Clinical Briefs in Primary Care

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Evidence-based updates in primary care medicine

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## Minimizing Risk of NSAID-associated Recurrent Gastrointestinal Bleeding

SOURCE: Chan FKL, Ching JYL, Tse YK, et al. *Lancet* 2017;389:2375-2382.

Gastrointestinal bleeding (upper and/or lower) is a well-recognized adverse effect of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). The COX-2 inhibitors (e.g., celecoxib) were offered to clinicians as an alternative to "non-selective" COX inhibitors (NSAIDs such as ibuprofen, diclofenac, naproxen, and many others). The putative advantage of celecoxib was an anticipated reduced risk of gastrointestinal bleeding, since relatively less COX-1 (the enzyme necessary to maintain gastric mucosal protection integrity) inhibition was occurring than with "traditional" non-selective NSAIDs. While the CLASS trial corroborated that during a six-month period, celecoxib incurred fewer serious bleeding events than non-selective NSAID therapy. This trial drew criticism later after an analysis of the study data at one year showed no meaningful differences between treatment arms.

Patients who have experienced a gastrointestinal bleed on NSAIDs are at particularly high risk to bleed again. Additionally, concern about cardiovascular risks associated with NSAIDs becomes problematic for our vasculopathic patients (post-stroke, myocardial infarction, stenting, etc.) who require antiplatelet treatment (e.g., clopidogrel, aspirin). Nonetheless, many such patients require both antiplatelet and NSAID treatment concomitantly. Chan et al reported on their double-blind study of *Helicobacter*-negative subjects (n = 514) randomized to celecoxib or naproxen, all of whom had experienced and resolved an episode of upper gastrointestinal bleeding. Because of prior cardiovascular events, all subjects also were taking 80 mg of aspirin per day.

At 18 months, there was a clear advantage to the celecoxib/aspirin group vs. naproxen/aspirin: 5.6% cumulative bleeding events for the former vs. 12.3% for the latter. Persons who have experienced an NSAID-related upper gastrointestinal bleed would be better served by taking celecoxib than naproxen if continuation of NSAID treatment is required. ■

## Rheumatoid Arthritis Disease Activity and Calprotectin Levels

SOURCE: Bae SC, Lee YH. *Postgrad Med* 2017;129:531-537.

Clinicians who see patients with inflammatory bowel disease (IBD), such as Crohn's disease or ulcerative colitis, likely will be familiar with using fecal calprotectin levels as a diagnostic tool. Indeed, some experience suggests that because of "skip areas" observed in IBD, fecal calprotectin may be as or even more sensitive to diagnose IBD than endoscopy. Calprotectin also is measurable in plasma and synovial fluid, and has been recognized recently as a good marker of disease activity in rheumatoid arthritis (RA).

There are several validated metrics for assessment of disease activity in RA, including C-reactive protein (CRP) and Disease Activity in 28 Joints (DAS28). Bae and Lee performed a meta-analysis of RA patients (n = 849) to evaluate the correlation of calprotectin with CRP and DAS28. Significant positive correlations were demonstrated. Common treatment for RA patients includes biologic agents such as TNF-inhibitors. Calprotectin levels have been demonstrated to be good indicators of disease activity in patients on TNF treatment. Hence, calprotectin may provide a metric for confirmation of optimized control of RA, providing additional insight into disease activity beyond clinical symptoms alone. ■

## Identification of Pneumococcal Pneumonia

SOURCE: Ceccato A, Torres A, Cilloniz C, et al. *Chest* 2017;151:1311-1319.

In approximately half of the cases of community-acquired pneumonia (CAP), an etiologic agent is not identified. CAP caused by *Streptococcus pneumoniae* (pneumococcal pneumonia) often is categorized as "invasive" (the bacteria was cultured from body fluids such as blood or pleural fluid) vs. "noninvasive" (body fluid cultures were negative, but urine antigen testing for *S. pneumoniae* was positive). Curiously, only pneumonia confirmed by invasive methodology has been incorporated into epidemiologic reporting of CAP traditionally. Cecatto et al noted that clinicians probably are significantly underestimating the burden of CAP by limiting the "gold standard" definition to cases identified "invasively."

