JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eDiabetes Review
Podcast Issue

Jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

Supported by educational grants from AstraZeneca, and Merck & Co., Inc.



VOLUME 2 — ISSUE 7: TRANSCRIPT

# Safety of the Newer Oral Diabetes Treatment Agents

Our guest author is Marc Rendell, MD from the Creighton University School of Medicine in Omaha, Nebraska.

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

- Identify the safety issues that affect selection criteria for treating patients with type 2 diabetes with GLP-1 receptor agonists.
- Identify the safety issues that affect selection criteria for treating patients with type 2 diabetes with DPP-4 inhibitors.
- Identify the safety issues that affect selection criteria for treating patients with type 2 diabetes with SGLT-2 inhibitors.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of the safety of the newer oral diabetes treatment agents. This program is a follow up to the Volume 2, Issue 6 *e*Diabetes Review newsletter—The New Agents for Diabetes: The Meaning of Safety.

**Unlabeled/Unapproved Uses**
Marc Rendell, MD has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

**MEET THE AUTHOR**

Marc Rendell, MD
Professor of Medicine
Creighton University School of Medicine
Director, Creighton Diabetes Center
Creighton University Medical Center
Omaha, Nebraska

**Faculty Disclosure**
Marc Rendell, MD has indicated that he has received grant/researching funding from AstraZeneca, Boheringer-Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Hanmi, Intarcia Therapeutics, Inc., Merck & Co., Inc., Pfizer and Co., and Sanofi.

**Release Date**
February 25, 2016

**Expiration Date**
February 24, 2018

**CME INFORMATION** ⇩ **PROGRAM BEGINS BELOW**

## ACCREDITATION STATEMENTS

**Physicians**

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

**Nurses**

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

## CREDIT DESIGNATIONS

**Physicians**

Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Nurses**

Podcast: These paired 0.5 contact hour Educational Activities are provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour, or a total of 3 contact hours for the 6 podcasts in this program.

**BOB BUSKER:** Welcome to this *e*Diabetes Review Podcast.

Today's program is a follow-up to our newsletter on the *Safety of the Newer Oral Diabetes Treatment Agents*. With us today is that issue's author, Dr. Marc Rendell, professor of medicine and director of the Diabetes Center at the Creighton University School of Medicine in Omaha, Nebraska.

*e*Diabetes Review is jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from AstraZeneca and Merck & Co., Inc.

Learning objectives for this audio program include:

- Identify the safety issues that affect selection criteria for treating patients with type 2 diabetes with GLP-1 receptor agonists.
- Identify the safety issues that affect selection criteria for treating patients with type 2 diabetes with DPP-4 inhibitors.
- Identify the safety issues that affect selection criteria for treating patients with type 2 diabetes with SGLT-2 inhibitors.

Dr. Rendell has indicated that he has received grant and or researching funding from AstraZeneca, Boheringer-Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Hanmi, Intarcia Therapeutics, Inc., Merck & Co., Inc., Pfizer and Co., and Sanofi. His discussion today will not reference the unlabeled or unapproved uses of any drugs or products.

I'm Bob Busker, managing editor of *e*Diabetes Review. Dr. Rendell, thank you for joining us today.

**DR. MARC RENDELL:** Thank you for inviting me.

**MR. BUSKER:** In your newsletter issue, doctor, you provided us with a snapshot of the constantly evolving evidence base describing the safety of what we can call the "newer" classes of diabetes treatment agents — the GLP-1 receptor agonists, the DPP-4 inhibitors, and the SGLT-2 inhibitor agents. Today, let's focus on how that information can be integrated into clinical practice. So start us out, if you would please, with a patient scenario.

**DR. RENDELL:** This is a 60 year old African American man who has had diabetes for 15 years. He had coronary angioplasty three years ago. He is treated with metformin 1,000 mg twice daily, and he is obese with a BMI of 34. His HbA1c level is 6.8 percent. His serum creatinine is 1.8 mg/dL.

**MR. BUSKER:** So this is a patient with longstanding type 2 diabetes. He's obese, and he's had CVD problems. His A1c is at 6.8%, which is really not all that bad in a patient with these kinds of comorbidities. But his creatinine is high, which might indicate kidney disease. Is that your key concern with this patient?

**DR. RENDELL:** Yes. His creatinine is a contraindication to continued use of metformin, so we have to stop metformin, and what we did is we began him on glimepiride 2 mg daily.

