



VOLUME 3 - ISSUE 4

LISTEN TO PODCAST

DOWNLOAD PODCAST

PHYSICIAN POST-TEST

NURSE POST-TEST

**Insulin Intensification with OADs**

- Recognize when treatment intensification is needed in patients receiving insulin monotherapy.
- Describe considerations for patients on insulin monotherapy who have advanced chronic kidney disease.
- Explain how to add oral agents to insulin monotherapy to maximize clinical benefit while minimizing risk.

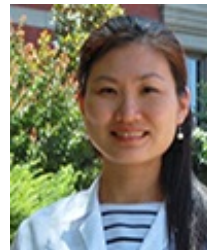
**Guest Faculty Disclosure**

Dr. Lee has indicated that she has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of this presentation.

**Unlabeled/Unapproved Uses**

Dr. Lee has indicated that there will be no references to the unlabeled or unapproved uses of any drugs or products.

MEET THE AUTHOR



**Clare Lee, MD, MHS**

Assistant Professor of Medicine  
Division of Endocrinology, Diabetes & Metabolism  
Johns Hopkins University School of Medicine  
Baltimore, Maryland

**Release Date:**  
February 09, 2018

**Expiration Date:**  
February 08, 2020

LISTEN TO PODCAST NOW

DOWNLOAD PODCAST

SUBSCRIBE NOW

PHYSICIAN POST-TEST

NURSE POST-TEST

OTHER RESOURCES

[Download the podcast transcript](#)

[Go to the companion newsletter](#)

NEWSLETTER ARCHIVE

SHARE WITH A COLLEAGUE

PROGRAM DIRECTORS

**Nestoras Mathioudakis, MD, MHS**

Assistant Professor of Medicine  
Clinical Director, Endocrinology, Diabetes & Metabolism  
Johns Hopkins University School of Medicine  
Baltimore, Maryland

**Kathleen Dungan, MD, MPH**

Associate Professor  
Associate Division Director for Clinical Services  
Division of Endocrinology, Diabetes and Metabolism  
The Ohio State University  
Columbus, Ohio

**Susan Porter, MSN, CRNP, CDE**

Clinical Nurse Practitioner and Certified Diabetes Educator  
University of Maryland, St. Joseph Medical Group Owings  
Mills Internal Medicine  
Baltimore, Maryland

**Podcast Transcript**

**BOB BUSKER:** Welcome to this eDiabetes Review podcast.

I'm Bob Busker, managing editor of eDiabetes Review. We're here today with Dr. Clare Lee, Assistant Professor of Medicine in the Division of Endocrinology, Diabetes & Metabolism at the Johns Hopkins University School of Medicine. And our topic — a follow-up to Dr. Lee's recent newsletter issue — is "Intensifying Insulin Monotherapy with Oral Agents."

eDiabetes 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 Merck & Co, NovoNordisk, and Sanofi.

Learning objectives for this audio program include:

- Recognize when treatment intensification is needed in patients receiving insulin monotherapy.
- Describe considerations for patients on insulin monotherapy who have advanced chronic kidney disease.
- Explain how to add oral agents to insulin monotherapy to maximize clinical benefit while minimizing risk.

Dr. Lee has indicated that 1) she has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of this presentation, and 2) there will be no references to the unlabeled or unapproved uses of any drugs or products.

**MR. BUSKER:** Dr. Lee, thank you for joining us today.

DR. CLARE LEE: Thank you for inviting me, happy to be here.

**MR. BUSKER:** In your newsletter issue, you presented a lot of information about both the older and newer oral antidiabetes agents and the benefits and cautions clinicians should be aware of when considering them as add-on to insulin monotherapy. Today, let's focus on how that information can translate into clinical practice. Please start with a patient scenario.

DR. LEE: Ms. K. is a 67-year-old woman with a history of type 2 diabetes, hypertension, and obesity. Her diabetes was diagnosed when she was in her 40s, and she has taken metformin since then. Her glycemic control recently deteriorated and you switched her regimen from metformin to glargine 30 units daily. At the last follow-up visit, glargine dose was increased to 36 units daily. She reports adhering to low carbohydrate diet and taking her insulin daily. Since starting insulin, she reports a few episodes of hypoglycemia that woke her up in the middle of the night. She presents to your clinic today and her HbA1C is 8.9%.

