

CASE STUDIES:

Managing Type 2 Diabetes From Diagnosis Through Disease Progression: Role of GLP-1 Receptor Agonists in Therapy

About This Activity

This enduring activity was developed in part from a CE-certified symposium held on Thursday, October 3, 2013, during OMED 2013 Osteopathic Medical Conference & Exposition in Las Vegas, Nevada.

Target Audience

This CE activity is intended for osteopathic physicians and other healthcare professionals involved in the care of patients with type 2 diabetes.

Learning Objectives

After completing this activity learners should be better able to:

1. Identify different concerns and pathophysiologic considerations that exist for patients at different times in the course of diabetes progression
2. Differentiate GLP-1 receptor agonists from traditional glucose-lowering agents with respect to A1C lowering effects, weight effects, and risks of hypoglycemia

3. Explain the differences between GLP-1 receptor agonist therapy and DPP-4 inhibitor therapy in patient-centered language
4. Describe how GLP-1 receptor agonists may be used as monotherapy, part of combination therapy strategies, with insulin, and over the course of diabetes

Credit Designation Statement

The American Osteopathic Association designates this activity for a maximum of 1.50 hours of Category-1B credit.

Planning Committee Disclosures

Laurie Ermentrout states that she has no relevant financial relationship to disclose.

Kate Mann, PharmD, states that she has no relevant financial relationship to disclose.

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Managing Recent-Onset Diabetes: Choosing Well-Tolerated Therapies With Durability to Add to Metformin or in Metformin-Intolerant Patients

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Introduction

Current treatment algorithms for type 2 diabetes mellitus (T2DM) recommend promptly starting pharmacotherapy, usually with metformin, for patients with moderate hyperglycemia in whom lifestyle changes are anticipated to be unsuccessful when used alone.^{1,2} Metformin, the most widely used first-line T2DM drug, has a long record of safety. This oral agent has been associated with improved glycemic, microvascular and cardiovascular outcomes, reduction in diabetes-related complications, a low risk of hypoglycemia and weight gaining, and is also available generically. Clinical data supporting metformin's use soon after diabetes diagnosis suggest that earlier use might preserve beta-cell function, and prolong the effectiveness of metformin, reduce lifetime glycemic burden, and thus prevent diabetes complications.³

Figure 1 shows categories of duration of diabetes at metformin initiation (adjusted for age and A1C level at initiation) and the percent per year experiencing secondary failure. If metformin was started within 3 months of diagnosis, the failure rate was 12.2%, but if it was started at 12 months from diagnosis, the failure rate was 21.4%. The separation is clearer in Figure 2, when looking at the level of A1C. If one waits to initiate metformin until the A1C level is above 9%, the failure rate is 19.4% per year, whereas the failure rate is much lower if metformin is started at an A1C level closer to 7%.³

Metformin is associated with initial gastrointestinal (GI) side effects and may not be tolerated by all patients, especially at higher doses. Caution is advised in using it in patients at risk for lactic acidosis especially in people advanced renal insufficiency, cirrhosis or alcoholism.⁴

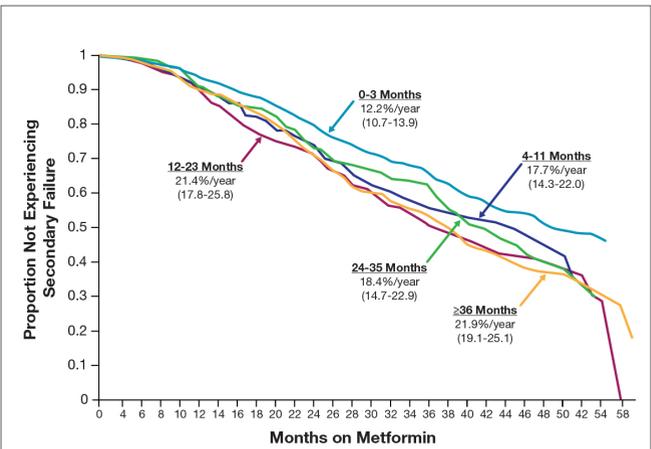


Figure 1. Kaplan-Meier plot of secondary failure of metformin monotherapy by categories of duration of diabetes at metformin initiation, adjusted for age and A1C level at initiation and the percent per year (95% confidence intervals [CIs]) experiencing secondary failure.

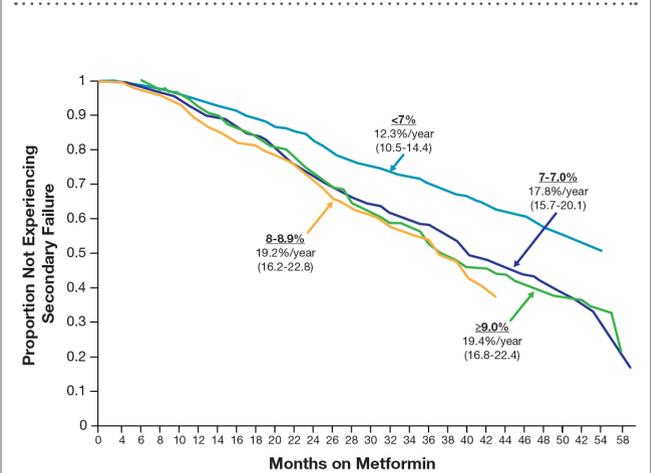


Figure 2. Kaplan-Meier plot of secondary failure of metformin monotherapy by categories of A1C level at metformin initiation, adjusted for age and diabetes duration at initiation and the percent per year (95% CIs) experiencing secondary failure.

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Case Study

Clinton is a 40-year-old African-American man, married with 4 children, who works as a foreman of a loading dock. He was diagnosed with T2DM 3 months ago. He weighs 220.5 lb and has a body mass index (BMI) of 31.6 kg/m². He is a current smoker. He is on no prescription medications. His current A1C level is 7.8%. He complains of sleep disturbance.

