



eDiabetes Review VOLUME 1, ISSUE 11

NEW OAD INSIGHTS

In this Issue...

As we conclude Volume 1 of eDiabetes Review, we turn to our Program Directors to provide insight on two of the key questions our subscribers have asked us to address.

SGLT-2 inhibitors are among the newest pharmacologic options available for managing hyperglycemia. Dr. Nestoras Mathioudakis, from the Division of Endocrinology, Diabetes, & Metabolism at the Johns Hopkins University School of Medicine in Baltimore provides an overview of the class, and reviews the recent trials investigating SGLT-2 use in combination with metformin, as triple OAD therapy, and in conjunction with insulin.

While incretin-based therapies - DPP-4 inhibitors and GLP-1 receptor agonists - are being used to improve glycemic management in a wide variety of patients, safety concerns have arisen regarding the safety of these agents. Dr. Om Ganda, from Harvard Medical School and the Joslin Diabetes Center in Boston, addresses the evidence surrounding the current controversies about the potential increased risk of heart failure and pancreatic disease with these agents.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Summarize the glycemic and nonglycemic effects of SGLT-2 inhibitors.
- Describe the recent data on the use of SGLT-2 inhibitors in dual and triple therapy, as well as in combination with insulin.
- Discuss the cardiovascular safety implications of recent clinical trials with DPP-4 inhibitors.

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Om P. Ganda, MD, discloses that he has received grant/research funding from Amarin Pharma, Inc., and has served on advisory boards for Amgen and Sanofi.

No other planners have indicated that they have any financial interest or relationships with a commercial entity whose products or services are relevant to the content of their presentations.

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Length of Activity

1.0 hour Physicians
1.0 contact hour Nurses

Launch Date

April 30, 2015

Expiration Date

April 29, 2017

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GUEST AUTHORS OF THE MONTH

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Guest Faculty Disclosure

Nestoras Mathioudakis, MD and Om Ganda, MD have indicated that they have no financial interests or relationships with a commercial entity whose products or services are relevant to the content of their presentation.

Unlabeled/Unapproved Uses

Nestoras Mathioudakis, MD and Om Ganda, MD have indicated that there will be references to SGLT2 inhibitors (specifically dapagliflozin) in type 1 diabetes based on the results of a randomized controlled trial by Robert Henry et al in *Diabetes Care* (2015; 38:412-419).

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COMMENTARY

SGLT stands for sodium glucose transporter, a critical component responsible for the reabsorption of glucose in the kidney. SGLT-2 is in the first part of the proximal tubule, and is responsible for 90% of the reabsorbed glucose in the kidney; SGLT1 is responsible for the other 10%. A television ad explains the mechanism simply: the kidneys filter out sugar



and return it to the body; the SGLT-2 inhibitor agent diverts some of this returning sugar to the urinary tract. The result is less circulating plasma glucose.

There are currently three FDA approved SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) commercially available in the US, with others in various stages of the approval process. In addition, there is current development of agents that target SGLT-1, as well as preliminary studies investigating the role of dual blockade of SGLT-2 and SGLT-1.

All SGLT-2 agents are approved for use in type 2 diabetes only, and can be used as second or third-line agents, including in combination with insulin. In addition, given their insulin-independent mechanism of action, they may have a role in type 1 diabetes as well.

In the clinical trials, SGLT-2 inhibitors were found to lower A1c by about 0.5 to 0.7%, similar to the DPP-4 inhibitors. They have also shown modest weight loss and BP-lowering effects. Genital infections are the most common adverse effect, and the risk of hypoglycemia is relatively low. However, both hypoglycemia and osmotic diuresis-related events increase when SGLT-2s are taken in combination with insulin.

Because SGLT-2s work in the kidney, they are contraindicated in patients with renal insufficiency. Glomerular filtration rate (GFR) < 60 is a relative contraindication for both canagliflozin and dapagliflozin; GFR < 45 is a relative contraindication for empagliflozin. All available agents are contraindicated for GFR < 30 and end-stage renal disease or hemodialysis.

