Clinical Briefs in Primary Care

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Online Supplement to *Clinical Cardiology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Integrative Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports*

Volume 22, Number 12 December 2017

CV Benefits of GLP-1RA Treatment in Type 2 Diabetes

SOURCE: Holman RR, Bethel MA, Mentz RJ, et al. *N Engl J Med* 2017;377:1228-1239.

Only in the last several years have randomized, clinical trials confirmed a cardiovascular (CV) benefit from glycemic control. To date, sodium-glucose cotransporter 2 (SGLT-2) inhibitors (canagliflozin, empagliflozin), glucagon-like peptide-1 receptor agonist (GLP-1RA; liraglutide, semaglutide), and bromocriptine have demonstrated CV risk reduction convincingly.

Among the SGLT-2 inhibitor and GLP-1RA classes of pharmacotherapy, there appears to be much more similarity than not. Should clinicians consider these salubrious CV effects a class effect? That is, should all members of the class be anticipated to experience similarly favorable CV outcomes?

The authors of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial randomized type 2 diabetics (n = 14,752) to either 2 mg of the GLP-1RA exenatide or placebo added to whatever ongoing diabetes regimen they already were receiving. The mean baseline A1c was 8.0%, and > 70% of participants presented with pre-existing CV disease.

After 3.2 years (mean) of intervention, exenatide failed to demonstrate a statistically significant improvement in the composite CV endpoint vs. placebo. Although all the answers are not known, the EXSCEL trial suggests there might be important differences among the class of GLP-1RA in reference to cardiovascular outcomes. Is it a class effect? Maybe not. ■

Morphine in Dyspneic Acute Heart Failure

SOURCE: Miró Ò, Gil V, Martín-Sánchez FJ, et al. *Chest* 2017;152:821-832.

Patients who experience acute heart failure (aHF) often are burdened with distressing dyspnea and its concomitant heightening of anxiety. Historically, clinicians have used morphine in these situations.

These decisions have been based on physiologic effects, such as preload and afterload reduction, as well as putative central nervous system effects, including reduced anxiety, breathlessness, and pain.

Unfortunately, morphine use in such settings is neither adequately supported nor refuted by clinical trial data.

Miró et al reviewed the data on a large population of aHF patients between 2011 and 2014 (n = 6,516). Investigators compared persons who received IV morphine within three hours of admission to an emergency department to those who did not.
From this larger population of aHF patients, a subgroup who could be matched for a wide variety of other variables was selected for analysis (n = 550). Patients treated with morphine demonstrated a hazard ratio for 30-day mortality of 1.66.

The authors suggested that based on these data, clinicians should avoid morphine use in aHF patients. ■

New Pharmacologic Direction for Parkinson's Disease

SOURCE: Athauda D, Maclagan K, Skene SS, et al. *Lancet* 2017 Aug 3. pii: S0140-6736(17)31585-4. doi: 10.1016/S0140-6736(17)31585-4. [Epub ahead of print].

Most clinicians are used to thinking about dopamine modulation when considering treatments for Parkinson's disease. Unfortunately, none of the current treatments can be designated as disease-modifying, even though such treatment provides transient symptomatic relief.

Current use of a glucagon-like peptide-1 receptor agonist (GLP-1RA) is limited to the management of type 2 diabetes. From where did the idea emerge that GLP-1RA might benefit Parkinson's patients?

The authors of studies about Parkinson's based on animal models have noted that a GLP-1RA not only crosses the blood-brain barrier, but produces sufficient neuroprotective and neurorestorative effects to improve motor function and memory. Investigators who conducted a subsequent

open-label, one-year pilot trial of exenatide in humans with Parkinson's disease found favorable effects that endured for an additional 12 months post-treatment.

Based on these early successes, Athauda et al performed a randomized, double-blind, placebo-controlled trial of exenatide administered in weekly, subcutaneous, 2 mg doses (n = 62) for 48 weeks added to whatever current regimen study participants were receiving. The primary outcome was the motor performance subscale of a Parkinson's disease rating scale, measured 12 weeks after discontinuing exenatide treatment.

Motor function improvements were demonstrated in exenatide-treated patients, whereas investigators noted deterioration in placebo patients. Larger, longer-term studies will be needed before GLP-1RA treatment could be confirmed as an appropriate consideration for Parkinson's patients. ■

CLINICAL BRIEFS IN PRIMARY CARE™
is published monthly by AHC Media, a Relias Learning company.