Biometrics:

- Height: 70 in.
- Weight: 220.5 lb (100 kg)
- BMI: 31.6 kg/m²

Vital signs:

- Pulse: 55 bpm
- Respirations: 22/minute
- Blood pressure (BP): 148/92 mm Hg

Medical history:

- Appendectomy 5 years ago
- No history of alcoholism
- No history of pancreatitis

Family history:

- Two brothers, both with T2DM, controlled with oral medications

Social history:

- Loading dock foreman
- Married; 4 children, ages 4, 6, 8, and 9
- Smoker (½ pack a day x 15 years)
- Social alcohol use (beer on weekends)
- Denies illicit drug use

Current medications:

- Multivitamin daily
- Occasional over-the-counter (OTC) medicines for headache

Question 1:

What is your priority for treating this patient?

- A. Focus on BP
- B. Focus on glucose
- C. Focus on lipids
- D. Focus on weight
- E. All of the above

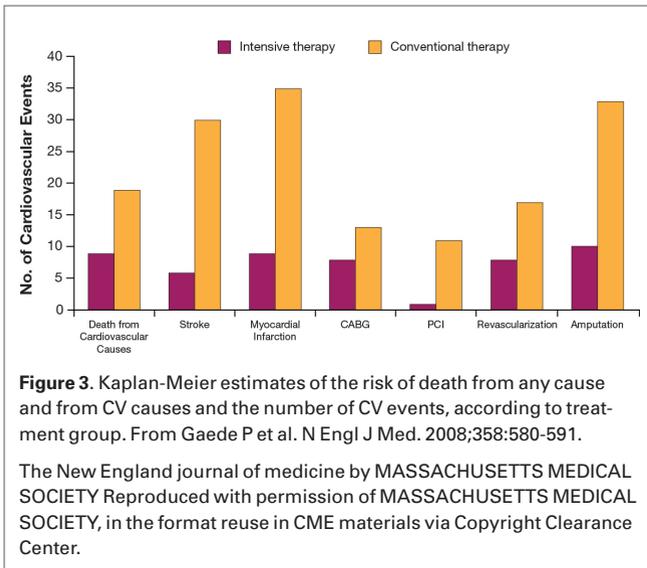
All of Clinton's parameters need attention. One could argue that addressing his weight would improve the other 3 parameters, but it is known that unless a patient is ready and willing to make a change in lifestyle and to address weight, such efforts are not likely to succeed. It has also been shown that physicians are often reluctant to bring up the topic of weight during an office visit.⁵

Bergenstal and colleagues studied physician approaches to patients with diabetes and with adverse CV risk factors and found that, after evaluating the metabolic profiles of

patients enrolled in the study, physicians assigned the highest treatment priority to glucose control (for 68% of patients, followed far behind by lipids in 11% of patients and BP in 9% of patients).⁶ The historical rationale for improving glycemia was the estimated 37% reduction in microvascular complications for each 1% reduction in A1C levels.⁷ While this is important, most patients with type 2 diabetes die from cardiovascular disease and cardiovascular risk factors must be addressed.

A meta-analysis performed by Huang found that in patients who had concurrent hyperglycemia, hypertension and dyslipidemia the greatest benefit with hypertension, then dyslipidemia, then finally glucose lowering.⁸ Hypertension is the most common among the comorbid disease conditions, occurring in 90% of patients with diabetes,⁹ and further increases the risk for disease- and treatment-related complications.¹⁰ The combination of hypertension and diabetes accelerates the progression of diabetes-related complications such as diabetic nephropathy, retinopathy, left ventricular hypertrophy, and diastolic heart failure, and doubles the risk of stroke and cardiovascular disease and all-cause mortality compared with non-diabetic patients with hypertension.¹¹

A comprehensive approach to the person with T2DM is the most effective. In the Steno-2 study, intensified therapy of modifiable risk factors in patients with T2DM and microalbuminuria was compared with standard treatment. The target limits for A1C, fasting cholesterol and triglycerides (TGs), and BP were much stricter than in the control group. In addition to lifestyle changes and diet modifications, all patients in this group received ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). This multifactorial approach led to significant reductions in both micro- and macrovascular event rates as well as death (**Figure 3**),¹² and was found to be cost-effective.¹³ Treatment guidelines now suggest a comprehensive approach to patients with diabetes, rather than a solely glucose-centric approach.^{2,4,14}



Question 2:

According to the current treatment guidelines, what is the recommended class of BP agent for Clinton?

- A. ACEI or ARB
- B. Calcium channel blocker
- C. Loop diuretic
- D. Thiazide diuretic

The American Diabetes Association (ADA) Standards of Medical Care¹⁵ and the American Association of Clinical Endocrinologists (AACE) Comprehensive Diabetes Treatment Algorithm² recommend the use of blockers of the renin-angiotensin system (eg, an ACEI or ARB) for the prevention of CV and renal complications.¹⁶ Statins are the mainstay for the management of dyslipidemia and the prevention of atherosclerosis.¹⁷ Smoking cessation will also be a key factor in reducing CV risk.¹⁵

Clinton is started on the following medications:

- Lisinopril 20 mg daily
- Atorvastatin 40 mg daily
- Metformin 500 mg daily to be increased in 1 week to 500 mg twice daily if tolerated, then to 1000 mg twice daily over the ensuing month

He is counseled on his therapeutic targets for reducing the risks of diabetes complications (A1C level <7%, BP <140/90 mm Hg, low-density lipoprotein [LDL] <100 mg/dL). Clinton understands that he must stop smoking and is referred to a smoking cessation program. He is referred to a registered dietitian for nutrition counseling. He agrees to begin walking 15 minutes a day after dinner with his wife.

He is counseled on the fact that diabetes is a progressive disease, that his medications will change over time, and that these changes will be discussed with him.

Medications 3 months later:

- Lisinopril 20 mg daily
- Atorvastatin 40 mg daily
- He is tolerating metformin 1000 mg twice daily
- A1C level = 7.4%
- Smoking reduced to 2 packs/week
- Weight increased to 228 lb
- BMI is 26.3 kg/m²
- BP = 128/72 mm Hg
- Total cholesterol = 147 mg/dL
- LDL = 78 mg/dL
- High-density lipoprotein (HDL) = 37 mg/dL
- TGs = 148 mg/dL

Clinton thinks he has gained weight because he is using hard candy and chewing gum in place of cigarettes.

Question 3:

How would you adjust Clinton's therapy to avoid further weight gain? Which is most likely to avoid further weight gain?