The March 2015 issue of *Diabetes Care*, the leading clinical journal in diabetes, was devoted specifically to the role of SGLT-2 inhibitors in diabetes management. Of the 12 articles published on the use of this drug class in diabetes, nine were randomized, controlled trials (RCTs). The issue reported on investigations into the glycemic efficacy as well as the important nonglycemic effects (ie, weight loss and blood pressure control) for the SGLT-2 inhibitors in patients with type 2 diabetes, as well as one small pilot study in type 1 diabetes.

The four papers reviewed in this newsletter address relevant clinical scenarios and inform our clinical practice by providing important information about the safety and efficacy of this newest class of glycemic control agents. As a caveat, however, we must remember that long-term efficacy data on clinical outcomes (cardiovascular disease, microvascular complications, etc) are lacking.

The incretin-based therapies — DPP-4 inhibitors and GLP-1 receptor agonists - are being used on an ever-expanding basis for the management of type 2 diabetes. The oral DPP-4 inhibitors in particular have gained wide acceptance, especially in the primary care arena; increased use of the injectable GLP-1 receptor agonists, while providing greater glucose-lowering, has been slower, most likely because of both clinician and patient resistance to "going on the needle." While a large body of evidence has shown that these agents are generally safe to use in a wide variety of patients, two safety-related controversies have arisen.

The most current controversy revolves around the cardiovascular safety of both DPP-4 inhibitors and GLP-1 receptor agonists. Earlier meta-analyses of many smaller studies suggested potential benefits of DPP-4 inhibitors in reducing major cardiovascular events.^{1,2} However, more recent research has identified the potential for an increased risk for congestive heart failure in patients treated with these agents. During the past several years, a number of randomized clinical trials exploring the cardiovascular safety of both incretin-based therapies were initiated. The first two of these, studying DPP-4 inhibitors, have been published and are summarized in this newsletter. While these trials were not powered to confirm or refute the heart failure concern, they do provide important data on the long-term cardiovascular safety of DPP-4 inhibitors in patients receiving "standard-of-care" treatment to prevent cardiovascular complications. Others trials, involving both DPP-4 inhibitors and GLP-1 receptor agonists, are being completed and will be published later this year and within the next few years.

More recently, an extensive 2014 meta-analysis of the available data from 84 RCTs found the overall risk of congestive heart failure was higher in patients treated with DPP-4

inhibitors in comparison with those treated with placebo/active comparators (MH-OR: 1.19[1.03; 1.37]; P = 0.015), suggesting that DPP-4 inhibitors as a class could be associated with an increased risk of heart failure (although without any clear evidence of differences among specific agents).³ Further, in April 2015, the FDA, describing that findings of its own sensitivity analyses of deaths occurring while patients were on saxagliptin treatment "suggested significant or near-significant increases in all-cause mortality," convened a meeting of its Endocrinologic and Metabolic Drugs Advisory Committee to assess the possibility of heart failure as an incretin class effect.⁴

A longer-standing controversy, regarding an increased possibility of pancreatitis and/or pancreatic cancer with the use of incretin agents, remains unsettled.^{5,6} Although they caution that the matter is not yet settled, the current position of the FDA and the European Medicines Agency (EMA) is that the incretin-mimetic agents appear to be clinically devoid of a significant adverse signal in this regard.⁶ However, due to concerns raised from certain animal data, there is a need for completion of the ongoing studies before a final determination can be made.⁷ Analysis of the large number of patients studied with saxagliptin in the SAVOR trial, reviewed in this newsletter, provides additional insight.

With the anticipated completion of most of the ongoing RCTs with DPP-4 inhibitors, and GLP-1 agonists in the foreseeable future, it is hoped that more definitive conclusions on both these safety issues can be drawn once those data become available.

