VOLUME 3 | ISSUE 2 | MARCH 2013

L|E|C|O|M Point

WELCOME TO LECOM POINT...
A DRUG INFORMATION SOURCE DIRECT AND TO THE POINT

American Diabetes Association Revises Standards of Care

Lucas Reinhartz, Kimberly Crowell, Kristin Ludolph, Courtney Roberts, PharmD Candidates;
Ryan Wargo, PharmD, BCACP; Marcus Campbell, PharmD, BC-ADM

The American Diabetes Association (ADA) issues clinical practice guidelines for the "Standards of Medical Care in Diabetes" every January. Some of the major revisions to the 2013 guideline include recommendations for a less stringent systolic blood pressure goal and individualization of blood glucose self-monitoring. These revisions and other changes are reviewed:

Hypertension: The new ADA recommended blood pressure goal in diabetic patients has been revised from <130/80 mmHg to <140/80 mmHg (B).[1-3] The primary data for this recommendation came from the result of the ACCORD trial, which found no statistical difference in the rate of nonfatal major cardiovascular events or all-cause death when SBP goal was increased to 140 mmHg. Only the annual rate of stroke showed statistically significant reductions withintensive treatment (SBP <120mmHg); however, serious adverse events were higher.[2] In addition, a subgroup analysis of the INVEST trial found a higher rate of all-cause mortality in diabetic patients with a targeted SBP of <130 mmHg compared to <140 mmHg.[3] For diabetic patients with confirmed BP ≥140/80 mmHg, the recommended treatment is to initiate pharmacological therapy followed by titration combined with lifestyle changes to achieve blood pressure goals (B).[1]

Dyslipidemia: Patients with type 2 diabetes often have elevated lipid levels leading to increased risk for CV complications. LDL cholesterol-targeted statin therapy remains the preferred treatment strategy for diabetic patients with dyslipidemia (A); however, recommendations regarding the use of combination therapy have changed. Combination therapy with a statin and a fibrate or niacin has been associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis and has not been shown to reduce the rate of CV events compared to monotherapy.[5-7] Based on clinical evidence, combination therapy has been shown not to provide additional benefit over statin therapy alone and is not generally recommended (A).[1]

Glucose Monitoring: The new ADA self-monitoring of blood glucose (SMBG) recommendations focus on the fact that each patient will require their own individualized frequency and timing of their tests. Patients on multiple dose insulin (MDI) or insulin pump therapy should do SMBG at least prior to meals and snacks, occasionally after meals, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they have normal levels, and prior to critical tasks (B).[1] This evidence was demonstrated in a database study finding that one additional SMBG per day decreased A1c by 0.20% (P<0.001) and a higher frequency of SMBG was related to better metabolic control and fewer acute complications.[4]

Hypoglycemia: The ACCORD trial found that patients with cognitive impairment at baseline were associated with a greater risk of severe hypoglycemia.[8] In addition, a longitudinal cohort study of older patients with type 2 diabetes showed that patients with a history of severe hypoglycemia were associated with a higher risk of dementia.[9] Therefore, it is recommended to re-evaluate treatment for patients who have experienced ≥1 severe hypoglycemic episodes and remain unaware about hypoglycemic care (E), to assess cognitive function regularly for patients with low or declining cognition, and suggest increased attention for hypoglycemia by clinician, patient, and caregivers (B). Also, insulin treated patients with hypoglycemia unawareness or an episode of severe hypoglycemia should be advised on how to raise their blood glucose (A).[1]

Prevention/Delay of Type 2 Diabetes: Pre-diabetic patients often present with other cardiovascular risk factors including obesity, hypertension and dyslipidemia. The Diabetes Prevention Program Outcomes Study found that appropriate management of these risk factors yields less cardiovascular events.[10] Therefore, it is recommended to screen and treat modifiable risk factors for CVD (B).[1]

(Continued on page 2)

Retinopathy Screening and Treatment: In the RISE and RIDE trials, researchers found that anti-vascular endothelial growth factor (VEGF) therapy with ranibizumab showed improved vision and reductions in the need for laser coagulation procedures in patients with macular edema.[11] On the basis of these two trials, therapy with anti-VEGF agents is now indicated for diabetic macular edema (A).[1]

Immunization: The Advisory Committee on Immunization Practices (ACIP) reports that acute HBV infection is about twice as high in diabetic versus non-diabetic adults age ≥23 years and that some evidence shows a higher fatality rate in diabetics with HBV.[12]Based on these reports, unvaccinated adults age 19 -59 years are recommended to receive the hepatitis B vaccination series, and vaccination for adults age 60 years or more should be considered (C).[1]