- A. Discontinue metformin, start a sulfonylurea
- B. Continue metformin, start a dipeptidyl peptidase-4 (DPP-4) inhibitor
- C. Continue metformin, start a thiazolidinedione
- D. Discontinue metformin, start a basal insulin

The full algorithm from the ADA and the European Association for the Study of Diabetes (EASD) position statement on the Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach is shown in **Figure 4**,⁴ An abbreviated algorithm showing treatment options when the goal is to avoid weight gain is shown in **Figure 5**,⁴ suggesting that the best answer from the ones above is to continue metformin and to start a DPP-4 inhibitor. DPP-4 inhibitors are once-daily oral agents that are well tolerated and are not associated with weight gain or hypoglycemia. They are considered weight neutral. Adding a sulfonylurea or a thiazolidinedione might increase the chances of further weight gain. Use of basal insulin in the absence of metformin can also be associated with weight gain.

ADA/EASD Treatment Algorithm

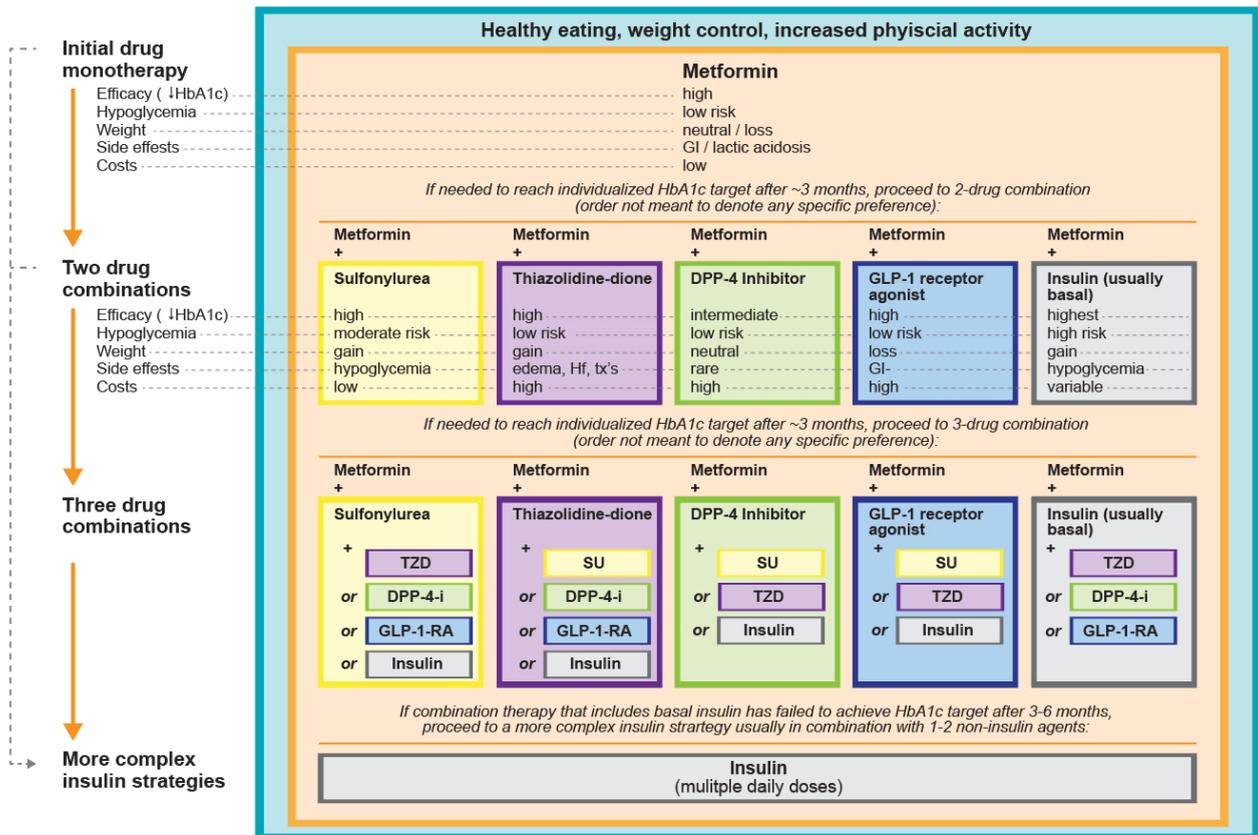


Figure 4. ADA/EASD treatment algorithm. From Inzucchi SE et al. Diabetes Care. 2012;35:1364-1379; Inzucchi SE et al. Diabetologia. 2012;55:1577-1596
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Figure 5 contains another option with high efficacy in A1C lowering and is associated with possible weight loss: a glucagon-like peptide-1 (GLP-1) receptor agonist (RA). GLP-1 RAs are given by subcutaneous injection, but unlike insulin, they are not associated with a risk of hypoglycemia (unless, as is also true for DPP-4 inhibitors, they are used with insulin or insulin secretagogues, in which case the dose of the other agent may need to be reduced).

You explain both options to Clinton; at the moment, he prefers an oral agent, explaining that he has a lot going on with his efforts and lifestyle modification, including smoking cessation, as well as trying to get his family to work with him to change their meal habits.

Question 4:

While you are willing to work with Clinton on this and revisit the situation at his next 3-month visit, you tell him that GLP-1 RAs have which of the following effects that DPP-4 inhibitors don't? (Choose all that apply.)

- A. Can cause slow, steady weight loss
- B. Decrease glucagon secretion
- C. Enhance feelings of fullness
- D. Increase insulin secretion
- E. Slow gastric emptying

Both DPP-4 inhibitors and GLP-1 RA increase insulin secretion and decrease glucagon secretion by virtue of their physiologic effects of GLP-1. Because GLP-1 RAs provide supraphysiological (or pharmacologic) levels of GLP-1, they also slow gastric emptying, enhance satiety (feelings of fullness), and can result in weight loss that is slow and steady. These supraphysiological levels that are positive in causing greater A1C lowering also come with transient GI adverse effects that patients must expect.

