Clinical Briefs in Primary Care

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Evidence-based updates in primary care medicine

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Spironolactone Best Add-on for Resistant Hypertension

SOURCE: Williams B, et al. *Lancet* 2015;386:2059-2068.

Resistant hypertension (r-HTN) is currently defined as persistence of uncontrolled blood pressure (BP) despite full therapeutic doses of three antihypertensive medications, one of which is diuretic. As evidenced by clinical trial data, the prevalence of r-HTN is generally in the 15-18% range. While it is appropriate to seek a secondary cause for r-HTN (e.g., sleep apnea, aldosteronism, etc.), an underlying correctable cause is not identified in most cases, so additional medications must be added to attain BP goals. While essentially any medication not already present in the three-medication regimen could be considered as an add-on, several clinical trials point to the utility of aldosterone antagonists such as spironolactone and eplerenone, demonstrating considerable success in controlling otherwise resistant hypertension. But is aldosterone antagonism the best way to go? Williams et al reported results of their double-blind, placebo-controlled, crossover trial in adults with r-HTN. Study subjects (n = 285) were randomized to one of four treatment arms: spironolactone, doxazosin, bisoprolol, or placebo added to their current three-drug regimen. Treatment periods lasted 12 weeks. Spironolactone provided statistically significant greater reductions in BP than the other two active agents; adverse effects and withdrawal were similar among the three active treatment arms. Spironolactone is an inexpensive and effective way to address r-HTN. ■

Good Cardiovascular News from the SGLT2 Inhibitor Class?

SOURCE: Zinman B, et al. *N Engl J Med* 2015;373:2117-2128.

Current FDA regulations require that new pharmacologic agents to treat diabetes must demonstrate cardiovascular safety in addition to glucose lowering. The rationale for this stipulation is that some very early clinical trials with sulfonylureas in type 2 diabetes (T2DM) suggested a negative effect on cardiovascular outcomes, and successive clinical trials have failed to demonstrate statistically significant improvements in cardiovascular outcomes, despite excellent glucose control. Indeed, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial suggested a potential worsening of cardiovascular outcomes and mortality in tightly controlled T2DM patients (A1c < 6.5). The cardiovascular safety trial for empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, is known as the EMPA-REG trial. Investigators randomized T2DM patients (n = 7020) to empagliflozin or placebo for 3 years. At the conclusion of the trial, the primary outcome (a composite of death from cardiovascular cases, nonfatal myocardial infarction, and nonfatal stroke) was 14% better in the treatment group than placebo (absolute risk reduction 1.7%). While these results were the source of much celebration when presented at the European Association for the Study of Diabetes meeting in Stockholm, Sweden, in September 2015, there are reasons for pause. First, clinical trials with two other SGLT2 inhibitors (dapagliflozin, canagliflozin), which work by essentially comparable mechanisms, have not yet completed their cardiovascular safety trials. On the other hand, the cardiovascular outcomes from trial data thus far accrued with both of these other agents does not suggest cardiovascular risk reduction. Until FDA-mandated cardiovascular risk trials are completed with each of the agents of this class, whether individual agents might provide particular cardiovascular benefits or not will remain speculative. Second, it is difficult to reconcile how a trial that did not show a reduction in fatal or nonfatal myocardial infarction and did not show a reduction in fatal or nonfatal stroke achieved a reduction in cardiovascular mortality. Isn't the combination of stroke + myocardial infarction the primary constituent of cardiovascular mortality? For the time being, physicians will have to defer to the statistical wisdom of clinical trial data experts to decipher this intuitively self-contradictory result. While some physicians may want to celebrate the possible discovery of a pharmacologic treatment for T2DM associated with improved cardiovascular outcomes, I am not there yet. ■

Vitamin D: Conclusions From an NIH Conference

SOURCE: Taylor CL, et al. *Am J Med* 2015;128:1167-1170.

Clinicians continue to have well-founded uncertainties about how to best capture potential benefits of vitamin D. Although there is no doubt that vitamin D deficiency impairs skeletal health, the optimum application of vitamin D supplementation for otherwise healthy persons is ill-defined.

Fairly strong evidence supports vitamin D supplementation in frail seniors to prevent falls. Beyond that, there is little definitive evidence on which to rely. Observational studies indicate that low vitamin D status is associated with risk for cardiovascular disease, cancer, diabetes, and other important disorders, but whether this relationship is causal is not yet known, and whether correction of such a causal relationship (if established) will improve outcomes remains to be determined. The NIH conference confirmed that 25(OH) vitamin D remains the preferred metric, while acknowledging that consensus does not exist to specifically define optimum vitamin D levels or a specific threshold indicative of deficiency. Equally confounding is the acknowledgement that methods for measuring 25(OH) vitamin D are not standardized and may vary from laboratory to laboratory by as much as 20%. Currently recommended supplemental doses of vitamin D (400-1000 IU/d) are generally considered safe, but concern for toxicity was expressed in reference to megadosing (10,000-50,000 IU/d). ■

Prostate Cancer Screening: Have Clinicians Been Listening?