<Click Here for References>

SGLT-2 Inhibitors Likely Coming to U.S. Market

Ketal Patel, PharmD Candidate; Marcus Campbell, PharmD, BC-ADM

Diabetes mellitus (DM) is highly prevalent in the United States. According to American Diabetes Association (ADA), 25.8 million children and adults in the United States have diabetes.[1] There are multiple classes of oral agents that are used for glycemic control. One of the newest classes is the SGLT-2 (sodium-glucose cotransporter-2) inhibitors. SGLT-2 inhibitors work by inhibiting the reabsorption of glucose from the kidney. SGLT-2 is located primarily in the S1 segment of the proximal tubule where 90% of the filtered glucose is reabsorbed.[2] Investigational SGLT-2 inhibitors include dapagliflozin, canagliflozin, and empagliflozin.[3]

The safety and efficacy of dapagliflozin was evaluated in a randomized, double-blind, placebo-controlled, trial in treatment naïve patients with type II diabetes.[4] A total of 485 patients with HbA_{1C} of 7-10% were randomized to once daily placebo or dapagliflozin 2.5, 5, or 10 mg administered either in the morning (primary cohort) or in the evening (exploratory cohort). The primary efficacy endpoint was the change in HbA_{1C} at week 24. Secondary efficacy endpoints included change from baseline in FPG (fasting plasma glucose) and body weight at week 24. Reductions in HbA_{1C} from baseline to week 24 in dapagliflozin 5 mg and 10 mg once in the morning groups were statistically significant ($p=0.0005$, $p<0.0001$) compared to placebo. Reduction in FPG from baseline to week 24 in dapagliflozin 5mg and 10 mg once in the morning groups were also statistically significant ($p<0.001$, $p<0.0001$) compared to placebo. All endpoints in the exploratory evening cohort were comparable with the primary cohort. There was an increase in incidence in signs and symptoms suggestive of UTIs and genital infections in dapagliflozin groups, although the increase was not significant.[4]

In a randomized, 52 week, double blind, active-controlled noninferiority trial, the efficacy, safety and tolerability of dapagliflozin was compared to glipizide in 814 patients with type 2 diabetes who were receiving metformin monotherapy. Patients included in the study had HbA_{1C} between 6.5-10% and were on a stabilized metformin regimen. Patients were randomized in a 1:1 ratio and received either dapagliflozin or glipizide titrated to max dose or goal fasting plasma glucose. The primary end point was change in HbA_{1C} from baseline to week 52 and secondary end points included change in body weight at week 52, incidences of hypoglycemia and proportion of patients with more than 5% decrease in body weight at week 52. Change in HbA_{1C} from baseline to week 52 for dapagliflozin was non-inferior to that of glipizide (-0.52%, -0.52% respectively). Absolute mean difference in body weight was statistically significant favoring dapagliflozin group compared to glipizide group ($p<0.0001$). The proportion of patients experiencing at least one hypo-glycemic episode by week 52 was >10 fold lower in dapagliflozin group compared to glipizide.[5] Dapagliflozin demonstrated noninferiority of glycemic control in patients not well controlled with metformin monotherapy with a favorable side effect profile.

Across 11 phase 2-3 clinical trials, concern of an association with dapagliflozin and breast and bladder cancers arose. There were nine bladder cancers reported in the 5,478 patients on the drug compared with one case in 3,156 controls; and there have also been nine cases of breast cancer in 2,223 women on the drug compared with just one in 1,053 female controls.

Similar to dapagliflozin, canagliflozin (Johnson & Johnson) has also demonstrated efficacy in lowering HbA_{1c}. In a 26 week, randomized, double-blind, placebo-controlled, phase 3 trial, HbA_{1c} was significantly reduced in canagliflozin 100 mg and 300 mg groups compared to placebo ($p<0.001$ for both). Canagliflozin also reduced FPG, 2-hr post-prandial glucose, body weight and systolic blood pressure significantly ($p<0.001$) and increased HDL-C compared to placebo ($p<0.01$).[6]

On Jan 09 2013, An FDA advisory panel expressed concerns about potential cardiovascular and bone-related safety risks with canagliflozin but still voted 10 to 5 to recommend approval. The FDA is expected to make a decision in March, and is not mandated to follow the recommendation of its advisory panel. However, they did follow recommendations of the panel when approval of dapagliflozin was declined in January secondary to the concerns of cancer. Another novel SGLT-2 inhibitor, empagliflozin, is also being investigated by Boehringer Ingelheim and Eli Lilly and the companies are seeking to file for new drug application this year.[7,8] SGLT-2 inhibitors represents a promising novel therapeutic option for the treatment of type 2 diabetes.

