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The essential monthly primary care update

By Louis Kuritzky, MD

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Coronary Calcium Scores enhance risk prediction

Source: Polonsky TS, et al. *JAMA* 2010; 303:1610-1616.

PROBABLY THE MOST WIDELY RECOGNIZED scoring system for predicting CV risk is the Framingham Risk Score (FRS). The United States Preventive Services Task Force (USPSTF) has recently published the opinion that novel risk markers such as C-reactive protein do not sufficiently enhance risk prediction enough to justify their routine utilization in addition to traditional scoring systems like FRS Coronary Calcium Score (CCS) has a number of appealing attributes that suggest consideration as a powerful prediction tool.

In the Multi-Ethnic Study of Atherosclerosis (MESA) trial of persons without known CHD at baseline, a CCS > 300 was associated with a 10-fold increased risk for CHD events. A critical issue, however, is whether new or additional prediction score tools add meaningfully to existing methods. A metric known as Net Reclassification Improvement (NRI) has been recently proposed to distinguish whether the incremental impact of a scoring system or risk factor upon already existing methods is meaningful.

Using the cohort of MESA (n = 6814 adults; age > 45), Polonsky et al compared risk prediction as derived from FRS vs FRS + CCS. The addition of CCS to FRS resulted in a statistically significant NRI. An additional 23% of persons who experienced CHD events but had not been identified by FRS as high risk were correctly reclassified by the addition of CCS. Similarly, an additional 13% of subjects not classified by FRS as low risk (and who did not suffer events), were reclassified as low risk by the addition of CCS. Whether the preferential (or additional) use of CCS for risk prediction can improve outcomes over traditional risk scores alone will require further definition, although many are already sufficiently encouraged by the predictive power of CCS to currently employ it. ■

Exacerbations of COPD: Not so innocent

Source: Donaldson GC, et al. *Chest* 2010;137:1091-1097.

ACUTE EXACERBATIONS OF COPD (AE-COPD) are sometimes misconstrued as minimally consequential "bumps in the road" along the journey of progressive COPD. Unfortunately, the toxicity of ae-COPD has been underappreciated; ae-COPD are associated with hospitalizations, loss of lung function that is typically not regained, and mortality. Donaldson et al direct our attention to a newly recognized additional burden of morbidity associated with ae-COPD: MI and stroke.

The Health Improvement Network (THIN) database contains anonymized medical records of patients seen by GPs in England and Wales. Over a 2-year period, 25,857 COPD patients provided a dataset with which to compare the incidence of MI and stroke during "stable" periods of COPD with the immediate post-ae-COPD period.

The incidence of acute MI was increased more than 2-fold in the 5-day period immediately following an ae-COPD; similarly, stroke incidence was increased more than 2-fold in the 49-day period immediately post-ae-COPD. Both findings were statistically significant.

No pharmacologic treatment of COPD has been proven to be disease-modifying. Yet, since various pharmacotherapies have been shown to reduce ae-COPD, perhaps such treatments will ultimately be shown to impact disease outcome by affecting the above-mentioned consequences of ae-COPD: increased stroke and MI. ■

Vitamin E, but not pioglitazone, improves NASH

Source: Sanyal AJ, et al. *N Engl J Med* 2010;352:1675-1685.

STEATOSIS IS THE ACCUMULATION OF FAT, derived primarily from triglycerides in hepatic cells. Progressive steatosis can lead to hepatic inflammation, which, when not associated with alcohol, is known as non-alcoholic steatohepatitis (NASH). Obesity and diabetes are the two conditions most commonly associated with NASH. Because as many as 15% of NASH cases may ultimately progress to cirrhosis, effective treatments are eagerly sought.

Since the pathologic underpinnings of NASH often include insulin resistance, hypetriglyceridemia, and type 2 diabetes, pharmacology with thiazolidinediones (TZD) appears logical. Unfortunately, results from pilot trials of TZDs have been conflicting.

The NASH Clinical Research Network, established by the NIDDK, conducted a

placebo-controlled trial of pioglitazone or vitamin E in non-diabetic NASH patients (n = 247). Subjects received 800 IU/d vitamin E, 30 mg/d pioglitazone, or placebo for approximately 2 years. The primary outcome was histologic status of NASH.

