Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

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Consequences of NSAID Use in Patients Receiving Post-MI Antithrombotic Prophylaxis

SOURCE: Olsen AMS, et al. *JAMA* 2015;313:805-814.

Most patients receive antiplatelet treatment after an acute coronary syndrome. Combinations of antiplatelet agents (e.g., ASA, clopidogrel) reduce risk of recurrent MI — particularly stent thrombosis — but do have a modest increase in bleeding risk. Well, what about our post-MI patients who are taking appropriately prescribed antiplatelet agents who also require treatment with NSAIDs for disorders like osteoarthritis, migraine, etc? How does such multidrug co-administration affect risks?

Olsen et al recently published results from data collected through Danish nationwide administrative registries that assessed bleeding events and cardiovascular events based on prescription data from 62,971 adults. The cohort evaluated included adults over age 30 (mean age = 68 years) who were admitted for a first MI in the 2002-2011 interval.

Rates of bleeding were doubled when NSAID users (that is, NSAIDS + antithrombotic treatment) were compared with non-users (that is, antithrombotic treatment alone). Equally concerning, the hazard ratio for cardiovascular (CV) events was 40% greater in NSAID users than non-users, irrespective of particular type of NSAID prescribed or duration of use.

This report should prompt clinician vigilance in post-MI patients taking antithrombotic therapy to limit the use of NSAIDs to the minimum necessary. ■

Psoriasis Is Associated with Insulin Resistance

SOURCE: Gyldenlove M, et al. *J Am Acad Dermatol* 2015;72:599-605.

The pathophysiology of psoriasis has much in common with rheumatoid arthritis (RA). Recently, pharmacotherapies that had been primarily used in RA have enjoyed successful application in psoriasis, leading to marked improvements or even remission. Of concern, both RA and psoriasis have been recognized as risk factors for cardiovascular disease. Psoriasis is also a risk factor for diabetes, but the mechanism remains ill-defined.

A consistent finding in patients with type 2 diabetes is the presence of insulin resistance, usually associated with obesity. Might psoriasis also be associated with insulin resistance, independent of obesity? To answer this question, Gyldenlove et al compared psoriatic patients with controls of similar age (mean = 44 years) and BMI (mean = 26, [overweight]), all of whom had undergone laboratory screening (fasting glucose and A1c) to exclude undiagnosed diabetes.

Insulin sensitivity was substantially reduced in patients with moderate-to-severe psoriasis compared to controls, even though there was no manifest glucose intolerance. Hence, psoriasis might be considered a prediabetic state. ■

Difficult Questions About Testosterone and Mortality

SOURCE: Eisenberg ML, et al. *Int J Impot Res* 2014;27:46-48.

The number of men receiving treatment for hypogonadism has increased dramatically over the past decade. At the same time, some clinical trials have suggested that there are safety issues with testosterone. For instance, one trial of frail seniors was stopped early because of an increased mortality signal. Other clinical trials have not demonstrated similar risk. Ultimately, the only way the question about testosterone safety can be convincingly answered is by performance of a large randomized, prospective trial, similar to the Women's Health Initiative (WHI).

In the meantime, other trial data may inform clinician choices about testosterone replacement. For instance, Eisenberg et al published their results of a retrospective analysis of the andrology database at Baylor College of Medicine (Houston, Texas), which included 509 hypogonadal men, approximately half of whom were treated with testosterone replacement (injectable or transdermal).

In a 10-year follow-up interval, the mortality rate trended lower in men receiving testosterone replacement than controls, but the difference was not statistically significant. Although such results cannot provide a definitive answer to the question of the relationship between testosterone replacement and mortality, they are reassuring for hypogonadal men who are enjoying symptomatic improvement through testosterone replacement. ■

Treatment of OSA Reduces Risk of Repeat Revascularization After PCI

SOURCE: Wu X, et al. Chest 2015;1478:708-718.

Obstructive sleep apnea (OSA) is associated with numerous comorbidities and downstream consequences, not the least of which are increased cardiovascular events, hypertension, and arrhythmias. The increased sympathetic tone associated with

OSA is usually considered a major culprit in the evolution of such adversities. While the associations between OSA are strong and consistent across numerous reports and diverse populations, outcomes trials showing concrete endpoint reduction through successful treatment of OSA are less evident.

The clinical trial data reported by Wu et al confirm very favorable results in a very specific population: Persons with sleep laboratory-confirmed OSA (n = 390) who had undergone PCI were followed over 4.8 years (median). The primary endpoint of interest was whether treatment of OSA affected the incidence of revascularization compared to untreated OSA. Treatment of OSA by CPAP was confirmed at 3-monthly intervals for the first year, and annually thereafter.

