Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

VOLUME 15, NUMBER 5 PAGES 9-10 MAY 2011

Long-Term CV Effects of Intensive Glucose Lowering: The ACCORD Study

Source: Gerstein HC, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 2011;364:818-828.

THE ACTION TO CONTROL CARDIOVASCULAR risk in diabetes (ACCORD) study is really three studies in one, providing information about blood pressure, glucose, and triglyceride treatment in high-risk diabetic patients. Probably the most unsettling component of ACCORD was the early termination of the comparison of tight glucose control (attainment of an A1c < 6) with standard control (A1c 7-7.9) due to an unanticipated INCREASE in mortality associated with tight control. The glucose control arm of ACCORD was designed to go on for 5 years, but intensive glucose control was stopped at 3.5 years. Though various explanations for these results have been offered, none is wholly satisfying.

Once the increased mortality of tight control was appreciated, ALL study subjects were switched to the standard control regimen and followed to the 5-year mark. This most recent publication details outcomes of persons who originally were treated with tight control, and then were switched to standard control for the next 17 months.

Just as had been seen in the initial results of ACCORD, the group that had been assigned to tight control (even though now they had been receiving more relaxed control, and their A1c had risen 7.2%) continued to experience a statistically significant 19% greater risk for death. During Phase 2 of ACCORD, the frequency of hypoglycemia was the same between the standard control group and the group that had changed from tight to standard control; hence, although the greater frequency of hypoglycemia seen in tight control had received some focus as a culprit in inducing greater mortality, this follow-up suggests that is not the case. Why tight control is associated with increased mortality remains unknown. ■

Cysteine as a Biomarker for Sleep Apnea

Source: Cintra F, et al. Cysteine: A potential biomarker for obstructive sleep apnea. *Chest* 2011;139:246-252.

OBSTRUCTIVE SLEEP APNEA (OSA) IS CONsistently associated with cardiovascular misadventure: An increased risk for hypertension, tachycardia, cardiac arrhythmia, myocardial infarction, and stroke has been noted. OSA seems to reset the sympathetic nervous system to a higher level of activity, thus explaining some of these adversities. Tools to identify OSA are somewhat cumbersome and expensive. Were biomarkers available to identify OSA, clinicians could better reserve expensive confirmatory testing for persons with higher pre-test likelihood of disease.

Animal studies have found that sleep deprivation and hypoxia produce elevations in cysteine (CYS). Cintra et al measured CYS levels in subjects undergoing sleep studies (n = 75) and a group of matched controls (n = 75). A non-obese OSA subgroup was included to ascertain whether obesity has an impact on CYS.

CYS levels were significantly higher (15%-17%) in OSA subjects than controls ($P < 0.01$), whether obese or lean. A 6-month period of CPAP treatment resulted in a reduction of CYS levels. No pathogenetic role of CYS is known, but if further studies confirm the relationship between CYS and OSA, it may serve as a reasonable screening tool for selecting those who might benefit from sleep studies. ■

Steroid or Steroid Plus Long-Acting Beta Agonist for Mild Persistent Asthma

Source: Postma DS, et al. Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control. *Chest* 2011;139:311-318.

THE LARGEST BODY OF ASTHMATICS IS classified as mild persistent asthma, defined as daytime symptoms more than once weekly but not daily, nocturnal symptoms less than once weekly, and essentially normal lung function between exacerbations. At this stage, long-term controller medications — inhaled corticosteroids (ICS) or leukotriene inhibitors (LKT) — are suggested, reserving combination inhaled corticosteroid/long-acting beta agonist (ICS/LABA) for refractory cases or patients who progress to moderate persistent asthma and beyond. LABA monotherapy is no longer considered appropriate for asthma patients at any stage of disease.

Ciclesonide (CIC) is a novel ICS with

at least two favorable attributes: once daily dosing, and minimal hypothalamic pituitary axis perturbation at typical clinical doses. This clinical trial compared low-dose CIC with low-dose fluticasone/salmeterol in patients with mild persistent asthma (n = 657). The two co-primary endpoints were time to first severe asthma exacerbation and number of poorly controlled asthma days.