References

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2. Monami M, Ahrén B, Dicembrini I, Mannucci E. [Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials](#). *Diabetes Obes Metab*. 2013 Feb;15(2):112-120.
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5. Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. [Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study](#). *JAMA Intern Med*. 2013 Apr 8;173(7):534-539.
6. Egan AG, Blind E, Dunder K, et al. [Pancreatic safety of incretin-based drugs--FDA and EMA assessment](#). *N Engl J Med*. 2014 Feb 27;370(9):794-797.
7. Bonner-Weir S, In't Veld PA, Weir GC. [Reanalysis of study of pancreatic effects of incretin therapy: methodological deficiencies](#). *Diabetes Obes Metab*. 2014 Jul;16(7):661-666.

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SGLT-2 VS SULFONYLUREA IN DUAL THERAPY

Leiter LA, Yoon KH, Arias P, et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. *Diabetes Care*. 2015 Mar;38(3):355-364.



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This was an RCT of nearly 1500 patients, all on a stable dose of metformin (at least 1500 mg/day) for 10 weeks. After a two-week run-in period with placebo, patients were randomized 1:1:1 to receive canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride at maximally tolerated dose of 6 mg or 8 mg daily. The study had a follow-up period of two years. The majority of study subjects were white or Asian. The mean duration of diabetes was about 6.5 years and the mean A1c was 7.8%.



By two years, canagliflozin was found to be more effective than glimepiride. At the 300 mg dose, the mean change in A1c was - 0.74% and at 100 mg dose it was - 0.65%, compared to glimepiride, which reduced the A1c by -0.55%. Canagliflozin 300 mg also resulted in more significant reductions in fasting glucose (- 22.5 mg/dl) compared to glimepiride (- 10.6 mg/dl). The nonglycemic effect was a 4.2% reduction in body weight (- 3.6 kg) in the canagliflozin 300 mg/day arm compared to a 0.9% increase (0.8 kg) in the glimepiride group. Systolic blood pressure was lowest in the canagliflozin 300 mg/day arm (- 3.1 mm Hg) compared to glimepiride, which resulted in 1.7 mmHg increase in systolic blood pressure.

The most significant adverse events were genital mycotic infections, which affected 15.6% of females and 9.1% of males in the highest dose of canagliflozin, although the rates of this side effect were similar in the lower dose of canagliflozin. UTI's were also common in canagliflozin, at 8.7% in the 300 mg arm. Osmotic diuretic-related adverse events occurred in 6.6% of participants, which was higher than in the glimepiride group (2.1%). There were no significant differences in volume depletion adverse events (syncope, orthostasis, etc.) between canagliflozin and glimepiride. However, hypoglycemia was much more common in the glimepiride group (40.9%) compared to the canagliflozin 300 mg/day (8.2%).

The strengths of this study were its long duration of follow-up of two years. Some of the limitations were the A1c criteria for eligibility of 7% to 9.5%, which may limit generalizability. In addition, there was underrepresentation of African American and Hispanic patients. Furthermore, the study did not include a placebo arm, although that might not have been ethically possible since the study subjects were not under good glycemic control initially.

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SGLT-2 IN TRIPLE THERAPY

Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S5; Study 05 Group. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: A 24-week randomized, double-blind clinical trial. *Diabetes Care*. 2015 Mar;38(3):365-372.



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This study randomized 219 participants to placebo versus dapagliflozin 10 mg as add-on therapy to at least 50% of maximal dose of metformin and a sulfonylurea. As in the previously reviewed study, the majority of study participants (~ 95%) were white. The mean duration of diabetes was about nine years, and 84%-88% of participants had a history of cardiovascular disease. The initial mean A1c was around 8%.

At 24-week follow-up, triple therapy with the addition of dapagliflozin resulted in an A1c reduction of 0.86%, compared to the placebo arm, which had a 0.17% reduction. Weight loss of 2.65 kg was seen in the dapagliflozin group, compared to 0.58 kg in the placebo group. Hypoglycemia occurred in ~ 13% of dapagliflozin group, compared to ~ 4% of the placebo group. Genital infections were much more common in the dapagliflozin group (2.2% of men and 7.9% of women), with no events in the placebo group. Orthostatic hypotension was not a significant adverse event in the dapagliflozin group with only one subject (0.9%) reporting this symptom.