**MR. BUSKER:** What are the key things in this patient's presentation that indicate you should consider intensifying her diabetes regimen?

DR. LEE: Her insulin regimen was intensified a couple of months ago, and despite that she is still having the A1C above the goal of 7% or 7.5% given her age. She is at the same time experiencing episodes of hypoglycemia, which makes you worry that she is perhaps experiencing both hyper- and hypoglycemia. Maybe her A1C would even worse than 8.9%, had it been not for the hypoglycemia. These things combined make you concerned that her glycemic control remains off target.

**MR. BUSKER:** Why do you think her control is deteriorating?

DR. LEE: There could be several reasons. Number one, type 2 diabetes involves the progression of beta cell failure, which can contribute to requiring more therapy as the disease progresses. We know that Ms. K. has had diabetes for a few decades, so it may not be surprising that she is requiring more medications in addition to a healthy lifestyle. Furthermore, she has obesity, which could bring in insulin resistance as yet another factor contributing to glycemic deterioration. At the same time, we need to be mindful of lifestyle and medication adherence factors that could also play a role.

We know that Ms. K. avoids high carb diets, but perhaps things she is unaware of in her diet may be contributing to high glucose. She reports medication adherence, but sometimes we have to really delve into that to make sure the patients are tolerating the medications and no practical aspects of obtaining the medications may be playing a role, such as not being

able to afford the medications or getting access. These are factors that we need to gently probe and make sure they are not contributing to glycemic deterioration.

**MR. BUSKER: What oral diabetes medications would you consider adding to this patient's regimen?**

DR. LEE: Of the several medication options we have for oral therapy, metformin should come to mind first. There is a consensus in the field that metformin is by far the most preferred oral therapy choice because it's efficacious, it's affordable, and we have a long history of a familiar safety profile. We also know that Ms. K. has taken metformin in the past.

**MR. BUSKER: Do we know why she was taken off the metformin? It's common, isn't it, for patients to remain on metformin when they begin insulin therapy?**

DR. LEE: That's right. In this case it remains unknown why metformin was discontinued in her diabetes management, but quite a few people out there may be only on insulin for their diabetes management for several reasons.

One reason could be a decline in renal function, which would prompt a reduction or stopping of metformin and substituting instead with insulin. Another common reason for stopping metformin would be intolerance to the gastrointestinal side effects. Those are two prominent reasons for stopping metformin.

In another case, if the patient has a severe hyperglycemia while on metformin alone, a provider may try to switch the therapy from metformin to insulin to quickly intensify the diabetes management, and along the way the person may remain on insulin when they could be on combination or revert to oral therapy after the hyperglycemia is somewhat controlled to near goal again.

**MR. BUSKER: What other oral medications might you consider as add-on to this patient on insulin?**

DR. LEE: Another option is an SGLT-2 inhibitor, which is the newest medication in our diabetes armamentarium. SGLT-2 is shown to reduce the A1C by about 0.6% and it improves the fasting as well as postprandial hyperglycemia without causing much hypoglycemia.

Another benefit may be a reduction in blood pressure and cardiovascular benefits that have caused some excitement in the field of diabetes and cardiology world.

We also have DPP-4 inhibitor as an oral therapy that can be added to insulin. It is shown to reduce the A1C by about 0.5% by improving the fasting and postprandial hyperglycemia. The nice thing about DPP-4 is that it is generally very well tolerated, with minimal gastrointestinal side effects, and it does not cause hypoglycemia.

Another oral therapy option would be pioglitazone, which has been around for quite a bit, but we don't use it regularly because it may increase the risk of hypoglycemia, not to mention some concerns about increased risk of osteoporosis and concern for possible increase in bladder cancer risk.

Speaking of the increased risk of hypoglycemia, sulfonylurea should be avoided in this case with Ms. K, who has told you about hypoglycemia, because of the well-known increased risk for hypoglycemia when you use sulfonylurea in combination with insulin.

In contrast, SGLT2 inhibitors and DPP-4 inhibitors are useful in lowering the dose of insulin when combined with insulin. As a result of that and also because of their innate properties, overall they do a great job of reducing the risk of hyperglycemia.