**MR. BUSKER:** Why would you choose a sulfonylurea?

**DR. RENDELL:** Bob, cost is an issue for this patient, as it is for many patients. Glimepiride is off patent and low cost.

**MR. BUSKER:** That's very understandable, and I think, a pretty common scenario. How did this patient do on his 2 mg of glimepiride a day?

**DR. RENDELL:** One month later he came back and unfortunately he had fasting glucose values often down to 50 mg/dL which were accompanied by occasional dizziness and sweating. In other words, he had hypoglycemic reactions.

**MR. BUSKER:** Hypoglycemia episodes, most likely attributable to the sulfonylurea. What did you do to modify his treatment?

**DR. RENDELL:** We know that hypoglycemia is very undesirable, in particular due to his history of coronary disease. I stopped the glimepiride, reviewed his diet, and noted that he'd had good control while on metformin, so we made an attempt to intensify dietary management by restricting carbohydrates.

**MR. BUSKER:** And the results of this dietary intervention?

**DR. RENDELL:** Three months later he returned. He no longer had hypoglycemia, but his fasting glucose had climbed, often up to 150 mg/dL, and he had post-supper glucose values often over 200 mg/dL. And his HbA1c had increased to 7.7%.

**MR. BUSKER:** So on the dietary intervention alone, he avoided hypoglycemia. But his glycemic control, both fasting and postprandial, slipped significantly. How did you address this?

**DR. RENDELL:** What we did is we actually restarted glimepiride at a lower dose of 1 mg daily.

**MR. BUSKER:** I think a lot of our listeners are going to question why — after the hypoglycemia problems caused by the sulfonylurea — that you tried it again. Give us your rationale for that, if you would please.

**DR. RENDELL:** It is worth trying a lower dose of a sulfonylurea to see if we can reach a happy medium with improved glucose control but without hypoglycemia. In many patients it's possible to titrate sulfonylureas in this way successfully.

**MR. BUSKER:** Was that retitration strategy successful in this patient?

**DR. RENDELL:** No, unfortunately not. Three months later he returned and was having occasional what he called "spells" in the late afternoon after working. His glucose measured on those occasions was often down in the 60 mg/dL range.

**MR. BUSKER:** So the sulfonylurea continued to cause hypoglycemia, which as you noted is particularly unsafe in patients with coronary disease. What did you do next?

**DR. RENDELL:** I stopped the glimepiride, I offered the patient a choice between albiglutide, which is a GLP1 receptor agonist, and linagliptin, which is a DPP4.

**MR. BUSKER:** Now why those particular choices?

**DR. RENDELL:** Hypoglycemia is undesirable in this man who has coronary disease. We want to choose agents with minimal risk of hypoglycemia. Both these incretin agents have an indication in renal impairment, which this patient clearly has, and they are less likely to cause hypoglycemia than sulfonylureas because their action is glucose-dependent with minimal stimulation of insulin release when glucose levels are normal alone. His creatinine levels are high, so SGLT-2 inhibitors are less likely to be effective. He also has a history of urinary tract infections, which is a relative contraindication to the use of SGLT-2 inhibitors.

Now, albiglutide, unlike other GLP1 agonists such as exenatide, has been tested and is effective and relatively safe in patients with renal failure. Linagliptin has primarily hepatic excretion, so it is a favored DPP4 agent in this patient who has renal impairment.

**MR. BUSKER:** You've given this patient a choice between taking a pill or going on an injectable. How do you help him make that decision?

**DR. RENDELL:** It is important to discuss the safety issues foremost and first. Albiglutide has significant incidence of injection site reactions, and in the registration studies did show an excess of pancreatitis relative to comparator therapy. Linagliptin, on the other hand, has relatively few safety issues in comparison. Conversely, albiglutide is relatively convenient in being a once-a-week injection. And then finally, cost figures into the equation, much depends on the insurance coverage for this patient. We want to give the patient choices.

Now after all that, the patient did choose linagliptin, but his insurance did not cover it, and we wound up having to use glimepiride at a much-reduced dose of a 0.5 mg daily.

**MR. BUSKER:** So the patient wound up on glimepiride at 0.5 mg a day. How did that work for his control?

**DR. RENDELL:** Bob, he did not do badly, it was certainly not our best choice, but coupled with encouragement to adhere to his diet, he did relatively well — not perfect, but not out of control, and that's where he stands at this day.

