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The essential monthly primary care update

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Prevention of Cardiovascular Events with Aspirin and Vitamin in Type 2 Diabetics

Source: Sacco M, et al *Diabetes Care.* 2003;26:3264-3272.

Pooled data (n = 50,000) on primary prevention of cardiovascular disease with aspirin (ASA) indicates as much as 28% reduction in coronary heart disease, albeit no demonstrable effects upon total mortality or stroke. Recent data from the Primary Prevention Project, a large scale trial of persons with known cardiovascular risk factors (n = 4495) have corroborated that low-dose ASA provides a 40% or greater risk reduction for cardiovascular death.

The benefits of primary prevention with ASA specifically in diabetics remains less certain though meta-analysis suggests substantially lower benefits for diabetics afforded by primary prevention (7%) than we have seen demonstrated for secondary prevention (25%).

Sacco and colleagues report on the diabetic cohort of the Primary Prevention Project trial (n = 1031) who were randomly assigned to low-dose ASA (100 mg/d) and vitamin E. Consonant with recently published major clinical trials (HOPE, Heart Protection Study), no perceptible benefit from vitamin E was found. Disappointingly, no statistically significant benefits of ASA in this diabetic population could be confirmed, as far as cardiovascular death, stroke, or MI (composite end point) or total cardiovascular events. Indeed, there was a trend toward increased cardiovascular deaths. It is postulated that non-platelet-related vasculopathic forces in diabetic patients may counterbalance beneficial platelet effects of ASA. ■

Cinnamon Improves Glucose and Lipids of Type 2 Diabetics

Source: Khan A, et al. *Diabetes Care.* 2003;26:3215-3218.

There is a strong connection between diet and diabetes, but "best diet" remains elusive. Choosing foods with favorable glycemic index (lesser rate of rise of glucose) has been shown to positively effect diabetic control. Some spices, for instance bay leaves, cinnamon, cloves, and turmeric have been noted improve insulin sensitivity in vitro.

Animal studies have provided intellectual fodder for a putative role of cinnamon (CINN) in enhanced insulin activity, favorably affecting glucose uptake, glycogen synthesis, and insulin receptor phosphorylation. The effects of CINN supplementation in humans has been heretofore unknown.

Finely ground CINN mixed with flour was packaged into 500 mg capsules and administered in doses of 1 g, 3 g, or 6 g daily for 60 days. Subjects continued their regular diet (and medication) otherwise unaltered.

CINN produced an 18-29% decrease in fasting glucose levels at 60 days, but no dose-response curve was seen (ie, all doses reduced glucose to a similarly favorable degree). Comparable reductions in total cholesterol (13-26%) and LDL cholesterol (10-24%) were also demonstrated. Favorable effects were seen at CINN ingestion levels from 1-6 g/d. Whether even lower levels might be beneficial remains to be determined. ■

Depression Care on Pain and Functional Outcomes Among Adults with Arthritis

Source: Lin EB, et al. *JAMA.* 2003;290:2428-2434.

Arthritis is the most commonplace cause of disability in the United States, with as many as one-third of persons older than age 65 manifesting osteoarthritis (OA) of the knee. It is not uncommon for this same population to suffer comorbid depression, magnifying dysfunction associated with OA. No previous trial has examined the impact of depression treatment upon pain or functional outcome in OA.

The population studied comprised subjects with both knee OA and non-suicidal unipolar depression (n = 1801). Patients were randomized to "usual care" or a program of antidepressant pharmacotherapy and 6-8 psychotherapy sessions.

OA pain intensity and its interference with daily activities were statistically significantly improved in the active treatment group. Scores on the Hopkins Symptom Checklist were much more likely to improve among intervention recipients than "usual care" (41% vs 18%).

Specifics about individual pharmacotherapies are not included in the study, for instance, we do not know which specific antidepressant agents were used. Antidepressants with norepinephrine reuptake inhibi-

tion activity have already demonstrated favorable effects in some pain syndromes. At any rate, successfully addressing depression in persons suffering pain from OA with counseling and pharmacotherapy has been shown to reduce OA-related morbidity. ■

Efficacy and Safety of Low-Dose Aspirin in Polycythemia Vera

Source: Landolfi R, et al. *N Engl J Med*. 2004;350:114-124

The increased red cell mass diagnostic of polycythemia vera (PCV) results in blood hyperviscosity, which is associated with increased thrombotic events. Initial enthusiasm for the concept of ASA thromboprophylaxis in PCV was dampened by a 1986 trial of aspirin (ASA) at a dose of 900 mg/d, in which an unacceptably high incidence of major GI bleeding was seen. In non-PCV populations, low-dose ASA has been shown to provide effective thromboprophylaxis, with lesser risk of major GI bleeding.