When Goal is to Avoid Weight Gain

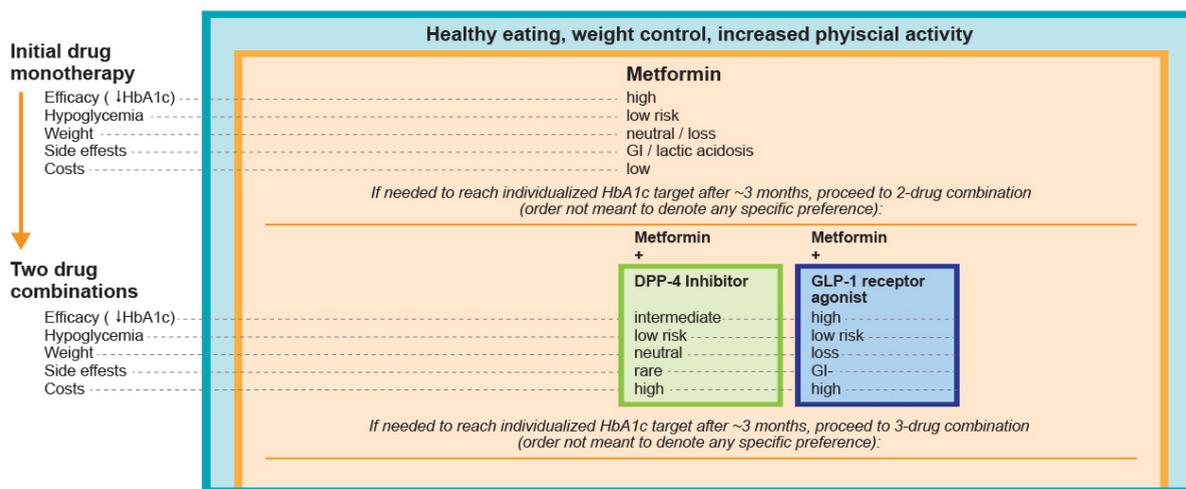


Figure 5. When goal is to avoid weight gain. Adapted from Inzucchi SE et al. Diabetes Care. 2012;35:1364-1379; Inzucchi SE et al. Diabetologia. 2012;55:1577-1596

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Medications 3 months further along:

- Lisinopril 20 mg daily
- Atorvastatin 40 mg daily
- Metformin 1000 mg twice daily
- Sitagliptin 100 mg/day
- A1C level = 7.8%
- Weight back to 220 lb
- BP = 120/70 mm Hg
- LDL = 80 mg/dL

Clinton has further intensified his walking and has started some resistance training. His family is working with him on nutrition. Everyone is pleased that he has stopped smoking. He is somewhat frustrated that despite his efforts he is not achieving his A1C goal. He still blames his sugar intake (too many sodas) from the good work he has done with smoking.

Question 5:

What action do you take with regard to Clinton's glycemic control?

- Do nothing, continue on current regimen for another 3-6 months
- Switch from a DPP-4 inhibitor to a GLP-1 RA
- Switch from a DPP-4 inhibitor to a basal insulin
- Increase the dose of the DPP-4 inhibitor or take DPP-4 and GLP-1 at some time—this might allow an important teaching point about not taking together

Doing nothing would be considered clinical inertia, allowing Clinton to languish at an unacceptably high level of glucose for too long.^{18,19} Current guidelines suggest that if patients are not achieving goal in 3 months, then therapy should be intensified.^{1,2,4} Clinton should be praised for the positive efforts he has made in his overall health and be offered effective tools to achieve his glycemic targets, an A1C level <7%. At this juncture, he is still obese and would do well with a weight-beneficial agent with greater glucose-lowering potential. Consider a GLP-1 RA, with the knowledge that patients who switch from a DPP-4 inhibitor to a GLP-1 RA^{20,21} show further decreases in A1C level, decreases in weight, and increases in patient satisfaction,²² despite having to use an injectable agent. Show Clinton the injectable pen device and the ultrafine needle.

Case Study at 1 Year

Biometrics:

- Height: 70 in.
- Weight: 209 lb
- BMI: 30 kg/m²

Current medications:

- Multivitamin daily
- Occasional OTC medicines for headache
- Lisinopril 20 mg daily
- Atorvastatin 40 mg daily
- Metformin 1000 mg twice daily
- Exenatide 10 mcg twice daily (1 hour before breakfast, 1 hour before dinner)

Relevant measurements and laboratory values:

- A1C level = 6.8%
- FPG = 116 mg/dL
- BP = 120/70 mm Hg
- Total cholesterol = 136 mg/dL
- LDL = 66 mg/dL
- HDL = 45 mg/dL
- TGs = 100 mg/dL

Clinton is pleased with his progress; his A1C level is under control, as are his BP and lipids. He has quit smoking. He has lost weight and almost reached the point of no longer being obese. He may now consider a Web-based/remote or structured multidisciplinary program, or even medical therapy for weight loss. Clinton understands that he is not a candidate for surgery (BMI ≥ 35 kg/m²). He wonders why his lipids have improved. Some of the improvement can be explained by his weight loss but GLP-1 RAs have shown some modest improvements in CV risk markers (both BP and lipids).²³ However, these do not take the place of statins or antihypertensive agents.

You congratulate Clinton on all of his hard work; he thanks you for working with him slowly, surely, and steadily to stay motivated and to keep moving toward his goals. You remind Clinton that T2DM is a progressive disease and that other changes may need to occur over time, but that you are sure that by working together, control can be maintained.

Summary

Involving patients with T2DM in treatment decision-making and taking a patient-centered approach to care, with attention to CV risk factors in addition to glucose control, can enhance the chances of therapeutic success. Knowing that CV disease is the primary cause of mortality for these patients, that obesity contributes to CV risk, and that glycemic control reduces the risk

for microvascular complications such as blindness, nerve damage, and kidney disease should help patients appreciate the need for a multifactorial approach to care.

The use of metformin early in the course of diabetes reduces the rate of treatment failure; combination therapy with drugs with complementary mechanisms of action, such as the incretin-based therapies (DPP-4 inhibitors or GLP-1 RAs), when A1C goals are not being met reduces the exposure of patients to uncontrolled hyperglycemia. We want to be clear that we are adding metformin with incretins—not incretins with incretins. Being able to explain the differences between DPP-4 inhibitors and GLP-1 RAs can help with the appropriate use of the right agent, for the right patient, at the right time. GLP-1 RAs can be especially beneficial in patients when a low risk of hypoglycemia and the opportunity for weight loss is desirable.