<Click for References>

Once Weekly Exenatide Vs Once Daily Liraglutide

Brett Snyderman, PharmD Candidate; Marcus Campbell, BC-ADM

A 26-week, open-label, multi-center, randomized, parallel-group trial sought to compare once weekly exenatide versus once daily liraglutide in patients with type 2 diabetes. The results of the DURATION-6 trial were published in the January 12th issue of The Lancet in the article titled "Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomized, open-label study". Study authors hypothesized that once weekly exenatide would be at least non-inferior and/or superior to once daily liraglutide in decreasing glycated hemoglobin (HbA_{1c}) from baseline.

912 patients were randomized 1:1 to receive either once daily liraglutide (1.8mg) or once weekly exenatide (2mg) for 26 weeks. All patients had type 2 diabetes, uncontrolled by lifestyle modification and taking maximum or near maximum doses of oral antihyperglycemic drugs. The primary outcome of the study was change in HbA_{1c} from baseline at 26 weeks. Results showed that once daily liraglutide decreased HbA_{1c} more than once weekly exenatide (-1.48% and -1.28%; p=0.02) and did not demonstrate non-inferiority for once weekly exenatide (95% CI 0.08-0.33). However, both treatment groups did demonstrate a clinically important decrease in HbA_{1c} from baseline. 271 (60%) of subjects receiving liraglutide and 243 (53%) of subjects receiving exenatide achieved HbA_{1c} levels $\leq$ 7% (p=0.0011). The liraglutide treatment group also demonstrated greater weight loss than the exenatide group (-3.57 and -2.68 kg, p=0.0005) in all patients regardless of body mass index (BMI). Those receiving liraglutide experienced adverse events at a greater frequency than those receiving exenatide; including

nausea (21% and 9%), diarrhea (13% and 6%), headache (8% and 6%), and vomiting (11% and 4%).

Clinicians can use the results of this study when evaluating treatment options for uncontrolled type 2 diabetic patients. |Although once daily liraglutide demonstrated a greater decrease in HbA_{1c} and BMI than once weekly exenatide, both drugs demonstrated clinically relevant improvements in glycemic control and weight loss. Well-designed randomized controlled trials are needed to further evaluate this comparison. The pros and cons of each medication should be weighed on an individual basis when choosing the best medication for the patient, including dosing frequency, possible adverse effects, and cost.

<Click here for references>

Watch for future improvements to the CDIR website

&

Remember to submit your drug information questions!

The **LECOM** School of Pharmacy operates out of two locations. Consistent with LECOM's core value of creating student-centered education, two distinct learning pathways are offered for the Doctorate of Pharmacy (PharmD) degree providing students the option of choosing a pathway most suited to their learning needs. In Erie, PA, an accelerated three-year pathway is offered enabling students to complete the PharmD degree in three calendar years; in Bradenton, FL, a traditional four-year pathway is offered. Both curricula offer the same spectrum of didactic courses, credit hours, and experiential education and experiences. The full array of supporting services and state-of-the-art physical facilities exists at both campuses.

Managing Editor: Marcus W. Campbell, PharmD, BC-ADM

Drug Info Team: Ryan Wargo, PharmD, BCACP; Danielle Debias, PharmD; Justin Scholl, PharmD; Alejandro Vazquez, PharmD; Michael Mueller, Ph.D.; Katherine Tromp, PharmD; Abbey Powers, PharmD; Kathryn Samai, PharmD, BCPS; Stephanie Peshek, PharmD; Julie Wilkinson, PharmD, BCPS; Marcus Campbell, PharmD BC-ADM

LECOM Bradenton
5000 Lakewood Ranch Blvd.
Bradenton, FL 34211-4909

941-756-0690 Phone
941-782-5721 Fax

LECOM
SCHOOL OF PHARMACY
CENTER FOR DRUG INFORMATION AND RESEARCH

LECOM Erie
1858 West Grandview Blvd/
Erie, PA 16509-1025

814-866-6641 Phone
814-866-8123 Fax