The incidence of coronary revascularization was almost twice as high in the untreated OSA group than in the treated OSA group (26.1% vs 14.1%, P = 0.019). Although there were statistically significant differences between groups as far as overall mortality or cardiovascular events, outcomes at 5 years tended to favor the CPAP-treated OSA patients. OSA treatment reduces the need for revascularization in persons who have undergone PCI. ■

Ongoing Saga of Homocysteine and Vasculopathy

SOURCE: Catena FC, et al. *J Am Soc Hypertens* 2015;9:167-175.

The relationship between homocysteine (hCYS) and vascular disease has been recognized for at least 2 decades. Indeed, the strength of the association between plasma hCYS levels and coronary atherosclerosis surpasses that of cholesterol. Once this relationship was publicized, a flurry of enthusiasm for modulation of hCYS ensued, based largely on the strong observational data and the simplicity with which hCYS can be lowered: supplementation with folate and B vitamins. Since these treatments are not associated with meaningful toxicity at appropriate doses, there appeared to be much to celebrate: an easy, inexpensive fix for an important health problem.

After a bevy of trials in which hCYS lowering failed to show risk reduction for CV events, need for revascularization, etc., one editorialist confidently announced "The homocysteine hypothesis is dead!". Well, apparently some still feel a faint pulse.

Catena et al published their data looking at the relationship between hCYS and carotid disease among hypertensive patients. They found that carotid intima-media thickness was linearly related to hCYS levels, independent of age, BP, and CRP.

Since no clinical trials have shown a favorable impact of hCYS modulation, why should clinicians care? The authors bring up the interesting proposition that since elevated hCYS is a recognized risk factor for vasculopathy, it might help influence treatment decisions for management of persons at risk for CVD. Perhaps, for instance, elevated hCYS might tip the balance of a treatment decision for persons with a strong family history of vascular disease, but borderline risk factors (e.g., BP, lipids, glucose). ■

Clindamycin vs TMP-SMX for Skin Infections

SOURCE: Miller LG, et al. *N Engl J Med* 2015;372:1093-1103.

The treatment of cellulitis, with or without a local abscess, has become more complicated since MRSA (methicillin-resistant *Staphylococcus aureus*) has assumed the causal role of "guilty until proven otherwise" in such settings. Although there has been some suggestion in the literature that antibiotic treatment may not be necessary once an abscess — even a MRSA abscess — has been incised and drained, oftentimes there is sufficient cellulitis surrounding the abscess that clinicians may feel uneasy to omit antibiotics. Hence, the decision for treatment of uncomplicated skin infections boils down to which antibiotic?

Miller et al performed a double-blind, randomized comparison trial among patients (n = 524) with cellulitis and/or abscess, including 155 children. Subjects were randomized to treatment with 10 days of either oral clindamycin (CLIN) or trimethoprim-sulfamethoxazole (TMP-SMX). The primary outcome of the trial was clinical cure at 7-10 days post-antibiotic treatment.

There was no difference in clinical cure rate between the two treatment arms, nor was there any meaningful difference in adverse events, including *Clostridium difficile*-associated diarrhea (no cases, either treatment arm). The efficacy and safety of CLIN and TMP-SMX for uncomplicated skin infections appear comparable. ■

Roflumilast for Acute Exacerbations in COPD

SOURCE: Martinez FJ, et al. *Lancet* 2015; 385:857-866

Acute exacerbations of COPD (AE-COPD) are potentially highly consequential: in-hospital mortality is approximately 10%, and up to 25% of patients admitted to the ICU die. Additionally, AE-COPD is associated with a decline in pulmonary function that is not regained once the exacerbation is resolved. Fortunately, several of the tools we use to treat COPD are associated with reduced frequency of exacerbations.

Roflumilast (ROF) is a PDE-4 inhibitor that has been shown to reduce AE-COPD and has FDA labelling for that indication. Martinez et al have published the results of their multicenter randomized, double-blind, placebo-controlled trial that sought to determine whether ROF reduces exacerbations compared to placebo in severe COPD patients who are already on background combination therapy of inhaled long-acting beta-agonist plus inhaled corticosteroid (n = 1945).

After 1 year of treatment, the rate of AE-COPD was statistically significantly lower in persons who were treated with ROF than placebo. The adverse events rates were similar in the ROF and placebo groups. Additionally, hospital admissions for AE-COPD were significantly reduced in the ROF group vs placebo. The addition of ROF to the regimen of patients with severe COPD already using combination therapy with beta-agonists and inhaled corticosteroids can reduce exacerbations and hospitalizations related to exacerbations. ■

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Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Leslie Hamlin.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: leslie.hamlin@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

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