**MR. BUSKER: This patient, as you presented her, has a history of obesity. What effect do these oral add-on medications have on weight?**

DR. LEE: In patients with type 2 diabetes and obesity, wouldn't it be nice to be able to treat both with the diabetes medications we're giving them? In this case we are absolutely able to do so because metformin, for example, is well known to promote some weight loss while being a potent agent for lowering blood glucose. In addition, we can consider SGLT2 inhibitors now, which can cause a modest amount of weight loss of about a few kilograms. In contrast, DPP-4 inhibitors appear to be weight-neutral.

Sulfonylureas and pioglitazones are known to promote weight gain. And as you may know, insulin itself promotes weight gain. So the combination of sulfonylurea with insulin or pioglitazone with insulin would not be helpful in patients who are challenged by obesity.

**MR. BUSKER: Thank you for that case and discussion. We'll return with Dr. Clare Lee from Johns Hopkins in just a moment.**

**MR. BOB BUSKER**

This is Bob Busker, managing editor of eDiabetes Review. eDiabetes Review is a combination newsletter and podcast

program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to clinicians treating patients with type 2 diabetes.

In the month following each newsletter, a case-based podcast discussion, like the one you're listening to now, is available to help translate that new clinical information into practice. These podcasts are also available as downloadable transcripts.

Subscription to eDiabetes Review is provided without charge or prerequisite.

Continuing education credit for each newsletter and each podcast is provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. For more information on this educational activity, to subscribe and receive eDiabetes Review without charge, and to access back issues, please go to our website: [www.ediabetesreview.org](http://www.ediabetesreview.org)

Thank you.

**MR. BUSKER:** Welcome back to this eDiabetes Review podcast. We've been talking with Dr. Clare Lee from the Division of Endocrinology, Diabetes & Metabolism at the Johns Hopkins University School of Medicine about the cautions and benefits clinicians need to be aware of when intensifying insulin monotherapy with oral agents. Let's continue with another patient scenario, Dr. Lee.

DR. LEE: Mr. G. is a 59-year-old man with a history of type 2 diabetes, hypertension, and chronic kidney disease. His diabetes was diagnosed 10 years ago and he started metformin. Sitagliptin was added to his regimen several years ago. His chronic kidney disease was diagnosed a few years ago, and it recently progressed to stage 4. As a result, you recommended that he stop his oral diabetes medications and start glargine 30 units daily.

After three months of insulin monotherapy, repeat HbA1C is 9.3%. Mr. G. is reluctant to add another injectable medication.

**MR. BUSKER:** What do you see as contributing to his poor glycemic control?

DR. LEE: There are some similarities to the previous case, such as the worsening glycemic control. It's probably multifactorial, including the progression of beta cell failure and perhaps some component of lifestyle such as nonadherence to the medications or dietary nonadherence. What's different about this case, however, is that Mr. G.'s diabetes regimen changed quite a bit in the setting of worsening kidney disease. His oral medications were stopped and he was started on a basal insulin at the last visit. He now has a hemoglobin of 9.3%, which suggests his current basal insulin is not adequate to control his most likely postprandial hyperglycemia, and this calls for an intensification of his diabetes medication.

**MR. BUSKER:** His stated preference is no additional injections. That would rule out both prandial insulin and a GLP-1 receptor agonist. Of the oral diabetes medications we've been discussing, which ones might be appropriate to add to this patient's regimen?

DR. LEE: Among the several options we have for oral agents; unfortunately we are unable to use metformin in this because of the severity of his chronic kidney disease. Similarly, SGLT2 is contraindicated in stage 4 chronic kidney disease.

On the other hand, one DPP-4 inhibitor, linagliptin, is approved for use without renal dose adjustment. It would be a reasonable option in this case, although keeping in mind that the A1C reduction power for linagliptin is quite modest at about 0.5%.

Another option, since Mr. G. prefers not to have an additional injectable medication, would be pioglitazone. It is also approved for use without renal dose adjustment.

**MR. BUSKER:** On the other side of the coin, what oral medications should this patient avoid?

DR. LEE: To drive home the point about limiting the number of options for oral therapy in treating our patients who have chronic kidney disease, we have to be careful to reduce or stop metformin depending on the severity of the chronic kidney disease. Likewise, sulfonylurea is cleared renally and has to be adjusted or stopped for patients with kidney disease.

