Clinical Briefs in Primary Care™

The essential monthly primary care update

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Fibrates: Generally safe, but do they improve outcomes?

Source: Jun M, et al. Effects of fibrates on cardiovascular outcomes: A systematic review and meta-analysis. *Lancet* 2010;375:1875-1884.

According to this meta-analysis, the answer to the question above very much depends upon which outcome you believe is important. Conclusions are derived from 18 trials (45,058 participants) between 1950 and 2010. Although the results of individual fibrate (i.e., gemfibrozil, fenofibrate) trials have been somewhat disappointing, the combined data look more encouraging.

For instance, in the pooled data there was a 10% relative risk reduction for major cardiovascular (CV) events, and an almost 20% relative risk reduction for nonfatal coronary events in trials of fibrate vs placebo. Surprisingly, despite these favorable effects upon CV endpoints, there was no statistically significant reduction in all-cause mortality, CV death, or cardiac death.

When compared with other interventions to reduce CV risk (e.g., BP reduction, statins, antiplatelet therapies), the degree of absolute risk reduction achieved through fibrate therapy is substantially less. As might be anticipated, in trials where subjects had a higher baseline triglyceride level, risk reduction was greater.

Most at-risk patients in the United States are already receiving statins. The ACCORD trial was the only large trial in which patients that were already being treated with a statin then received a fibrate; no additional benefit from the fibrate was discerned. Nonetheless, fibrates will continue to have a role in high-risk patients, and in patients with marked triglyceride elevation at risk for pancreatitis. ■

Safety of testosterone replacement

Source: Basaria S, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363:109-122.

Of late, there has been a renaissance of interest in identification and management of hypogonadism in older men. This new enthusiasm is based upon a recognition that subnormal testosterone is both common and consequential. For instance, prevalence studies suggest that as many as 40% of healthy men older than age 50 have a subnormal morning total testosterone level. Subnormal testosterone is associated with changes in sexual function, mood, muscle mass, and central obesity. Observational data indicate that low testosterone is also associated with increased mortality. The advent of better-tolerated, easy-to-use testosterone replacement modalities (e.g., patches, gels, buccal tablets), has simplified the treatment approach, but the question about long-term testosterone safety is unanswered.

In the Testosterone in Older Men with Mobility Limitations study of senior men (n = 209; mean age, 74 years), subjects were treated with testosterone 1% gel to achieve mid-normal testosterone levels. The trial was discontinued early upon the recommendation by the Data and Safety Monitoring Board because of an increase in adverse events in the treatment group, including some serious events. For instance, there were 23 CV adverse events in the treatment group, compared with 5 in the placebo group.

The small size of the trial and the highly selected group (men with physical limitations) makes it difficult to generalize about the results. Nonetheless, clinicians should recognize that testosterone replacement may be associated with important adverse events. Larger, long-term studies will be necessary to establish the safety profile of testosterone replacement. ■

Glucosamine and low back pain

Source: Wilkens P, et al. Effect of glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: A randomized controlled trial. *N Engl J Med* 2010; 304:45-52.

The burden of suffering attributed to low back pain (LBP) is readily identified by all who practice primary care. Indeed, it is recognized as the largest single component of dollars expended on long-term disability in the United States. Unfortunately, there is little evidence that supports any currently available interventions to alter the natural history of LBP and restore functionality. Because glucosamine has shown promise in other forms of osteoarthritis, and because lumber osteoarthritis is commonplace in persons with LBP, a trial of glucosamine for patients with both disorders was intuitively appealing.

In this randomized, double-blind trial, subjects were randomized to either 1500

mg/day glucosamine sulfate or placebo for 6 months. Outcomes were assessed at 6 months (end of active therapy) and again 6 months later (after a 6-month hiatus in treatment).

The Roland Morris Disability Questionnaire is specifically designed to address functional status in persons suffering LBP. In addition to this metric, degree of pain reduction and quality of life were assessed.