**MR. BUSKER:** And the episodes of hypoglycemia? Did those recur on this reduced dose?

**DR. RENDELL:** He did not have recurrent hypoglycemia on this much-reduced dose. As we have said, sulfonylureas can be effectively titrated if you have nothing else that you can work with.

**MR. BUSKER:** Thank you for that case and discussion, doctor. And we'll return with Dr. Marc Rendell from the Creighton University School of Medicine in just a moment.

**SUSAN PORTER:** Hello. I'm Susan Porter, clinical nurse practitioner and certified diabetes educator at the Johns Hopkins University School of Medicine. I'm one of the program directors of *e*Diabetes Review.

If you found us on iTunes or on the web, please be sure to subscribe. This podcast is part of Johns Hopkins *e*Diabetes Review, a new educational program providing monthly activities certified for CME credit and nursing contact hours, with expert commentary and useful practice information for clinicians treating patients with type 2 diabetes.

For additional information, or to subscribe to receive our newsletters and podcasts without charge, please visit www.ediabetesreview.org. Thank you.

**MR. BUSKER:** Welcome back to this *e*Diabetes Review podcast. I'm Bob Busker, managing editor of the program. We're speaking with Dr. Marc Rendell, from the Creighton University School of Medicine, about how safety information about the newer type 2 diabetes treatment agents can impact current practice. So if you would, doctor, let's continue by looking at another patient.

**DR. RENDELL:** I have a 69 year old woman with a 12 year history of diabetes. She underwent aortic valve replacement one year ago. Her BMI is 45.6, her diabetes is currently treated with 84 U of glargine insulin and 25 mg of metformin extended release. She admits that she overeats. Her HbA1c level is out of control at 9.8%, and her creatinine is normal at 0.6 mg/dL.

**MR. BUSKER:** She's elderly and obese, has CVD issues, and her control is very poor on glargine and a maximum dose of metformin. What are your impressions and initial treatment steps for this patient, doctor?

**DR. RENDELL:** This is a patient where diabetes is complicated by obesity, and she would certainly benefit from an agent which reduces over-ingestion of calories, so we started extended release exenatide.

**MR. BUSKER:** Why an extended release GLP1 receptor agonist?

**DR. RENDELL:** Our main target is really her overeating and her obesity. Other GLP1 agonists are available, but extended release exenatide has a lower side effect profile compared to daily agents and is favored by many health plans.

**MR. BUSKER:** Would you change her other medications?

**DR. RENDELL:** No. Although it is standard practice to reduce the insulin dose when adding a GLP1 receptor agonist, in this case she is very hyperglycemic and not at risk of hypoglycemic events.

**MR. BUSKER:** What about her age? She's 69 years old. Does that have any impact on your decision-making process?

**DR. RENDELL:** Exenatide extended release has a much-reduced side effect profile compared to twice daily exenatide. There is much less GI discomfort and hence less risk of vomiting, with dehydration and renal failure. The spectrum of age in exenatide studies includes many patients in their seventh and eighth decades of life.

**MR. BUSKER:** How did she do on this extended release GLP-1 regimen?

**DR. RENDELL:** She did remarkably well. Her glucose levels came down to normal, and we were able to reduce her insulin dose by 25%. Now SGLT-2 inhibitors are an alternative choice with benefits in treating obesity, although they do not suppress appetite.

**MR. BUSKER:** Were there other considerations about recommending an SGLT-2 inhibitor for this patient?

**DR. RENDELL:** We could have opted for an SGLT-2 inhibitor, keeping in mind that with this level of hyperglycemia there is likely to be significant glucose in her urine, and that increases the likelihood of genital and urinary tract infections. The patient was actually offered a choice, and it is important that doctors and their patients discuss the options realistically, including all the safety risks.

**MR. BUSKER:** Thank you for that case and discussion, doctor. Let me ask you to bring us one more patient now if you would, please.

**DR. RENDELL:** This is an 83 year old woman with diabetes in very good health. She has done well on metformin extended release for the past two years, but her HbA1c, which was initially in the low 7% range, had increased progressively to 8.6%. We start her on an SGLT-2 inhibitor, two months later she complains of a vaginal yeast infection. She has typical findings of vaginal candidiasis. We treat her successfully with fluconazole with topical antifungals. Two months later she asks for a refill of fluconazole due to recurrent yeast infections. She is told to stop the SGLT-2 inhibitor but pleads with us to continue. The yeast infection recurs in one month and she finally agrees to stop the agent and start insulin. And we begin glargine insulin together with a DPP4 inhibitor to target postprandial hyperglycemia.