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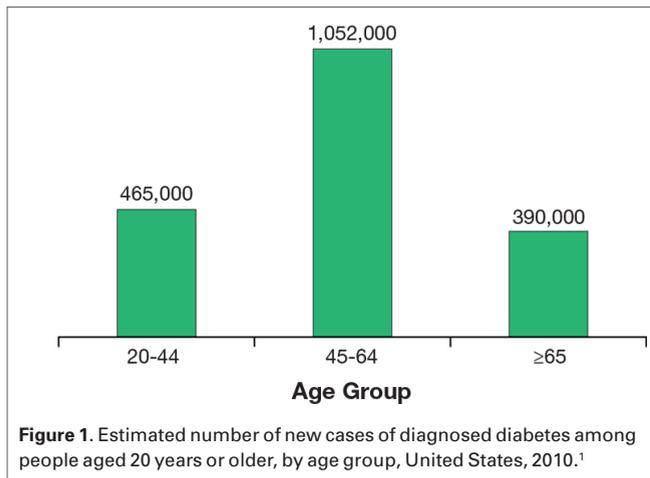
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What to Do When There is a Loss of Glycemic Control: Insulin or Incretins?

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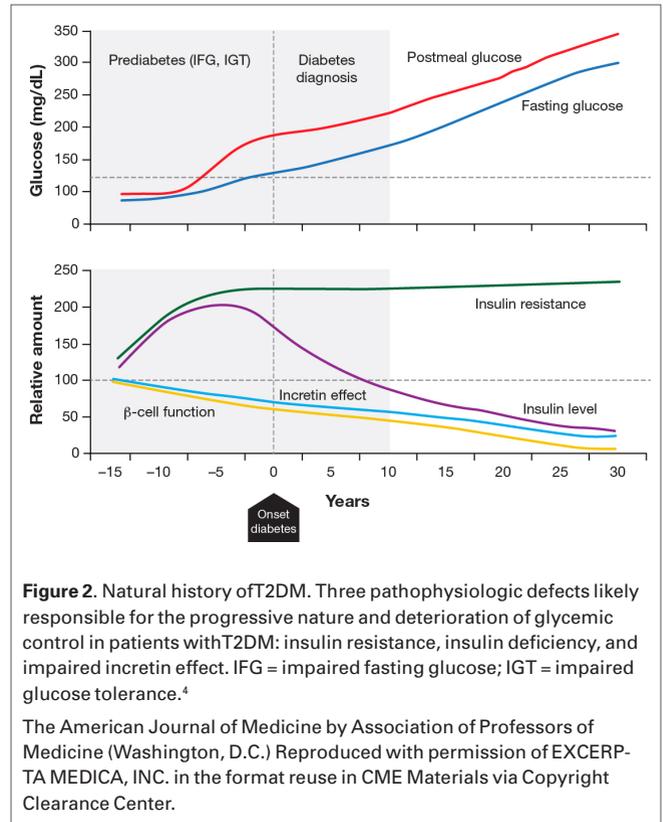
Introduction

The Centers for Disease Control and Prevention report that individuals aged 45-64 years comprise the largest group of newly diagnosed patients with diabetes (Figure 1),¹ although patients aged 65 and older still constitute the greatest absolute number of patients with diabetes.² Middle-aged patients with type 2 diabetes mellitus (T2DM), particularly women and those younger than 55, have a 2-3 times higher risk of all-cause and cardiovascular (CV) mortality than people without diabetes,³ even after adjusting for smoking history.



T2DM is a progressive disease characterized by gradual defects in both insulin sensitivity (increasing insulin resistance) and insulin secretion by pancreatic beta cells, as well as excessive secretion of glucagon by alpha cells and an impaired incretin effect (Figure 2).⁴

Numerous drugs are now available for the treatment of T2DM that target different pathophysiological aspects of the disease. Combination therapy may therefore offer advantages for achieving or maintaining glycemic control, specifically when agents with complementary mechanisms of action are used.



Case Study

Hannah is a 54-year-old Caucasian woman with a 5-year history of T2DM. She is divorced, has 2 children, and works as a headhunter. She weighs 181 lb (82 kg) and has a body mass index (BMI) of 32.2 kg/m², which classifies her as obese. Although Hannah indicates a desire and readiness to lose weight and has attended medical nutritional counseling, she has been unable to substantially change her habits and lose any significant amount of weight. Her comorbidities include hypertension, dyslipidemia, and osteoarthritis. Her current fasting blood glucose (FBG) level is 174 mg/dL, postprandial glucose (PPG) levels (2 hr) are approximately 240 mg/dL, and her glycated hemoglobin (A1C) level is 8.6%.

Biometrics:

- Height: 62 in.
- Weight: 181 lb
- BMI: 32.2 kg/m²

Vital signs:

- Pulse: 66 bpm
- Respirations: 15/minute
- Blood pressure (BP): 130/78 mm Hg

Medical history:

- Postmenopausal
- Hypertension
- Dyslipidemia
- No history of pancreatitis, thyroid cancer

Family history:

- Father with T2DM; mother died at age 52 of a myocardial infarction.
- Her older sister (age 60) has T2DM treated with insulin

Social history:

- Occupation: headhunter
- Past smoker (quit 20 years ago)
- Social alcohol use (a glass of wine with dinner, most nights)
- Denies illicit drug use
- Water aerobics twice a week
- Divorced, 2 children ages 14 and 12, both in good health

Current medications:

- Metformin 1000 mg daily x 4 years
- Glyburide 5 mg daily x 3 years
- Lisinopril/hydrochlorothiazide 20/12.5 mg/day x 8 years
- Atorvastatin 40 mg/day x 4 years

Known allergies:

- Peanuts

Physical examination:

- Obese-no other signs of peripheral resistance or endocrinopathy
- Diminished lower-extremity reflexes
- Fundoscopic examination reveals bilateral background diabetic retinopathy with no evidence of macular edema

Pertinent laboratory values:

- A1C level = 8.6%, FPG = 174 mg/dL, PPG = 240 mg/dL
- BP = 130/78 mm Hg
- Serum creatinine = 1.4 mg/dL
- Low-density lipoprotein (LDL) = 94 mg/dL; triglycerides (TG) = 189 mg/dL; high-density lipoprotein (HDL) = 37 mg/dL

Hannah has CV risk factors (dyslipidemia, hypertension) but no evidence of CVD. She is already showing some evidence of microvascular complications of T2DM, specifically diabetic retinopathy, which is often the first complication to appear.⁵ This serious microvascular complication is a leading cause of blindness in the United States.⁶ Randomized, controlled clinical trials in patients with type 1 diabetes and those with T2DM have shown the beneficial effects of intensive glycemic control^{7,8} and intensive treatment of elevated BP⁸ on the progression of diabetic retinopathy.