The authors studied all cases of CAP (n = 5,132) in non-immunocompromised adults

treated at their Barcelona, Spain, emergency department over a 14-year interval. Of these, only 15% were confirmed to be pneumococcal. Slightly more patients were confirmed to be infected by *S. pneumoniae* through urinary antigen testing (54%) than by body fluid cultures (46%). Additionally, the 30-day mortality was the same regardless of which tool confirmed the diagnosis, dispelling the notion that CAP diagnosed though the "invasive" path is more lethal. Both methods of diagnosis are valid indicators of the pathogen, but there is no reason to consider urine antigen testing as indicative of less pneumonia lethality. ■

## The Best BP for High-risk Hypertension Patients

SOURCE: Böhm M, Schumacher H, Teo KK, et al. *Lancet* 2017;389:2226-2237.

The authors of the Systolic Blood Pressure Intervention Trial (SPRINT) randomized almost 10,000 high-risk, non-diabetic patients to intensive treatment (systolic blood pressure [SBP] goal: < 120 mmHg) vs. "standard" treatment (SBP goal: < 140 mmHg) and demonstrated that the group assigned to intensive treatment experienced a statistically significant reduction in both cardiovascular (CV) and all-cause mortality. Although the "costs" of intensive treatment were not trivial (more medications, more cost, more serious and non-serious adverse events), the lesson for many clinicians was that striving for SBP control better than < 120 mmHg was of merit in patients willing to shoulder the increased complexity and potential adverse effect profile of intensive treatment. But this may not be the end of the story.

Böhm et al analyzed the outcomes of two large, previously published CV trials: ONTARGET (n = 25,127) and TRANSCEND (n = 5,810). They chose to examine CV outcomes within these two trials for patients similar to the SPRINT population (high-risk adults) in relation to on-treatment BP. According to their analysis, achieving an SBP < 120 mmHg was associated with a 14% increase in composite CV outcomes compared to an SBP 120-140 mmHg. Similarly, hazard ratios for all-cause mortality and CV mortality were approximately 30% higher in persons who achieved the lower BP threshold (< 120 mmHg).

While these results might dampen enthusiasm for those who endorse the above-mentioned results of SPRINT, differences between the data sets, as well as the fact that this report relies on post-hoc analysis, include a substantial proportion of diabetics and post-stroke patients in the analysis of ONTARGET/TRANSCEND, both of whom had been excluded from SPRINT, and may have made an important difference in outcomes. ■

## Dietary Omega-3 Fatty Acids Inversely Associated with Diabetic Retinopathy

SOURCE: Chew EY. *JAMA* 2017;317: 2226-2227.

In the spirit of full disclosure, with rare exception (folate for reproductive age women), I am not an advocate for supplements. I want to make sure readers can clearly identify the difference between omega-3 fatty acid supplements and omega-3 fatty acids as provided by fish in the diet. The use of supplements by Americans has been fairly stable over the past decade at about 50%, despite little in the way of substantive scientific evidence support their use. However, let's not confuse the difference between the potential benefits of enhancement of diet with enhancement of intake through supplements. For instance, data from the Women's Health Initiative suggest that the cardiovascular effects of calcium intake through dietary enhancement differ from those of calcium supplements. The PREDIMED clinical trial was a prospective investigation that compared a Mediterranean diet augmented with extra virgin olive oil and nuts with a control (n = 7,447). Approximately half of the PREDIMED participants were diabetic. After a follow-up of six years, the hazard ratio for new retinopathy requiring intervention was approximately half that for the Mediterranean diet group compared to the control group. Although it may be tempting to extrapolate these observations to simply take an omega-3 fatty acid supplement of comparable quantity, it remains to be determined whether this isolated ingredient from fish, when taken as a single-entity intervention, will provide similar benefits. ■

## The Potential Long-term Payoff of Good Initial Diabetes Control

SOURCE: Svensson E, Baggesen LM, Johnsen SP, et al. *Diabetes Care* 2017;40:800-807.

Experts often opine that treatment of diabetes is "a marathon, not a sprint," suggesting that careful, slow steps are wise. In reference to risk for hypoglycemia, this philosophy is likely to be particularly apt, and yet some data suggest that prompt control of type 2 diabetes (T2DM), with strong early reductions in A1c, may produce long-term benefits.

Svensson et al reported on a large population of T2DM patients (n = 24,752) in Denmark among whom baseline A1c and degree of A1c reduction within the first six months could be correlated with outcomes over the next 2.6 years (mean follow-up). The group was restricted to only those patients whose initial treatment had been metformin. The authors found that both the lowest six-month achieved A1c level and greatest absolute degree of A1c correlated with greatest risk reduction for cardiovascular outcomes.

Although the window of observation of these patients is only modest (< 3 years), these results encourage clinicians to pursue the best control of T2DM we can attain without incurring significant adverse events, such as hypoglycemia. ■

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