SOURCE: Jemal A, et al. *JAMA* 2015;314:2054-2061.

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Prostate cancer screening has been an embattled topic for more than a decade. While intuitively appealing to both the clinician population and mid-life males, outcomes from large clinical trials could not confirm improvements in overall survival subsequent to screening, and, with the exception of one large trial with contentious results, data were similarly unsupportive of even reduced mortality related to prostate cancer itself. Showing how the same data can be perceived differently by different experts, the U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA) screening. The American Cancer Society endorses it in men > 50 years of age with at least a 10-year life expectancy. The American Urologic Association recommends PSA screening in men 55-59 years of age. In 2008, the USPSTF recommended against PSA screening in men > 75 years of age, after which there was a minimal decline. Did clinicians heed the 2012 USPSTF advice to cease screening in asymptomatic men regardless of age? Jemal et al reviewed data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population (n = 446,000) to compare PSA screening rates between 2005 and 2013. They found an 18% decline in prostate cancer screening between 2010-2013, which was independent of age and included both younger men and men > 75 years of age. Modeling methods have been published that suggest we might experience an increase in prostate cancer mortality by omission of universal screening; to date, that has not been the case, but it may require a longer window of observation before reaching definitive conclusions. ■

Potential Benefits of Down Titration Through Inhaled Steroid Discontinuation

SOURCE: Suissa S, et al. *Chest* 2015;148:1177-1183.

For patients with moderate to severe chronic obstructive pulmonary disease (COPD), combination treatment often includes anticholinergics, long-acting beta-agonists, and inhaled corticosteroids (ICS), the latter two treatments most commonly combined into a single inhalation device. As many as 85% of COPD patients are prescribed ICS, though many may fall below the threshold for ICS treatment recommended by FDA labeling or guidelines. Observational data have reported an increased incidence of pneumonia in COPD patients who used ICS, which prompts the question of whether discontinuation of ICS reduces the likelihood of pneumonia. Suissa et al used the Quebec health insurance database to evaluate a population of COPD patients who had been prescribed ICS (n = 103,386). Among this population, a comparison was made of the incidence of pneumonia in patients who continued to be treated with ICS vs those COPD patients who had discontinued ICS. The period of observation was approximately 5 years. They found that the likelihood of serious pneumonia was reduced by 37% in patients who discontinued ICS vs those who remained on ICS. Risk reduction was demonstrated as quickly as the first month post-ICS cessation. Among ICS treatments, risk reduction was more dramatic with fluticasone cessation (42%) than budesonide (13%), but omitting either ICS was beneficial for pneumonia risk reduction. The authors suggested that ICS may be currently over-prescribed, and that limiting their use could reduce the risk for pneumonia without compromising quality of care. ■

Expanding Safe Prescribing for Metformin

SOURCE: Tuot DS, et al. *Diabetes Care* 2015;38:2059-2067.

Metformin is the pharmacologic foundation of most guidelines for management of type 2 diabetes (T2DM), based on its efficacy, safety record, and the availability of favorable clinical trial outcomes data. Although serious adverse effects from metformin are rare, significant renal insufficiency increases the risk for lactic acidosis, which can be fatal. Original FDA labeling suggested renal safety boundaries based on serum creatinine (sCR), but when first devised, the boundaries (sCR < 1.4 for women, < 1.5 for men) were based on doses of metformin up to 3000 mg/d. Currently, the maximum approved dose (2550 mg/d) is not thought to be meaningfully more efficacious than 2000 mg/d, hence the commonplace prescription of metformin 1000 mg twice a day. Recent recommendations suggest that metformin is safe when eGFR is > 45 mL/min, but the risk rises significantly when eGFR < 30 mL/min (30 mL/min to 45 mL/min eGFR is an "indeterminate" zone). Using data from the National Health and Nutrition Examination Survey (NHANES) population (n = 3902), the investigators determined that as many as 15% of patients who were excluded from metformin based on sCR would have been eligible for metformin based on a eGFR of > 45 mL/min. In an era of progressively more expensive interventions for T2DM, clinicians may wish to re-evaluate the boundaries of safe prescribing for metformin. ■