Of the DPP-4 inhibitors, linagliptin is an exception, but all the other ones are contraindicated in severe kidney disease. Similarly, SGLT-2 inhibitors are not approved for use in patients with chronic kidney disease.

**MR. BUSKER:** So specifically for this patient's situation and preferences, what oral medication would you prescribe to intensify his insulin therapy?

DR. LEE: Our options are quite limited in patients with chronic kidney disease. Therefore, we may have to consider adding linagliptin and combining that with pioglitazone in addition to his basal insulin.

**DR. BUSKER: How soon after adding an oral would you recheck his A1C to determine how well the intensification of his regimen is working?**

DR. LEE: While you are actively titrating the patient's diabetes medications, it's crucial to check the HbA1C every three months to keep the pace and appropriately titrate the diabetes regimen.

**MR. BUSKER: Thank you for that case and discussion, Dr. Lee. I think we've got time for one more patient scenario, please.**

DR. LEE: Mr. J. is a 52-year-old man with a history of type 2 diabetes and coronary artery disease that is status post-stent and well controlled heart failure. Since his diabetes diagnosis five years ago, he has taken detemir 40 units nightly. Recently his glycemic control worsened, with HbA1C of 9.7%. He lives alone and recalls falling while walking downstairs on waking up in the middle of the night last week with hypoglycemic symptoms of jitteriness and sweatiness. Fortunately, he was able to get right back up without any injury and got a snack to treat his hypoglycemia.

**MR. BUSKER: Your thoughts on intensifying his diabetes regimen?**

DR. LEE: I'd like us to pay attention to the fact that he not only has a HbA1C above his treatment target, but at the same time he has hypoglycemic episodes that are concerning. Both of these combined suggest a large fluctuation in his glucose, the lows and the highs, and both of these scenarios are undesirable in treating his diabetes.

DR. LEE: So with HbA1C of 9.7% while taking detemir 40 units nightly, it's clear that he needs regimen intensification and it would be nice to do it without adding another injectable. Let's consider some of our oral medication options, in particular paying attention to the cardiovascular benefits that may be associated with some of these medications.

For example, metformin is again our best bet in reducing the blood glucose and also providing some cardiovascular protection.

Another option to consider is SGLT2 inhibitor, which can reduce the A1C by about 0.6%. In addition, DPP-4 inhibitor is an oral agent that can lower the A1C about 0.5%. Both of these agents are favorable in older adults who have hypoglycemia because they are not shown to increase the risk of hypoglycemia.

**MR. BUSKER: Let's focus for a moment on this patient's coronary artery disease. Would he be a candidate for one of the SGLT2 agents?**

DR. LEE: SGLT2 inhibitors have been causing quite an excitement in the diabetes and cardiology world, with recent trials showing some impressive cardiovascular benefits, in particular, a reduction of cardiovascular deaths by 24% using empagliflozin and canagliflozin. And so, with those benefits of cardiovascular mortality reduction and also the ability to lower blood pressure, there has been some debate in the field as to how soon we should be adding these medications to patients with type 2 diabetes.

I think in this case it's clear to say that SGLT2 can be a good regimen to be added in Mr. G., who has a known cardiovascular disease and remains under inadequate glycemic control despite his basal insulin. I would recommend adding an SGLT2 inhibitor because its benefits are probably greater than the harms of using this agent in Mr. G.

**MR. BUSKER: One final question on this patient. Which of the oral medications should be avoided in this patient?**

DR. LEE: The medications I would recommend avoiding in older adults who live alone, like Mr. G., and are at high risk of hypoglycemia, would be sulfonylurea and pioglitazones, which have been shown to increase the risk of hypoglycemia when combined with insulin therapy.

**MR. BUSKER: Dr. Lee, thank you for sharing your insight and expertise in today's cases. One final question about oral diabetes medications: what additional data are needed to clarify their best use?**

DR. LEE: We need more data looking at using multiple oral medications and how they may interact with each other to improve the glycemic control in patients with type 2 diabetes. We would like to see more long-term data on the newer medications, particularly SGLT2 inhibitor and DPP-4 inhibitor with regard to their efficacy and safety.

