessarily mean that lowering blood glucose levels will reverse this risk; the increased glucose levels could simply be a marker and not a cause of mortality.

REFERENCE

Sorkin JD, Fleg JL, Muller DC, et al. The relation of fasting and 2-h postchallenge plasma glucose concentrations to mortality. *Diabetes Care*. 2005;28:2626-2632.

Watchful Waiting Acceptable Option for Inguinal Hernia
Clinical Question:

Is it safe to defer surgical repair ("watchful waiting") in asymptomatic or minimally symptomatic men with inguinal hernias?

Bottom Line:

Watchful waiting is a safe and acceptable option for men with asymptomatic or minimally symptomatic inguinal hernias. Acute complications rarely occur, and patients who delay surgery are not at an increased risk of operative or postoperative complications. (LOE = 1b)

Study Design:

Randomized controlled trial (single-blinded)

Funding:

Government

Setting:

Outpatient (any)

Allocation:

Concealed

Synopsis:

Although many men with inguinal hernia are asymptomatic or minimally symptomatic, surgical repair is usually recommended to prevent complications, such as acute bowel incarceration. The investigators enrolled 720 men, aged ≥ 18 years, with asymptomatic or minimally symptomatic inguinal hernias. Subjects were randomized (concealed allocation assignment) to watchful waiting or to standard inguinal hernia repair. Complete follow-up occurred for 2–4.5 years for 90% of enrollees. Patients aware of treatment group assignment self-reported outcomes. Primary outcomes included

pain and discomfort interfering with usual activities and overall quality of life. Secondary outcomes included complications. Twenty-three percent of patients assigned to watchful waiting crossed over to received surgical repair, and 17% of subjects assigned to surgical repair crossed over to watchful waiting. Using intention-to-treat analysis, there were no significant differences reported between the two groups in pain-limiting activities or overall quality of life. Postoperative complications occurred similarly in patients initially assigned to surgical repair and in those who crossed over from watchful waiting. One watchful waiting patient experienced acute hernia incarceration without strangulation within two years, and one patient had acute incarceration with bowel obstruction at four years, with an overall complication rate of watchful waiting of 1.8/1,000 patient years. The sample size of 720 patients had a 90% power to detect a 10% difference for each of the primary outcomes.

REFERENCE

Fitzgibbons RJ Jr, Giobbie-Hurder A, Gibbs JO, et al. Watchful waiting vs repair of inguinal hernia in minimally symptomatic men. A randomized clinical trial. *JAMA*. 2006;295:285-292.

GERD Therapy Minimally Effective in Chronic Cough
Clinical Question:

In children and adults with non-specific cough, is treatment for gastroesophageal reflux effective in decreasing cough?

Bottom Line:

Treatment for gastroesophageal reflux disease (GERD) in patients with chronic cough may be effective in some patients, but the effect is not universal or consistent. It might be worth a try, but don't expect many patients to improve. (LOE = 1a)

Study Design:

Meta-analysis (randomized

controlled trials)

Funding:

Foundation

Setting:

Outpatient (any)

Synopsis:

For this meta-analysis, the researchers searched Medline, the Cochrane Controlled Trials Registry and EMBASE for research evaluating treatment of GERD in patients with cough lasting ≥ 3 weeks. They also searched the references of articles and contacted authors. Two reviewers independently reviewed the literature searches and selected the 11 studies included in this review. This approach to chronic cough has only been studied in 338 patients, and, for some results, the number of patients is small.

Two studies in children found some improvement in GERD symptoms but did not find a consistent effect on cough. The study results could not be combined for meta-analysis. In adults, only three studies, enrolling a total of 49 patients, evaluated the presence of cough at the end of the trial. None of these studies found a benefit, and there was not a significant benefit when the studies were combined. Cough scores in other studies also were not consistently improved with proton pump inhibitors; two studies of omeprazole, when combined, showed a small but significant improvement in cough scores, whereas two studies of other proton pump inhibitors failed to find an improvement. Two crossover studies, in which each patient received placebo and then active treatment, showed a significant improvement in cough scores during treatment, but the two studies only included 35 patients.

REFERENCE

Chang AB, Lasserson TJ, Kiljander TO, et al. Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. *BMJ*. 2006;332:11-14.