Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

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When Basal Insulin is Not Enough: Add Prandial Insulin or a GLP-1 Agonist?

Source: Digenio A, et al. *Postgraduate Med* 2014;126:49-59.

Because of its strong efficacy, long-term durability, and predictability when titrated with algorithms employed in clinical trials, basal insulin remains a mainstay of treatment for type 2 diabetic patients who are not able to attain or maintain glycemic control with oral agents alone. Because diabetes is progressive disorder, even patients who are initially well controlled on basal insulin will likely require "fine tuning" of their diabetes regimen, usually with agents that preferentially affect postprandial glucose levels.

GLP-1 agonists (e.g., albiglutide, dulaglutide, exenatide, liraglutide) can impact postprandial glucose levels by means of blunting glucagon release, as well as modulating gastric emptying. In patients who have achieved fasting glucose control on basal insulin — when postprandial glucose is the target — would prandial insulin or GLP-1 agonist better serve their needs?

Digenio et al report on a "real world" data analysis that looked retrospectively at a large population of General Electric Centricity electronic health records (n = 33,848) from persons who had either prandial insulin or a GLP-1 agonist added to basal insulin when glucose control was not adequate.

At follow-up 6 months-1 year later, GLP-1 agonists and prandial insulin provided similar A1c reductions, but there were substantial differences in weight (gain with rapid acting insulin vs. loss with GLP-1 agonist) and hypoglycemia (more frequent with insulin).

Current ADA/EASD guidelines include weight gain and risk of hypoglycemia as critical considerations for advancement of therapy. These data support the concept that in "real world settings," GLP-1 agonists perform essentially as well as rapid acting insulin, with less hypoglycemia and weight loss instead of gain. ■

Performance of Lorcaserin, a 5-HT2c Receptor Agonist, for Weight Loss

Source: Aronne L et al. *Postgraduate Med* 2014;126:7-18.

Clinicians may have some ambivalence about employing pharmacologic therapies for weight loss-based upon several reality-based observations: 1) Some weight-loss drugs have been taken off the market after a brief sojourn due to serious toxicity (e.g., dexfenfluramine, of notorious Fen-Phen history); 2) Some weight-loss drugs have been taken off the market after sustained use, even though early utilization seemed safe enough (e.g., sibutramine [Meridia]); 3) Many patients who embark upon pharmacotherapeutic courses of weight-loss medication do not lose an amount of weight that is meaningful to them cosmetically (essentially all currently available medications).

One of the primary reasons that patients become dissatisfied with weight-loss pharmacotherapy is that the amount of weight lost does not typically result in achievement of ideal body weight, or anything even close to that. Our role in use of weight-loss agents should include re-orientation of the patient to include not just cosmetic effects of obesity, but long-term health consequences such as metabolic derangement, hypertension, diabetes, and cancer risks.

Currently available anorectic agents do perform well enough to achieve meaningful thresholds of weight reduction that lead to favorable metabolic changes. Two placebo-controlled clinical trials of lorcaserin (Belviq) [BLOOM and BLOSSOM, combined n = 6380] can inform us about what type of impact to anticipate with this 5-HT2c agonist:

At one year of lorcaserin treatment, 47% had lost at least 5% of their body weight, and 22% had lost at least 10% of their body weight. As has been observed in numerous prior interventions that achieve this degree of weight loss, improvements in glycemic status, blood pressure, and lipids were also seen. Although an oral "magic bullet" to assist patients in attaining ideal body weight would be desirable, lorcaserin provides modest — but clinically relevant — weight loss. ■

Comparing GLP-1 Agonists: Dulaglutide vs. Liraglutide

Source: Dungan K, et al. *Lancet* 2014; 384:1349-1357

All currently available GLP-1 agonists (albiglutide, dulaglutide, exenatide, liraglutide) have four attributes in common: glucose-dependent stimulation of insulin secretion, glucose-dependent blunting of glucagon secretion, improved satiety, and delay in gastric emptying. These physiologic effects are associated with improved glucose control, less risk for hypoglycemia, and weight loss. Head-to-head trials can inform us about potential differences among the agents, but within this class there is much more in similarity than difference.

To date, head-to-head comparisons of GLP1 agonists have suggested a modest A1c reduction advantage for liraglutide (Victoza). The most recently FDA-approved GLP1 agonist, dulaglutide (Trulicity), is the subject of this head-to-head trial vs. liraglutide. In the AWARD-6 trial, patients (n = 599) were randomized (open-label) to maximum as per-labeling dose of once-weekly dulaglutide 1.5 mg or once-daily liraglutide 1.8 mg.