According to Healthy People 2020, only 53.4% of adults aged 18 years and older with diagnosed diabetes in 2008 had a dilated eye examination in the past year. The national goal is to improve this by 10% by 2020.⁹ Healthy People 2020 is also seeking to improve the percentage of patients with diabetes with an A1C level <7%. Hannah's A1C level is above the general goal recommended by the American Diabetes Association (ADA) of 7% and her PPG level is well above that recommended by ADA (<180 mg/dL). FBG levels are also not well controlled (recommended target range 70-130 mg/dL).¹⁰ It is therefore safe to say that her glucose regimen should be intensified.

Question 2:

What is your A1C goal for Hannah?

1. <8%
2. <7.5%
3. <7%
4. ≤6.5%
5. <6% if achievable without hypoglycemia

The key to successful treatment of diabetes is individualization of glycemic targets and therapeutic choices. Results of recent clinical trials have shown that treatment is no longer a case of "one size fits all."¹¹ Although treatment goals in general are to achieve an A1C level <7% (ADA) or ≤6.5% (American Association of Clinical Endocrinologists [AACE]),¹² choosing a specific A1C target range for a given patient requires taking several factors into consideration, including an assessment of the patient's risk for hyperglycemia-related complications versus the risks of therapy, all in the context of the overall clinical setting. Comorbid conditions, psychological status, capacity for self-care, economic considerations, and family and social support systems also play a key role in the intensity of therapy

Question 1:

What is your assessment of Hannah's current status? Choose all that apply.

- A. She has microvascular complications
- B. She has cerebrovascular disease
- C. She has CV risk factors
- D. She has postprandial hypoglycemia-this is true as well
- E. Her glucose regimen should be intensified

Framework for Setting Individualized Glycemic Targets

Most Intensive Level, Approximately 6.0%

- Highly motivated, adherent, knowledgeable, strong self-care capability
- Adequate resources or support systems
- Low risk of hypoglycemia
- Short duration of T2DM (+ legacy effect)
- Long life expectancy
- No microvascular disease
- No CVD
- No coexisting conditions

Least Intensive Level Approximately 8.0%

- Less motivated, nonadherent, less knowledgeable, weak self-care capability
- Inadequate resources or support systems
- High risk of hypoglycemia
- Long duration of T2DM (- legacy effect)
- Short life expectancy
- Advanced microvascular disease
- Established CVD
- Multiple, severe coexisting conditions, or both

A1C Range

ADA: 7% in general;
AACE: ≤6.5% in general

Figure 3. Framework for setting individualized glycemic targets. From Ismail-Beigi F. *N Engl J Med.* 2012;366:1319-1327.

(Figure 3).¹³ In Hannah's case, and with her input, an A1C goal of <7% is chosen, with an interim goal of <7.5% to be achieved as a first mark.

Question 3:

Hannah's A1C level is 8.6% on metformin and glyburide. What change in therapy would you make to achieve the goal that you have set for her?

- Add basal insulin
- Add a dipeptidyl peptidase-4 (DPP-4) inhibitor
- Add a glucagon-like peptide-1 (GLP-1) receptor agonist (RA)
- Add a thiazolidinedione (TZD)

Although many physicians feel comfortable with traditional agents such as TZDs, their use may be associated with weight gain and may worsen fluid retention, both of which would be undesirable in Hannah. Recall that Hannah has pedal edema and is obese. Furthermore, there are some concerns about osteoporosis with TZDs. Recent data suggest that pioglitazone inhibits bone formation but does not seem to affect bone resorption. Postmenopausal women rather than premenopausal women or men are particularly vulnerable to this side effect.¹⁴ Furthermore, a TZD is unlikely to lower her A1C level by >1%.

You discuss starting insulin with Hannah. Insulin is the most potent treatment of hyperglycemia and the most likely to get her to goal. Her sister gained 10 lb when

she started insulin and is against this option. Hannah has heard of newer medications that might be more "weight friendly."¹⁵ Although she has struggled with her weight, she is becoming receptive to a discussion of other options and actions that she can take. This appears to be a good time to reintroduce the topic of lifestyle modification.

Remind patients that reducing caloric intake and increasing physical activity is key to achieving and maintaining weight loss. A hypocaloric diet is essential for initial weight loss.¹⁶ Physical activity recommendations include for patients with diabetes according to AACE include ≥150 minutes/week of moderate-intensity exercise that may include flexibility and strength training, aerobic exercise, or cross-training, where the heart rate increases to 70% of maximum.¹⁶ Hannah is willing to commit to embark on a slow but steady increase in walking from 20 minutes every other day to being able to achieve a brisk walk and a total of ≥150 minutes/week of moderate-intensity exercise.

Regarding glucose control, you introduce the idea of an injectable GLP-1 RA, which can lower blood glucose levels by ~1% and may also be associated with weight loss. You tell Hannah that she may experience gastrointestinal (GI) distress (eg, nausea) temporarily as she titrates up to a dose that will be effective in bringing her glucose levels down. This agent affects feelings of fullness (satiety) in addition to increasing insulin and suppressing glucagon. In fact, you tell Hannah, these

agents have been compared with basal insulin and work just about as well in terms of A1C lowering, will target her postprandial hyperglycemia to a greater extent, and will not have risks of hypoglycemia or weight gain.¹⁷⁻¹⁹ With this introduction and the hope for weight loss that is accompanied with improved glucose control she is willing to give this a try.

Hannah is started on 0.6 mg of liraglutide in a prefilled pen, injected subcutaneously once daily for 1 week, in addition to her current glucose-lowering medications. At 1 week, she should increase the dose to a therapeutic dose of 1.2 mg, if she is able to do so without intolerable GI side effects. At this point, consider discontinuing the sulfonylurea if the glucose is responding to the GLP-1 RA. Although hypoglycemia does not occur with liraglutide monotherapy because of its glucose-dependent insulin secretory effects, hypoglycemia may occur when used with insulin secretagogues. A medication that globally increases insulin secretion will overwhelm the glucose dependent insulin secretion.