The strengths of this study were that it included a placebo arm and that it evaluated a clinically relevant scenario. The main limitation was the short follow-up period of only 24 weeks.

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SGLT-2 AND/OR DPP-4 IN DUAL VERSUS TRIPLE THERAPY

Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: A randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care*. 2015 Mar;38(3):376-83.



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This study randomized 534 participants to three treatment arms:

Arm 1: DPP-4 inhibitor (saxagliptin) + SGLT-2 inhibitor (dapagliflozin) + metformin

Arm 2: saxagliptin + metformin

Arm 3: dapagliflozin + metformin

The racial distribution of study participants was 70% white, 11% African American, 6% Asian, and 13% other. The mean duration of diabetes was 7.6 years. The mean A1c was approximately 8.9%.

At the end of this 24 week study, the mean A1c reductions were greatest in the combination DPP-4 + SGLT2 + metformin arm. When compared to saxagliptin + metformin, there was a mean difference of - 0.59% in the triple combination therapy arm; when compared to dapagliflozin + metformin, there was a mean difference of - 0.27% versus the triple combination group. In this study, the triple combination group resulted in an 80 mg/dl reduction in postprandial glucose and 38 mg/dl reduction in fasting plasma glucose. Among study subjects, 41% met the A1c goal of < 7% in the triple combination group compared to approximately 20% in both dual combination groups. There was a 2.1 kg body weight reduction in the triple combination group, no change in body weight in the saxagliptin + metformin group, and 2.4 kg body weight reduction in the dapagliflozin + metformin group.

Interestingly, in this study, the highest rates of urinary tract infections and genital infections were observed in the dapagliflozin and metformin dual therapy arm. UTIs were seen in 5% and genital infections in 6% of study subjects in that arm, compared to 0.6% in the saxagliptin + metformin group and 0% in the triple combination group. Hypoglycemia was not a common adverse event in any of the groups.

The strength of this study was that it was the first to test use of an SGLT-2 inhibitor as dual or triple therapy with metformin. The limitations include the lack of a placebo arm, which was likely not ethical given the lack of glycemic control of the study participants. There was also short (24 week) follow-up, which makes it difficult to draw inferences about the durability of these observed effects on glycemic control.

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SGLT-2 + INSULIN

Neal B, Perkovic V, de Zeeuw D, et al; CANVAS Trial Collaborative Group. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. *Diabetes Care*. 2015 Mar;38(3):403-411.



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This large study (4330 participants) randomized participants with type 2 diabetes on a stable insulin dose (at least 20 units per day for 8 weeks) to receive either canagliflozin 100 mg, canagliflozin 300 mg, or placebo. The study included mainly white and Asian participants, with only 2-3% of study subjects in each arm being African American. The mean duration of diabetes was approximately 16 years. The median insulin dose per day was approximately 60 units, with most participants (~ 60%) receiving basal plus bolus. Concurrent oral drug therapy included metformin (~ 60% of subjects) and a sulfonylurea (~ 25% of subjects). Mean A1c was 8.3%. Patients were followed for one year.



As expected given the longer duration of diabetes in the study participants, there was a high prevalence of microvascular and macrovascular complications in this study. Approximately 20% of participants had a GFR < 60 ml/min/1.73 m² and ~ 25% had microalbuminuria. At the 52 week follow-up, the canagliflozin 300 mg/day group had a mean reduction in A1c of 0.69%, compared to 0.55% in the 100 mg/day group and 0.03% in the placebo group. There was a higher incidence of genital mycotic infections in both canagliflozin groups compared to placebo. Severe hypoglycemia occurred in 6% of the canagliflozin 300 mg/day group compared to 4% of the placebo group. Osmotic diuresis-related adverse events were more common in the high-dose canagliflozin group (10%) compared to placebo (2%).