At 96 weeks, vitamin E did demonstrate a statistically significant rate of NASH histologic improvement, but pioglitazone did not. Even though there were some favorable histologic effects, neither intervention showed a reduction in hepatic fibrosis, so we remain uncertain about whether vitamin E can impact the development of serious long-term liver disease. Pioglitazone did not achieve an effect on the primary outcome, but explanations for why TZDs may still be considered for NASH therapy are presented by the authors. ■

Best use of home BP monitoring

Source: Pickering TG, et al. *J Am Soc HTN* 2010;4:56-61.

The largest body of information guiding treatment of hypertension (HTN) is based upon office BP management. Nonetheless, home BP monitoring (HBPM) is documented to be a better predictor of CV risk than office BP. For instance, patients with high office BP but low HBPM are recognized to be at substantially lower risk than office BP predicts; similarly, high HBPM pressures compared to office BP portends greater risk than indicated by office BP alone. Simply the fact that HBPM offers the opportunity for many more BP readings than is readily accessible in clinical care provides both a more comprehensive and consistent BP profile.

Recording HBPM twice daily (morning and evening), when averaged over 1 week, provides a sufficient BP profile to help guide management. By HBPM, HTN is > 135/85 mmHg and normotension is < 125/75 mmHg. Borderline HBPM (125-135/75-85 mmHg) merits consideration of 24-hour ambulatory BP monitoring for further clarification. The authors, writing on behalf of the American Society of Hypertension, provide a list of validated home BP monitoring devices at: www.dableeducational.org/. ■

Suicide risk with anticonvulsants

Source: Patorno E, et al. *JAMA* 2010;303:1401-1409.

Although the term "anticonvulsant" is indicative of a therapeutic class, pharmacologically the class is diverse. Despite dissimilarities, an analysis by the FDA (2008) discerned a relative doubling of suicide behavior/ideation in anticonvulsant recipients compared to placebo, resulting in a change in labeling.

The HealthCore Integrated Research Database provides data with which to assess the relative risk for suicidal acts in persons receiving a variety of anticonvulsant agents. During a 5-year interval (2001-2006), almost 300,000 new prescriptions for various anticonvulsants were documented in this population. When compared to treatment with either topiramate or carbamazepine (reference drugs), important distinctions emerged in reference to suicidal acts and violence. For instance, the hazard ratio for suicidal acts was 1.42 for gabapentin, 1.84 for lamotrigine, and 1.65 for valproate, compared to topiramate.

The mechanism by which some anticonvulsants incur an increased suicide risk is not known, despite the recognition that anticonvulsants can have impact upon mood. The first 2 weeks after initiation is recognized to be a higher risk period. Clinicians should be vigilant for behavior or mood changes in patients treated with anticonvulsants, noting lesser apparent risk for topiramate or carbamazepine. ■

For type 2 diabetes, after metformin, what next?

Source: Phung OJ, et al. *JAMA* 2010;303:1410-1418.

In the absence of contraindications, metformin is the preferred initial treatment for most patients with type 2 diabetes (DM2). Unfortunately, monotherapy is unlikely to maintain adequate glycemic control, requiring additional treatment. Although the addition of insulin to metformin is an appropriate next step, and has been labeled Tier 1 in the most recent guidelines published by the American Diabetes Association, some patients are reluctant to use insulin, and the considerable weight gain experienced by some insulin users, as well as risk of hypoglycemia, is problematic.

Among the non-insulin therapeutic choices, there is a great degree of variation in tolerability issues, such as amount of weight gain and frequency/severity of hypoglycemia that may help guide treatment decisions. Phung et al analyzed data from 27 randomized controlled trials (n = 11,198), most of which were 6 months or less in duration, to compare weight changes and hypoglycemia when non-insulin agents were added to metformin.

As might be anticipated, when TZDs, sulfonylureas, and glinides were added to metformin there was a 1.8-2.1 kg weight gain. GLP-1 mimetics, alpha-glucosidase inhibitors, and DPP-4 inhibitors were either weight neutral or associated with minimal weight loss. Sulfonylureas were associated with higher rates of hypoglycemia.

Of course, progressive treatment of DM2 must be individualized, and should include consideration of characteristic tolerability issues such as weight gain and hypoglycemia. ■

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

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