CIC alone was not superior to placebo in time to first severe asthma exacerbation, but ICS/LABA was. Other aspects of asthma control were comparable between the two regimens. Although ICS alone is advocated as appropriate initial treatment for mild persistent asthma, this comparison trial suggests that ICS/LABA provides at least one aspect of superiority. ■

Bisphosphonates and Femoral Fractures

Source: Park-Wyllie LY, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA* 2011;305:783-789.

ALTHOUGH BISPHOSPHONATES (BIS) HAVE A proven track record for reduction of osteoporotic fracture, reports of so-called "atypical" femoral fracture associated with BIS use has called for re-examination of the risk-benefit ratio of BIS. To do so, a case-control study of more than 200,000 Canadian women who had received BIS was performed. In this population, 716 atypical fractures occurred, and 9,723 typical osteoporotic fractures occurred.

BIS treatment of osteoporosis has been shown to reduce typical fractures by about one-fourth. Since typical fractures are 15-20 times more common than atypical fractures, approximately four times as many more atypical fractures than have been reported would have had to occur to make the risk-benefit ratio unfavorable. Additionally, not all atypical fractures are attributable to BIS use. Finally, the increased risk for atypical fracture was much more common in subjects who used BIS for more than 5 years.

Atypical fractures are an appropriate concern. Nonetheless, the typical fracture risk reduction far outweighs risk of atypical fracture induction. Risk for atypical fracture might be reduced by suggesting a drug holiday after 5 years of BIS use, particularly in women at the lower end of the spectrum of risk. ■

Can Antihypertensive Treatment Benefit Persons Without Hypertension?

Source: Thompson AM, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: A meta-analysis. *JAMA* 2011;305:913-922.

CLINICAL TRIAL DATA HAVE SHOWN THAT more than one-third of persons with prehypertension (130-139/86-89 mm Hg) will develop frank hypertension over a 4-year interval. Indeed, the lifetime risk of developing hypertension in the U.S. general population is approximately 90%. Although treatment of hypertension provides important risk reduction, clinicians rightfully wonder whether providing antihypertensive treatment to high-risk individuals (e.g., diabetics, persons with manifest cardiovascular disease) — at the stage of prehypertension or even before — might be beneficial.

Thompson et al performed a meta-analysis on 25 clinical trials that treated persons with prehypertension or normotension (total n = 40,395). Antihypertensive treatment classes included beta-blockers, ACE inhibitors, ARBs, calcium channel blockers, and diuretics, either alone or in combination.

Outcomes consistently favored antihypertensive treatment: The relative risk of stroke was reduced by 23%, MI by 20%, CHF by 29%, and all-cause mortality by 13%, all of which were statistically significant. These results suggest that patients at high risk of cardiovascular disease may benefit from use of antihypertensive pharmacotherapies at lower blood pressure than traditionally used as a threshold. ■

More Salt, Fewer Deaths in Diabetes: Who Would Have Thunk It?

Source: Ekinci EI, et al. Dietary salt intake and mortality in patients with type 2 diabetes. *Diabetes Care* 2011;34:703-709.

IN THE GENERAL POPULATION, THERE IS A linear and reversible relationship between salt intake and blood pressure (BP): more salt in begets higher BP, and salt restriction lowers BP. Although it is generally accepted that BP lowering through antihypertensive medications in hypertensive diabetics improves cardiovascular outcomes, whether BP reduction attainable through lifestyle measures, such as salt restriction, might produce similar improvements has not been well documented. Indeed, salt restriction has the capacity to activate neurohumoral systems that are potentially particularly detrimental to diabetics; for instance, salt restriction can activate the sympathetic nervous system and the renin-angiotensin-aldosterone system, and can reduce insulin sensitivity — each of which can be problematic — particularly for diabetics.

Ekinci et al performed a prospective cohort study on diabetics attending a single diabetes clinic (n = 638). Salt intake was ascertained by 24-hour sodium excretion at baseline and each follow-up visit for the ensuing 10-year period of observation.

After adjustment for other risk factors, the relationship between salt intake and mortality was INVERSE. Specifically, for every 100 mmol INCREASE in sodium excretion, all-cause mortality DECREASED by 28%! Arguments about salt have raged for decades; the authors point out that other previous studies (but none previously specifically in diabetics) have NOT consistently found an association between salt intake and mortality. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.
This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.