The strengths of this study include its very large sample size and relatively long follow-up of one year. In addition, the study included a placebo arm and a high-risk patient group, which makes the finding generalizable to the population of patients with poorly controlled diabetes and established complications. One of the possible limitations of this study was whether participants were truly blinded to the intervention, since the side effects of SGLT-2 inhibitors may have been recognizable by participants.

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DPP-4 AFTER A CORONARY EVENT (EXAMINE)

White WB, Cannon CP, Heller SR, et al; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013; 369:1327–1335.



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In this noninferiority RCT, 5380 high-risk patients with type 2 diabetes were randomized to alogliptin or placebo within 15-90 days after an acute coronary event. Median age was 61.0 years, median duration of diabetes 7.2 years, and mean A1c 8.0%. Previous antihyperglycemic therapy was continued, and all patients received other treatments per standard of care. Median follow-up was 18 months. The mean reduction in A1c level during the trial was 0.36% in the alogliptin group, compared to placebo ($P < .001$).

The primary composite end-point of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke was not different between the two groups (HR 0.96; upper limit of CI 1.16; $P < .001$ for noninferiority). There were no differences in total mortality or cardiovascular mortality between the two groups. The drug was well tolerated, with no major adverse effects: specifically, there were no significant differences in the rates of hypoglycemia, pancreatitis, or cancer. Also, there was no significant difference in the rates of heart failure (HR 1.07; 95% CI 0.79-1.46)

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DPP-4 AND HEART FAILURE (SAVOR-TIMI 53)

Scirica BM, Bhatt DL, Braunwald E, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013; 369:1317–1326.



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Scirica BM, Braunwald E, Raz I, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation*. 2014 Oct 28;130(18):1579-88.



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In the first of two publications of this RTC, 16,492 patients with type 2 diabetes were randomized to saxagliptin or placebo, and followed for a median of 2.1 years. Previous antihyperglycemic therapy was continued and all patients received other treatments per standard of care. Of the total cohort, 78% of patients had prior ASCVD, and others were also at high risk due to multiple risk factors. Median age was 65.1 years; median duration of diabetes 10.3 years, and mean A1c was 8.0%.

The study found the mean A1c level was reduced by 0.20% in the saxagliptin group ($P < .001$). The primary composite end-point of cardiovascular mortality, myocardial infarction, and ischemic stroke was not different (HR 1.00, 95% CI 0.94-1.11, $P < .001$ for noninferiority). No differences were reported in the rates of hypoglycemia, pancreatitis, or cancer. Of note, however, among the various secondary endpoints, hospitalization for heart failure was greater for saxagliptin group (3.5% vs 2.8%; HR 1.27 (95% CI, 1.07-1.51, $P < .007$).

The 2014 publication in *Circulation* provided further analysis of the increased rates of heart failure found in this trial. The authors found that subjects with previous heart failure, low eGFR (≤ 60 ml/min), and those with elevated baseline N-terminal pro B-type natriuretic peptide (BNP) were at greatest risk of heart failure—and in such patients, the risk of heart failure was highest with saxagliptin.

The mechanism of increased risk of heart failure seen with saxagliptin remains unclear. Further, in the EXAMINE trial summarized in this newsletter, there was a nonsignificant trend toward increased risk of heart failure with alogliptin (HR for both studies combined 1.24, 95% CI 1.07-1.44, $P = .004$).

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META-ANALYSIS OF INCRETIN AGENTS AND HEART FAILURE

Yu OH, Filion KB, Azoulay L, Patenaude V, Majdan A, Suissa S. Incretin-based drugs and the risk of congestive heart failure. *Diabetes Care*. 2015 Feb;38(2):277-284.



