

trials. In a new, partly industry-supported, multinational trial, researchers randomized 208 patients (mean age, 42) with histories of recurrent vasovagal syncope to receive the β -blocker metoprolol (target dose, 100 mg twice daily) or placebo for 1 year. All had had positive responses to tilt testing.

During follow-up, syncope recurred in 75 patients. Recurrence rates were similar with metoprolol and placebo in both intent-to-treat and on-treatment analyses. Metoprolol also showed no prevention benefit in prespecified subgroups, including age (<42 vs. \geq 42) and response to tilt testing while on isoproterenol (positive vs. negative).

COMMENT:

This excellent study adds yet another strategy to the list of ineffective treatments for vasovagal syncope. Metoprolol is a selective β_1 -blocker, so we cannot exclude the possibility that a nonselective β -blocker might be effective, optimistic as that hope is. We need additional well-designed studies to determine whether other common, but still unproven, treatments (e.g., midodrine, fludrocortisone, paroxetine, increased salt and fluid intake) have therapeutic benefit.

— *Hugh Calkins, MD, The Johns Hopkins Hospital, Baltimore (Associate Editor, JW Cardiology)*

Sheldon R et al. Prevention of Syncope Trial (POST): A randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. Circulation 2006 Mar 7; 113:1164-70.

Metabolic Benefits of Calorie Restriction

Dramatic calorie restriction is associated with increased lifespan in rats. Whether such a relation exists in humans, however, remains unknown. In this randomized trial, researchers evaluated the 6-month effects of calorie restriction on various biomarkers of longevity.

A total of 48 overweight but otherwise healthy adults (body-mass index, 25–30 kg/m²; mean age, 38) were assigned to one of four groups: weight maintenance, 25% calorie restriction, 12.5% calorie restriction plus exercise, or very low calorie intake (890 calories daily until weight was reduced by 15%). Subjects were weighed and received reinforcement weekly; at months 3 and 6, they underwent a range of metabolic tests as inpatients.

Of the 48 subjects enrolled, 46 completed the study, yielding a 96% retention rate that the authors attribute to the generous compensation provided. At 6 months, all three intervention groups showed significant weight loss (10%–14% of baseline weight), as well as significant reductions in fasting insulin levels and DNA damage. Both the 25% calorie-restriction group and the 12.5% calorie-restriction group showed significantly reduced core body temperature.

COMMENT:

These improvements in biomarkers associated with longevity are, of course, only suggestive of an association between substantial calorie restriction and prolonged lifespan in humans. At the very least, the findings about the type of weight loss that can be achieved and maintained with intense behavioral intervention are impressive.

— *Thomas L. Schwenk, MD*

Heilbronn LK et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: A randomized controlled trial. JAMA 2006 Apr 5; 295:1539-48.

PE Is Common in COPD Exacerbation

Symptoms of pulmonary embolism (PE) and exacerbation of chronic obstructive pulmonary disease (COPD) are similar, and PE might consequently be underdiagnosed in patients with COPD. Researchers at an academic hospital in France performed spiral computed tomography angiography (CTA) in 211 current or former smokers hospitalized with severe COPD exacerbations that were considered to be of unknown origin (for example, no evidence of lower respiratory tract infection, pneumothorax, or iatrogenic cause).

Fourteen patients did not complete screening or had inconclusive CTA results. Of the 197 patients who underwent CTA, 43 (22%) had PE. Six additional patients had evidence of deep-vein thromboses on ultrasonography. Many clinical symptoms and signs (e.g., surgery, immobility, hypoxemia, dyspnea, pleuritic pain, tachycardia) were not significantly associated with PE. Only prior thromboembolic disease (risk ratio, 2.4), a decrease in PaCO₂ of 5 mm Hg from baseline (RR, 2.1), and malignancy (RR, 1.8) were significantly associated with PE.

COMMENT:

This single-center study should be replicated in other institutions. Nonetheless, the prevalence of pulmonary embolism in people with COPD exacerbations is very high. COPD exacerbation could represent another clinical situation in which we must be vigilant for PE.

— *Richard Saitz, MD, MPH, FACP, FASAM*

Tillie-Leblond I et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: Prevalence and risk factors. Ann Intern Med 2006 Mar 21; 144:390-6.

Combinations of Long-Acting Inhaled Agents for COPD



β -agonist and anticholinergic agents reduce symptoms in patients with chronic obstructive pulmonary disease (COPD). In this randomized, placebo-controlled, crossover study, European researchers examined the effect on lung function of combining the long-acting inhaled β -agonist formoterol and the long-acting inhaled anticholinergic tiotropium (Spiriva). The study was funded by the maker of tiotropium.

Each of 95 patients with COPD received 2-week courses of tiotropium alone (once daily in the morning), tiotropium plus formoterol (both once daily in the morning), and tiotropium once daily plus formoterol twice daily. At baseline and at the end of each 2-week period, pulmonary function was measured repeatedly during a 24-hour period.

Mean forced vital capacity, FEV₁, and inspiratory capacity increased from baseline levels with tiotropium alone. When once-daily formoterol was added to tiotropium, significant additional improvements in these measures were noted, mostly during the daytime. When formoterol was given twice daily, patients experienced additional incremental benefit overnight.

COMMENT:

This study demonstrates that combined therapy with two long-acting bronchodilators confers a short-term improvement in pulmonary function in patients with COPD; once-daily or twice-daily formoterol, added to tiotropium, were both better than tiotropium alone. Two remaining questions are whether these changes in pulmonary function are sustained during long-term treatment, and