Question 4:

Hannah asks if there is an oral form of the GLP-1 RA you prescribed for her. What do you tell her?

- A. Yes, DPP-4 inhibitors and GLP-1 RAs work the same way have the same side effect profile and efficacy
- B. No, beyond the differences in route of administration, GLP-1 RAs are associated with greater glucose lowering, and may also cause weight loss, whereas DPP-4 inhibitors are weight neutral

Although DPP-4 inhibitors and GLP-1 RAs are more similar to each other than other agents, as they both affect the incretin system but have different mechanisms of action, there are important differences. One works by inhibiting the enzyme that breaks down whatever GLP-1 exists in the system (DPP-4 inhibitors). The other acts directly on the receptor to increase the level of GLP-1 and stimulate insulin secretion and decrease glucagon levels (GLP-1 RAs).²⁰ Head-to-head studies have shown that GLP-1 RAs are more effective in lowering blood glucose levels than DPP-4 inhibitors.²¹⁻²⁴ The 2 classes of drugs both work only in the presence of high blood glucose levels-this is called glucose dependent insulin secretion, so both are associated with a low risk of hypoglycemia. Because of the greater potency, GLP-1 RAs also have weight loss effects. DPP-4 inhibitors do not cause weight gain.¹⁵ However, they are also associated with higher levels of GI side effects including nausea and vomiting.

Hannah is tolerating the 1.2-mg dose of liraglutide. She had minimal nausea for 1 week. The dose was then titrated to a maximal dose of 1.8 mg per the prescribing information after another week, as was needed to bring her A1C level towards her goal.

At 1 month: Pertinent laboratory values:

- A1C level = 7.5%, FPG = 118 mg/dL, PPG = 180 mg/dL
- BP = 120/78 mm Hg
- LDL = 70 mg/dL; TG = 132 mg/dL; HDL = 42 mg/dL

At 2 months: Pertinent laboratory values:

- A1C level = 6.9%, FPG = 114 mg/dL, PPG = 138 mg/dL
- BP = 120/78 mm Hg
- LDL = 70 mg/dL; TG = 132 mg/dL; HDL = 42 mg/dL
- Weight = (-5 kg)

Question 5:

Which of the following is correct about GLP-1 RAs?

- A. Nausea and weight loss are linked
- B. Weight loss and glycemic control are linked
- C. Every patient loses weight on a GLP-1 RA
- D. Patients with greater BMI tend to lose more weight than those with lower BMI

Patients should be counseled that the main goal of GLP-1-based therapy is to prevent diabetes-related complications through good glycemic control. Lowering A1C levels reduces the risk of serious complications such as retinopathy, nephropathy, neuropathy, and macrovascular disease (Figure 4).^{7,8,25}

Not every patient will lose weight with GLP-1 RAs, although patients with greater BMI's tend to lose more weight than those with lower BMI values.²⁶

Lifestyle modification remains important. The ADA has just issued new dietary guidelines,²⁷ and Hannah may benefit from a referral to a dietitian. Therapeutic lifestyle changes are important throughout the progression of disease.

It has been shown that weight loss effects of GLP-1 RAs are independent of glucose lowering (that is, patients will show improvement in A1C levels whether or not they lose weight). Although the mechanism of action of weight loss with GLP-1 RAs is not completely understood, these effects occur in the presence or absence of GI side effects, that is, they are not dependent on them. In addition to slowing of GI emptying, there appear to be central effects on satiety.²⁸

Lowering A1C Reduces Complications in Diabetes

A1C	DCCT 9.1% → 7.3%	Kumamoto 9.4% → 7.1%	UKPDS 7.9% → 7.0%
Retinopathy	↓63%	↓69%	↓17%-21%
Nephropathy	↓54%	↓70%	↓24%-33%
Neuropathy	↓60%	Significantly improved	—
Macrovascular disease	↓41%*	—	↓16%*

*Not statistically significant

Figure 4. Lowering A1C levels reduces complications in diabetes.^{7,8,24}

Question 6:

You and Hannah begin a discussion about weight loss. She asks which of the following diets would work best for her; you respond that which of the following will result in the most weight loss:

- A. Atkins
- B. The Zone
- C. Ornish
- D. Weight Watchers
- E. It doesn't matter, as long as you stick with it

The answer is, it doesn't matter, as long as patients persevere. In a randomized study, each popular diet modestly reduced body weight and several cardiac risk factors at 1 year.²⁹ Overall dietary adherence rates were low beyond a year, although increased adherence was associated with greater weight loss and cardiac risk factor reductions for each popular diet.³⁰ Typically people struggle to keep on a specialized diet and have high rates of weight regain. It may serve people better to make more moderate changes that may be easier to maintain over a lifetime.

On a program of modest exercise and nutrient-dense but calorie-restricted diet, along with use of a weight-beneficial treatment for her diabetes (eg, metformin and a GLP-1 RA), Hannah observes benefits in her glycemic control, weight, as well as small improvements in her cardiometabolic risk factors.^{31,32}

Summary

Treating the patient who has loss of glycemic control will typically require combination therapy to address the multifactorial and progressive nature of T2DM. An individualized approach is necessary, taking into account specific patient concerns and comorbid conditions, whether these be hypoglycemia, weight gain, medication cost, or CV risk. Newer agents such as incretin-based therapies offer the physician effective options for therapy that complement metformin, with low risks of hypoglycemia and low risks of weight gain. GLP-1 RAs are particularly effective when greater A1C lowering is required and when avoidance of weight gain or when weight loss is desirable. Given by subcutaneous injection by pen devices, these agents are relatively simple to administer and titrate to effective doses; adverse effects of nausea should be a major point of counseling to ensure that the patient will be able to adhere to treatment. An understanding that weight loss and glycemic control are independent of each other and are separate goals, and that lifestyle modification remains a critical aspect of diabetes self-management, remains central to successful outcomes.