Plasma thromboxane (a direct stimulator of platelet activation) levels are elevated as much as 10 fold in PCV, a situation parallel to that seen in acute coronary syndromes, in which ASA has been proven to provide dramatic risk reduction. Since even low-dose ASA results in substantially reduced platelet thromboxane production, but less GI bleeding, the potential merit of such a clinical trial is straightforward.

PCV patients lacking any other direct indication for ASA (eg, previous MI) were enrolled in a double-blind placebo-controlled randomized trial to compare 100 mg ASA with placebo (n = 518). The 2 primary end points of the study were: 1) nonfatal MI + nonfatal stroke + CV death; 2) nonfatal MI + nonfatal stroke + PE + DVT + CV death. Secondary end points included individual thrombotic components of the above.

After a mean followup of 3 years, ASA reduced the primary end point #2 by 60%; primary end point #1 was reduced 59%, but did not achieve statistical significance. The lower ASA dose (100 mg/d) demonstrated excellent safety, with no statistically significant increased risk of either major or minor bleeding compared to placebo. Landolfi and associates recommend consideration of low-dose ASA for thromboprophylaxis in PCV. ■

Coronary Artery Calcium Score Plus Framingham Score for Risk Prediction

Source: Greenland et al. *JAMA*. 2004;291:210-215

The Framingham risk score (FRS) is a commonly recommended tool for estimating risk of coronary events (CHD) in asymptomatic persons (asymptomatic for CHD, that is). It provides an assessment of the likelihood of experiencing a CHD event in the next 10 years. Despite inclusion of age, sex, smoking, BP, lipids, and glucose, the FRS is imperfect in identifying those at CV risk, especially for those determined to be at 'intermediate risk' (FRS = 10-19%). Another tool used for CHD risk stratification is coronary artery calcium scoring (CACS), as obtained by CT. The purpose of this trial was to ascertain whether combining the 2 enhances accuracy.

Asymptomatic persons older than 45 (n = 1461) with at least one CHD risk factor (but without prior MI or proven CAD) were enrolled. Diabetics were excluded because CACS has not proven effective in this population, who are by definition already recognized as high risk for CAD at presentation. Patients were followed up to 8.5 years (mean, 7 years).

For persons with a FRS of at least 10% (but < 20%), a CACS greater than 300 (highest quartile CHD risk) significantly modified risk prediction. For instance, a FRS 10-year risk prediction of 10% was increased to 13-19% when coupled with a CACS score > 300. Greenland and associates suggest that for low-risk (FRS < 10%) and high risk (FRS > 20%) individuals, CACS adds little. Prognostication about the intermediate risk group (FRS = 10-19%) is enhanced by combining the tools. ■

Intra-articular Hyaluronic Acid in the Treatment of Knee Osteoarthritis

Source: Lo GH, et al. *JAMA*. 2003; 290:3115-3121.

The use of hyaluronic acid (HUA) injection in human subjects began in 1997, following a history of similar treatment in veterinary medicine. HUA is a constituent of normal synovial fluid, and has been conceptualized as a 'joint lubricant.' Because of mixed efficacy responses in clinical trials, clinician acceptance of this treatment modality for osteoarthritis of the knee (OA) has been somewhat tepid.

This metaanalysis included 22 trials, with almost 3000 patients. To quantify treatment effects, an 'effect size' metric was used; 0.2-0.5 is a 'small' effect size, comparable to the advantage of NSAIDs over acetaminophen in OA treatment trials. Analysis included all recipients of HUA injection, but was further separated out into groups based upon whether subjects had received standard, or highest molecular weight HUA.

Overall, HUA was found to provide a modest benefit (effect size = 0.32); Lo and associates discuss that even this result may be overoptimistic, since publication bias was discerned amongst HUA injection trials. According to this analysis, whether highest molecular weight HUA is more advantageous than other configurations remains indeterminate. Lo et al call for further independent trials to provide greater clarification of HUA efficacy. ■

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