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To explore the possible relationship between incretin-based therapy and heart failure, Yu et al recently published a nested case-control study from the UK Clinical Practice Research Datalink, in which the authors analyzed 1118 patients hospitalized for the first episode of congestive heart failure. Each case was carefully matched to 20 control subjects from a pool of 57,737 patients in this databank and followed for a mean duration of 2.4 years. Mean age of these patients was 72.3 years, with mean duration of diabetes at 2.3 years. In these extensive analyses, current use of incretin-based drugs (including various DPP-4 agents and GLP-1 agonists) was not associated with an increased risk of heart failure (adjusted OR, 0.85; 95% CI, 0.62-0.16, P -trend = .39).

In additional sensitivity analyses, the differences in the risk of heart failure remained nonsignificant, after exclusion of patients with renal disease, or those treated with thiazolidinediones or insulin. The main limitation of this study is the relatively small number of case subjects on incretin therapy in this database, and only a few events among each agent of the incretin class, including saxagliptin.

Thus the confirmation of any adverse effect on incretin-based agents on the incidence of heart failure awaits the results of other on-going trials. The precise mechanisms underlying this relationship, if validated, also remain unclear.

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PANCREATITIS AND PANCREATIC CANCER (SAVOR-TIMI 53)

Raz I, Bhatt DL, Hirshberg B, et al. Incidence of pancreatitis and pancreatic cancer in a randomized controlled multicenter trial (SAVOR-TIMI 53) of the dipeptidyl peptidase-4 inhibitor saxagliptin. *Diabetes Care*. 2014 Sep;37(9):2435-2441.



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In the SAVOR-TIMI 53 trial, 16,492 patients ≥ 40 years old with type 2 diabetes and established cardiovascular disease or CV risk factors were randomized to saxagliptin or placebo. The investigators reported a small but equal number of pancreatitis events ($N = 35$) among the two groups, including 33 receiving saxagliptin and 31 patients on placebo (HR 1.09, 95% CI 0.66-1.79, $P = .80$). However, definite episodes of acute pancreatitis were confirmed in only 17 and 9 patients respectively (HR 1.88, 95% CI, 0.86-4.41, $P = .17$), and definite plus possible episodes in 22 and 16 patients, respectively (HR 1.36, 95% CI, 0.72-2.64, $P = .42$). Thus, within the 2.1 years of follow-up, the risk for pancreatitis in patients with type 2 diabetes patients treated with saxagliptin was low and apparently similar to placebo, indicating a nonsignificant trend in the increased risk of pancreatitis. The study authors caution that "further studies are needed to completely resolve the pancreatic safety issues with incretin-based therapy."

The question of pancreatic cancer is even more difficult to address, given the relatively short duration of follow-up in all the available studies thus far. In the SAVOR trial, there was a paradoxical, but nonsignificant trend toward a protective effect, with 5 and 12 cases in the saxagliptin and placebo arm, respectively (HR 0.42, 95% CI, 0.13-1.12, $P = .09$). However, this could be a chance finding; and again, additional trials with longer-term follow are required.

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IMPORTANT CME/CE INFORMATION

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Nurses

eNewsletter: This 1 contact hour educational activity is provided by the Institute for Johns Hopkins Nursing. Each newsletter carries a maximum of 1 contact hour or a total of 6 contact hours for the six newsletters in this program.

STATEMENT OF NEED

- Clinicians do not appropriately intensify therapy as necessary to maintain glycemic control.
- Conflicting data about the safety of incretin agents may unduly deprive patients of treatment benefits.
- Clinicians are not aware of and/or are not implementing strategies to maximize the value of SMBG readings to improve patient outcomes.
- Clinicians do not adequately understand or treat to control CVD risk factors in their patients with T2D.
- Clinicians do not have a sufficiently current knowledge base to effectively consult patients about potential T2D therapeutic advances.
- Clinicians do not adequately counsel and treat their overweight/obese patients with T2D.

INTENDED AUDIENCE

The target audience for this initiative includes: endocrinologists, primary care clinicians, nurse practitioners, physician assistants, Certified Diabetes Educators, and other health care practitioners whose work/practice includes treating patients with T2D.

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