We also need more data on cost effectiveness, especially involving these two new agents. And these oral medications may have some role in managing type 1 diabetes that we are not aware of at the moment. For example, metformin is sometimes used in patients with type 1 diabetes for cardiovascular risk benefits, and since we know that SGLT-2 inhibitor has cardiovascular benefits, it is up to future research to show us whether there is a role in using SGLT2 inhibitors in type 1 diabetes management.

**MR. BUSKER: Thank you, doctor. Let's wrap things up by reviewing what we've been talking about today in light of our learning objectives. First: recognizing when treatment intensification is needed in patients receiving insulin**

## **monotherapy.**

DR. LEE: We need to be mindful of checking HbA1C, which is a great marker for one's glycemic control, and at the same time asking the patient about any trouble with hypoglycemia, which can be useful in finding out whether there's large fluctuation in both the highs and lows of their glucose patterns. At the same time, we need to pay attention to their kidney function and cardiovascular portfolio to adjust what medications might best benefit them.

**MR. BUSKER: And our second learning objective: considerations for patients on insulin monotherapy who have advanced chronic kidney disease.**

DR. LEE: In the setting of chronic kidney disease some of the oral medication options will no longer be helpful. For example, metformin needs to be stopped at a GFR of 40 or someone who is in stage 4 chronic kidney disease, and many of the SGLT2 inhibitors and DPP-4 inhibitors will not be safe.

On the other hand, linagliptin, which is also a DPP-4 inhibitor, can be used without renal dose adjustment, as can pioglitazones.

**MR. BUSKER: Finally: explain how to add oral agents to insulin monotherapy to maximize clinical benefit while minimizing risk.**

DR. LEE: When deciding which oral medications to add to insulin monotherapy, first we should pay attention to how potent it is in reducing the A1C. For example, metformin, sulfonylurea, and pioglitazone are more potent in reducing the A1C than the newer agents such as SGLT2 inhibitors and DPP-4 inhibitors.

Alongside each medication's ability to lower blood glucose, we also should be mindful of each medication's impact on weight. For example, we know that metformin and SGLT2 inhibitors are helpful in promoting a modest amount of weight loss, which should be considered when treating patients with type 2 diabetes and obesity. In contrast, sulfonylurea and pioglitazones may promote some weight gain when combined with insulin monotherapy.

Another important consideration is risk of hypoglycemia, which is particularly worse when combining sulfonylurea or pioglitazone with insulin. In addition, we can consider the cardiovascular impact of each oral medication when we are deciding which one to add to insulin monotherapy. With the current evidence, we know that metformin and SGLT2 inhibitors are particularly beneficial in reducing the cardiovascular risks.

**MR. BUSKER: From the Johns Hopkins University School of Medicine — Dr. Clare Lee, thank you for participating in this eDiabetes Review Podcast.**

DR. LEE: Thank you, Bob, I really appreciate the opportunity today to speak with you on this important topic.

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

**This podcast is presented in conjunction with the eDiabetes 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 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 credit*<sup>™</sup>. 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](http://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.

eDiabetes Review is supported by educational grants from Merck & Co., Inc., NovoNordisk, and Sanofi. This program is copyright with all rights reserved by the Johns Hopkins University School of Medicine.

## CME/CE INFORMATION

### ACCREDITATION STATEMENT

#### 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.

#### Nursing

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 DESIGNATION STATEMENT

#### Physicians

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

#### 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.

### POLICY ON SPEAKER AND PROVIDER DISCLOSURE

It is the policy of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing that the speaker and provider globally disclose conflicts of interest. The Johns Hopkins University School of Medicine OCME has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Detailed disclosure will be made in the instructional materials.

[INTERNET CME/CE POLICY](#)

[INTENDED AUDIENCE](#)

[DISCLAIMER STATEMENT](#)

[CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY PARTICIPANTS](#)

[STATEMENT OF RESPONSIBILITY](#)

[HARDWARE & SOFTWARE REQUIREMENTS](#)

[STATEMENT OF NEED](#)

[COMPLETE CME INFORMATION](#)

All rights reserved - The Johns Hopkins University School of Medicine. Copyright 2018.

This activity was developed in collaboration with DKBmed.