Executive Editor: Leslie Coplin
Physician Editor: Stephen Brunton, MD
Editor: Jonathan Springston

STATEMENT OF FINANCIAL DISCLOSURE
To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Brunton reports he is a retained consultant for Abbott Diabetes, Actavis, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Cempra, Janssen, Lilly, Merck, Novo Nordisk, Sanofi, and Teva; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Dr. Kuritzky (author) is a retained consultant for and on the speakers bureau of Allergan, Daiichi Sankyo, Lilly, and Lundbeck. Ms. Coplin, Mr. Springston, and AHC Media Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

SUBSCRIBER INFORMATION
Customer Service: (800) 688-2421
Email Address: jspringston@reliaslearning.com
Website: AHCMedia.com

Address Correspondence to: AHC Media, a Relias Learning company, 111 Corning Road, Suite 250, Cary, NC 27518.

AHC Media
A RELIAS LEARNING COMPANY

Searching for Answers on Knee Osteoarthritis

SOURCE: Bartels EM, Henrotin Y, Bliddal H, et al. *Osteoarthritis Cartilage* 2017;25:1641-1646.

It is well-recognized that overweight and obesity are associated with osteoarthritis. Lest one becomes overly simplistic and assigns degenerative joint changes solely to the extra stress of excess weight, one should recognize that osteoarthritis of the hands also is associated with obesity, although it would be difficult to conjure any additional joint-loading burden.

At the same time, data consistently show that for knee osteoarthritis, weight loss is associated with symptomatic and functional improvement. The mechanism of this is incompletely understood, since weight loss has not been shown to affect the progressive degradation of cartilage typical of osteoarthritis.

Bartels et al studied biomarkers of collagen breakdown in persons with knee osteoarthritis who lost weight, wondering whether these potentially more sensitive indicators would corroborate that the symptomatic improvements seen with weight loss were actually reflecting less cartilage degradation that was too subtle to be identified radiographically. At the conclusion of the trial, changes in biomarkers were not found to be associated with symptomatic improvements. ■

Cardiorespiratory Fitness and Mortality

SOURCE: Ehrman JK, Brawner CA, Al-Mallah MH, et al. *Am J Med* 2017;130:1177-1183.

In both men and women in the United States, levels of cardiorespiratory fitness are inversely related to mortality. An encouraging epidemiologic study of women (the Nurses' Health Study, n = 72,488) found that even brisk walking for about 30 minutes daily was associated with near maximal cardiovascular (CV) health benefits. Additionally, even sedentary women who became physically active later in life enjoyed CV risk reduction.

But does race make a difference? African-Americans demonstrate higher CV event rates and mortality than Caucasians, which has been linked to disparities in hypertension, access to care, and other causes. However, for similar levels of fitness, are outcomes different between ethnicities? Investigators performed a retrospective analysis of data from a nine-year follow-up of patients (n = 13,345) who had undergone exercise treadmill testing at Henry Ford Hospital in Detroit on at least two occasions.

Approximately 75% of the population was Caucasian and 25% African-American. An analysis of fitness level in relation to mortality showed no meaningful difference between groups: For both ethnicities, each one metabolic equivalent increment of cardiorespiratory fitness was associated with a 13-16% reduction in mortality. ■

Considering Systemic Treatment for Atopic Dermatitis

SOURCE: Simpson EL, Bruin-Weller M, Flohr C, et al. *J Am Acad Dermatol* 2017;77:623-633.

Most patients with atopic dermatitis can control their disease with topical agents, including corticosteroids, calcineurin inhibitors (e.g., pimecrolimus, tacrolimus), local hygienic measures (e.g., moisturizers), and, most recently, a topical phosphodiesterase-4 inhibitor (crisaborole). A recent panel of eczema experts convened to provide advice about when clinicians should consider systemic treatment.

Their first recommendation was to optimize topical treatments. Patients refractory to topicals should be assessed for the presence of contact allergy (e.g., patch testing), as well as for the presence of viral, bacterial, or yeast cutaneous disease. Prior to the institution of systemic therapy, a trial of phototherapy should be considered.

If none of these interventions are sufficient, there are five different systemic therapies to consider: azathioprine, cyclosporine, dupilumab, methotrexate, and mycophenolate. At this stage of disease, most patients will be best served by referral to a dermatologic specialist. ■