**MR. BUSKER:** Now these recurrent fungal infections — are those typical with the SGLT-2 inhibitors?

**DR. RENDELL:** No. Fortunately, genital infections only affect a minority of women treated with these agents, typically 4% to 5%, and the incidence of urogenital infections declines with increasing duration of use.

**MR. BUSKER:** When yeast infections do occur, are they usually this difficult to treat?

**DR. RENDELL:** They can be, as are urinary tract infections, which can also occur in some patients taking SGLT-2 inhibitors.

**MR. BUSKER:** Are there predisposing factors for UTI that should be considered when using SGLT-2 inhibitors?

**DR. RENDELL:** High glucose levels lead to increased urinary glucose excretion, which promotes the infections. So be aware that patients with poor diabetes control are more likely to suffer this side effect of SGLT-2 treatment.

**MR. BUSKER:** Overall with the SGLT-2 inhibitor class of agents, what additional concerns should clinicians be aware of?

**DR. RENDELL:** Clearly, genital and urinary infections are a potential issue, and very recently the FDA has warned that sometimes the urinary infections can be quite severe and, particularly in elderly patients, can lead to deterioration, including cognitive dysfunction.

There has also been a very recent concern over diabetic ketoacidosis, which requires attention and prudence. We must realize that these agents are far less effective in the presence of renal impairment. Very recently the FDA issued a warning about decreased bone density and increased fractures in patients treated with canagliflozin. The increased fracture risk with canagliflozin has not been borne out with other SGLT-2 inhibitors. In particular, in the EMPA-REG study, this was not observed as a problem, so this may not be a class effect.

**MR. BUSKER:** Now you just mentioned EMPA-REG. About the same time your newsletter issue came out, the initial results of that EMPA-REG study were also published. Would you review those for us briefly?

**DR. RENDELL:** Yes, the EMPA-REG study results were a complete surprise to the sponsors and to us, the investigators in the study. These were patients at increased risk of cardiac events, diabetic patients, of course. Those patients who received empagliflozin had a 14% risk reduction for death from cardiovascular causes and a stunning 32% risk reduction for all-cause mortality, and there was a 35% reduction in hospitalization for heart failure. These results had very little to do with improvement in glucose levels, since the divergence in cardiovascular events between the empagliflozin and placebo groups happened within three months. It is plausible that the diuretic effect of empagliflozin was preponderant in preventing cardiac overload in these at-risk patients.

**MR. BUSKER:** We've discussed both the potential safety hazards and the benefits of SGLT-2 inhibitor therapy. Bottom-line it for us: in your opinion, do you think clinicians and patients are likely to accept a potentially higher level of side effects to achieve the cardiovascular benefits?

**DR. RENDELL:** There is no doubt that the striking results of empagliflozin will influence our choice of regimens going forward. It is very likely that empagliflozin and perhaps other SGLT-2 inhibitors, if their upcoming long-term results are as successful,

will join metformin as the second line of therapy in type 2 diabetes. Nevertheless, we must recognize that our role as physicians is to balance benefit and harm. That is an individual decision each physician must make together with each patient. That is why we are doctors. We must not treat solely based on results in populations; each patient is an individual.

**MR. BUSKER:** Doctor, thank you for today's cases and discussions. I'd like to ask you to look to the future for us now. What changes might clinicians expect to see in the next few years?

**DR. RENDELL:** Certainly the positive results of the EMPA-REG trial will encourage much greater use of the SGLT-2 inhibitors and the development of more agents based on inhibition of glucose transport proteins. We now appreciate that type 2 diabetes, which requires insulin, is better treated with combined long-acting insulin and a GLP1 receptor agonist. Pen devices are being developed that deliver fixed ratios of degludec insulin and liraglutide, and other combinations will soon follow. Patients treated with combined insulin and GLP1 agonists have superior glucose control with less hypoglycemia and less weight gain.

What is coming are combined SGLT-1 and SGLT-2 inhibitor agents, which decrease intestinal glucose absorption, thereby lowering glucose absorption in the urine as a promoter of infections. These agents are going to happen in the not too distant future, and hopefully they will lower the incidence of both genital and urinary tract infections with other agents.