The degree of A1c reduction at 26 weeks with dulaglutide (1.42%) was slightly greater than liraglutide (1.36%), which did meet the threshold for non-inferiority (the primary outcome of the study). The adverse-effect profiles were very similar, except for a substantially lesser degree of hypoglycemia (0.34 vs. 0.52 events/year) with dulaglutide.

Maximum dose once-weekly dulaglutide is non-inferior to maximum dose once-daily liraglutide. ■

Screening for Lung Cancer with Low-dose CT

Source: Gould MK. *N Engl J Med.* 2014; 371:1813-1820.

The United States Preventive Services Task Force (USPSTF) gave a level B recommendation in support of annual low dose computed tomography (LDCT) to screen for lung cancer in appropriate risk groups. The USPSTF decision was largely based on the National Lung Screening Trial (NLST), a mega-trial (n = 53, 454) in the United States that randomized subjects to annual LDCT or chest X-ray. The primary endpoint of the study was lung cancer mortality; all-cause mortality was a secondary endpoint. Inclusion criteria included at least a 30-pack/year history of smoking (if cessated, within 15 years), ability and willingness to complete follow-up for abnormal findings, and absence of problematic comorbidities that might otherwise compromise long-term survival.

The good news is that LDCT was associated with a 20% relative risk reduction in lung cancer mortality, and a 7% reduction in all-cause mortality, both of which were statistically significant. Should we end the discussion there?

Perhaps not. The NLST has several stark limitations. First, literally 95% of "positive" findings on LDCT were false-positive, and harm to patients during the follow-up evaluations were substantial, including death. Second, a not-inconsiderable number of "incidentalomas" were also detected, and follow-up data on whether things findings favorably (or unfavorably) affected study subjects' lives have not yet been published.

Finally, an issue about the absolute magnitude of benefit: Although the 20% relative reduction in lung cancer mortality sounds impressive, the absolute risk reduction was very small; In the LDCT group, 356 of 26,309 died (1.3%) vs. 443 of 26,035 in the chest X-ray group (1.7%), for an absolute risk reduction of 0.348%.

Although most major organizations have endorsed USPSTF recommendations, the American Academy of Family Physicians (AAFP) has issued a note of caution, based upon lack of replication of these data in a community setting. Instead of universal screening, they suggest a "shared decision-making" approach reminiscent of their advice about prostate cancer screening in the recent past. ■

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Rethinking Acetaminophen for Acute Low Back Pain

Source: Williams CM. *Lancet* 2014;384: 1586-1596.

The natural history of acute low back pain (aLBP) indicates that somewhere between 60-70% of episodes have spontaneously resolved by 3 weeks, and 80-90% by 3 months. We would hope that the goals of clinicians in their choice of pharmacotherapy and activities (physical therapy, exercise) are to shorten time to recovery, improve functional status during recovery, and provide symptom relief. A Cochrane Database analysis has confirmed the efficacy of NSAIDs for aLBP. What about acetaminophen? (Note: for readers who choose to review the original reference on this article, the word "paracetamol" is used in the original title, because that is the preferred term in the United Kingdom and Australia for what we call "acetaminophen" in the United States).

In this double-blind, placebo-controlled study conducted in Sydney, Australia, patients with aLBP (n = 1, 096) were randomized to treatment with pro re nata acetaminophen (up to 4000 mg/d) or placebo and followed for 3 months. The primary outcome was aLBP recovery, defined as a score of ≤ 1 on a 1-10 pain scale for at least 7 consecutive days.

No differences were found in time to recovery between groups. The authors suggest that although replication of their data with another clinical trial would make these conclusions more definitive, clinicians should be circumspect about use of acetaminophen in aLBP. ■

Non-obstructive Coronary Artery Disease: Not So Innocent After All

Source: Maddox TM, et al. *JAMA* 2014; 312:1754-1763

It has become abundantly clear that coronary events (i.e., MI) are not simply a result of "clogged pipes." To the contrary, it has been documented that the majority of plaque ruptures occur within coronary arteries that have been atherosclerotically categorized as "non-obstructive." In this report, obstructive coronary disease (obCAD) was defined as ≥ 50% stenosis of the left main coronary artery or ≥ 70% stenosis in other coronary arteries. Non-obstructive coronary disease (nobCAD) was defined as 20-49% stenosis, and < 20% stenosis was categorized as "no apparent CAD" (napCAD).

The authors of this report studied all patients who underwent coronary arteriography in Veteran Administration hospitals from 2007-2012 (n = 37,684). Within this cohort, 8384 patients were reported to have noCAD. They tracked the rate of admission for acute MI in the year following arteriography.

Compared to persons with no apparent CAD, the hazard ratio for MI at 1 year for persons with nobCAD was 2.0-4.5 (dependent upon the number of vessels involved); for persons with obCAD, the hazard ratio was 9.0-19.5 (dependent upon the number of vessels involved). ■