Although glucosamine was well tolerated, it did not produce a statistically significant improvement at either the 6-month or 12-month follow-up. Unless there exists another indication for the use of glucosamine, clinicians remain without supportive data to employ it for LBP associated with lumbar osteoarthritis. ■

Effects of allopurinol upon exercise in patients with angina

Source: Noman A, et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: A randomised, placebo controlled crossover trial. *Lancet* 2010;375:2161-2167.

Allopurinol has been shown, in heart failure, to reduce myocardial oxygen demand. The mechanism by which this occurs is not uncertain, nor is it known whether such favorable effects occur in persons without heart failure. If, during exercise, an intervention could similarly reduce myocardial oxygen demand, it could prove useful in persons with angina.

To address this question, the authors randomized subjects (n = 65) with chronic stable exercise-induced angina to high-dose allopurinol (600 mg/day) or placebo. Inclusion criteria required consistency of time to ischemia on baseline Bruce protocol exercise treadmill testing. Subjects received 600 mg/day allopurinol for 6 weeks (or placebo) and were then crossed over.

Allopurinol did produce a statistically significant increase in time to ST depression, as well as time to onset of chest pain, with no adverse effects. As a result, the authors suggest that there may be a role for allopurinol based upon cost, efficacy, and safety. Before embarking upon utilization of allopurinol for angina, clinicians must recognize that allopurinol is known to cause (rarely) a hypersensitivity vasculitis, which has a case fatality rate of approximately 25%. ■

Is obesity a factor in asthma?

Source: Pakhale SM, et al. A comparison of obese and nonobese people with asthma: Exploring an asthma-obesity interaction. *Chest* 2010;137:1316-1323.

Population studies have shown that obesity is related to the incidence of asthma. Compared to non-obese subjects, the odds ratio per year for developing asthma among obese individuals is approximately 1.5, and increases as the degree of obesity increases. Although mechanisms through which obesity might contribute to incident asthma are poorly understood, several prospective studies have demonstrated the same relationship.

Of course, some persons who carry a diagnosis of asthma have been misdiagnosed. In this study by Pakhale et al, subjects diagnosed as asthmatic underwent formal pulmonary function testing to confirm their diagnosis. Overall, of 496 subjects, asthma was ultimately ruled out in 150 of them. Likelihood of misdiagnosis was increased especially in older males.

There was one subgroup of obese individuals among whom the likelihood of asthma misdiagnosis stood out: If an obese individual had had an urgent visit for respiratory symptoms in the past 12 months, the misdiagnosis of asthma was more than 4-fold greater than in non-obese persons.

Based upon this information, it is suggested that clinicians should consider performing objective confirmation of the diagnosis of asthma (as with pre-and post-bronchodilator spirometry), particularly among obese older males. ■

A new tool for treatment of plantar warts

Source: Gamil H, et al. Intralesional immunotherapy of plantar warts: Report of a new antigen combination. *J Am Acad Dermatol* 2010;63:40-43.

Plantar warts, most commonly found on the plantar surface of the feet but also seen on the hands and other sites, are often challenging to treat. Although available tools include destructive therapies (e.g., cryotherapy, bichloroacetic acid), topical immune modulators (e.g., imiquimod), oral agents (e.g., cimetidine, levamisole), and simple surgical excision, each of these modalities has limitations. Hence, new methods of intervention are sought.

Gamil et al investigated the use of intralesional measles/mumps/rubella vaccine (MMR, as used in standard childhood immunizations) in a pilot trial. Vaccine was injected once every 3 weeks for a maximum of three injections, in 23 subjects.

Although the duration of treatment was only 6 weeks (injections at time 0, 3 weeks, and 6 weeks), patients were followed for 9 months to evaluate for recurrence.

Complete clearance of warts occurred in 20 of 23 patients, 1 patient had partial clearance, and 2 had no response. Only 1 patient experienced recurrence over 9 months. Other than local pain during the actual process of injection, the only other reported adverse effect was a transient flu-like syndrome in 1 patient.

MMR is inexpensive and well tolerated, and intriguing as a novel immunomodulatory path for attacking plantar warts. ■

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