Finally, outside of the area of diabetes, per se, the coming of the PCSK9 inhibitors to lower LDL cholesterol to extremely low levels, will raise the question if we can effectively counteract the effect of diabetes in promoting cardiac events. There is also a major effort going on to develop antiinflammatory agents and selective vasodilators to slow the progression of diabetic nephropathy.

The assessment of long-term effects of newer treatments will continue. Many long-term studies will conclude in the next few years, and there are questions. The GLP1 agonists have many favorable effects, but they all tend to increase heart rate. The lixisenatide cardiac study showed neither benefit nor harm from this agent, and we now await studies and their results with other GLP1 agents.

The long-term study comparing glimepiride with linagliptin will conclude in about two years and those results, if they show much less heart disease with linagliptin, could mean the end of sulfonylurea treatment in the older type 2 diabetes population. The PCSK9 inhibitors I mentioned will presumably have a very beneficial effect in cardiac disease and diabetes, but there are lingering questions about the effect of very low cholesterol on neurologic function, and particularly on cognitive function. We must always remember that the balance of benefit and safety is constantly reassessed, and every doctor and every patient contributes to this ongoing analysis.

**MR. BUSKER:** Well said, doctor. Let's wrap things up by reviewing today's podcast in light of our learning objectives. So to begin: the safety issues clinicians need to consider when treating patients with GLP1 receptor agonist agents.

**DR. RENDELL:** GLP1 agonists are a very successful treatment. Their main use is prompted by the desire to treat obesity. We must be aware that although there is a minimal incidence of hypoglycemia with a GLP1 agonist, there are also safety issues. The greatest concern, which does occur, is pancreatitis. Although the data is fuzzy, we need to be aware that a patient who manifests symptoms of abdominal pain, nausea, or vomiting may not have side effects from the agent, but they may have actual pancreatitis, and we need to be vigilant.

Certainly, GLP1 agents are associated with nausea, vomiting, and diarrhea, and we must tell our patients that is a potential problem. We should always be available to our patients when they run into issues with a GLP1 agonist. If we do this, we can use the agents effectively and safely.

**MR. BUSKER:** And our second learning objective: safety issues to be considered when treating patients with DPP-4 inhibitors?

**DR. RENDELL:** DPP4 inhibitors are fairly innocuous. They do not cause gastrointestinal discomfort or side effects, and by and large, they do not cause hypoglycemia. But they have been associated with pancreatitis, so we must be vigilant for that possibility. Very recently there's been a warning coming out of FDA of unexplained joint pain occurring with these agents. We must recognize that if our patients complain of joint pain,

we need to look at the possibility that the DPP-4 agent could be involved.

**MR. BUSKER:** And finally: the safety issues to be considered when prescribing SGLT-2 inhibitor agents.

**DR. RENDELL:** SGLT-2 inhibitors have a relatively serious side effect in some patients, and that is recurrent genital infection. The FDA has recently warned about severe urinary tract infections. We should also be aware that these agents are less effective when there is renal impairment because, of course, their effect is mediated by the kidney.

The FDA's recent warning regarding canagliflozin and decreased bone density has to be considered, particularly in patients who have or are at risk for osteoporosis. Fortunately, recurrent, refractory fungal infections in these patients are relatively rare, as are severe urinary tract infections.

**MR. BUSKER:** Dr. Marc Rendell from the Creighton University School of Medicine, thank you for participating in this eDiabetes Review Podcast.

**DR. RENDELL:** Bob, it's been a pleasure spending this time with you and with your listeners.

**MR. BUSKER:** To receive CME credit for this activity, please take the post-test at www.ediabetesreview.org/test.

This podcast is presented in conjunction with the *e*Diabetes Review Newsletter, a peer-reviewed literature review certified for CME/CE credit, emailed monthly to clinicians treating patients with type 2 diabetes.

This activity has been developed for endocrinologists, primary care clinicians, nurse practitioners and nurses, physician assistants, certified diabetes educators, and other health care practitioners whose work or practice includes treating patients with type 2 diabetes.

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in this activity.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

For nurses, this 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour.

This educational resource is provided without charge, but registration is required. To register to receive eDiabetes Review via email, please go to our website: www.ediabetesreview.org.

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only.

Use of the names of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing implies review of educational format, design, and approach. Please review the complete prescribing information for specific drugs, combinations of drugs, or use of medical equipment, including indication, contraindications, warnings, and adverse effects, before administering therapy to patients.

*e*Diabetes Review is supported by educational grants from AstraZeneca and Merck.