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Managing Diabetes in Patients With Disease of Long Duration: GLP-1 Receptor Agonists and Insulin in Combination

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Introduction

Among US residents aged 65 years and older, 10.9 million, or 26.9%, had diabetes in 2010.¹ Older adults including patients with long duration of diabetes are often treated with insulin. Recent data show that glucagon-like peptide-1 receptor agonists (GLP-1RAs) may be used in combination with insulin for patients who have not achieved glycemic goals. This improved glycemic control has been associated with reductions in the insulin dose, a low risk of hypoglycemia, and possible weight loss.

Case Study

Claudia is a 68-year-old Latina of Honduran descent, married with 2 children, who works as a real estate agent. She was diagnosed with type 2 diabetes mellitus (T2DM) 10 years ago and has been a patient of yours for the last 3 years. Today, accompanied by her husband, she comes to see you for routine follow-up of her diabetes and presents with a complaint of fatigue. Over the past 6 months, she has lost 6 lb without any significant change in her diet or physical activity. Her current fasting blood glucose (FBG) level is 195 mg/dL and her hemoglobin (A1C) level is 9.1%.

Biometrics:

- Height: 66 in.
- Weight: 174 lb (180 lb at a visit 6 months prior)
- Body mass index (BMI): 28.1 kg/m²

Vital signs:

- Pulse: 68 bpm
- Respirations: 18/minute
- Blood pressure (BP): 128/78 mm Hg

Medical history:

- Hypertension, controlled with angiotensin-converting enzyme (ACE) inhibitor
- No history of pancreatitis

Family history:

- Both parents deceased—father (myocardial infarction [MI], T2DM), mother (hypertension, T2DM, breast cancer)
- Three siblings—all with hypertension, one with

gestational diabetes during her first pregnancy

Social history:

- Occupation: real estate agent (semi-retired)
- Non-smoker
- Social alcohol use (~2-3 drinks/week)
- Denies illicit drug use
- Married, 2 children ages 32 and 28, both in good health; walks with husband after dinner daily

Current medications:

- Metformin 1000 mg daily x 10 years
- Pioglitazone 30 mg daily x 3 years
- Lisinopril 20 mg/day x 8 years

Known allergies:

- Pollen

Question 1:

What is your assessment of Claudia's current diabetes status?

- A. Impaired glucose tolerance is the predominant issue
- B. Insulin resistance predominates
- C. She has limited beta-cell function at this time
- D. She is glucotoxic
- E. C and D

T2DM is a progressive disease. In T2DM, disease progression that typically starts with insulin resistance and abnormal insulin secretion but then is paralleled by a decline in the function of pancreatic beta cells, leading to further impairment of insulin secretion and activity.

This contributes to the hyperglycemia characteristic of the disease in later stages. When glucose is present in excessive amounts over a prolonged period it exerts negative effects on beta-cell function. This "glucotoxicity" sets in motion a cycle of events in which the hyperglycemia that results from impaired glucose regulation contributes to further beta-cell decline (Figure 1).^{2,3}

Question 2:

According to the 2013 American Association of Clinical Endocrinologists (AACE)⁴ task force on the new comprehensive diabetes management algorithm, what is the recommended therapy for Claudia, who has an A1C level >9% and symptoms of uncontrolled hyperglycemia, and is on 2 oral agents?

- A. Addition of a basal insulin
- B. Addition of a GLP-1 RA
- C. Addition of a sulfonylurea
- D. Any of the above

Vicious Cycle of Worsening Hyperglycemia and Glucose Toxicity in Face of Declining Beta Cell Function

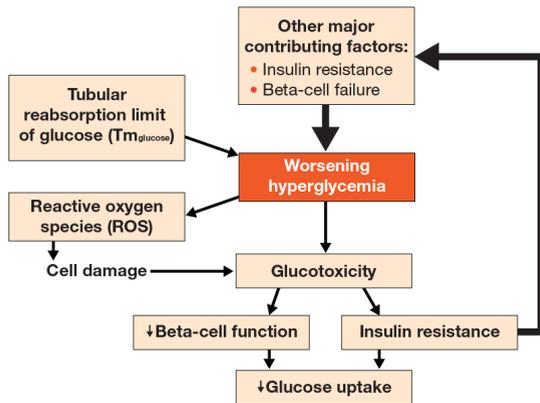


Figure 1. Vicious Cycle of Worsening Hyperglycemia and Glucose Toxicity in the Face of Declining Beta-cell Function. Adapted from Del Guerra S et al. *Diabetes Metab Rev Res.* Mar 2007;23(3):234-238; Del Guerra S et al. *Diabetes.* Mar 2005;54(3):727-735.

In the ADOPT (A Diabetes Outcome Progression Trial) study,⁵ the “durability” (that is, the length of time the drug was effective) of sulfonylureas was shown to be the least, that of metformin intermediate, and that of thiazolidinediones the longest, suggesting that sulfonylureas required beta-cell function to be effective. Thus, many clinicians believe that sulfonylureas are most useful early in the course of diabetes but much less so in diabetes of long duration. Thus, addition of a sulfonylurea would not be recommended at this juncture.

Although the ACE algorithm provides guidance as to what therapies to initiate and add, it respects individual circumstances that would lead to different choices.⁴ A GLP-1 RA might be a reasonable choice but would be unlikely to bring the A1C level to goal quickly and is more likely to affect postprandial glucose levels. Claudia has high fasting glucose levels, so a basal insulin that targets basal or fasting glucose levels would be most appropriate.

Furthermore, if at least a 2% reduction is needed to bring patients to an A1C level <7% (American Diabetes Association recommended goals),⁶ only insulin is likely to be effective. Finally in patients who are acutely symptomatic, insulin is recommended therapy.^{4,6}

Although many physicians prefer to delay initiation of insulin therapy until absolutely necessary,^{7,8} not allowing patients to languish at unacceptably high glucose levels with the attendant risk for diabetes-related complications

is also important. Data show that less than 20% of patients are truly unwilling to start insulin therapy.⁹ Adding basal insulin is a simple and effective approach to initiating insulin therapy.

Physicians can promote patient acceptance of insulin by reviewing the benefits of controlled A1C levels, discuss the benefits of a effective therapy with few side effects, and addressing patient concerns. Further, having the patient give herself her first injection in the office can really improve initiation and continuation of insulin therapy.

Question 3:

What starting dose of basal insulin, based on Claudia’s weight, would you prescribe for her if using recommendations from the ACE algorithm?

- A. 10 units
- B. 8-16 units
- C. 16-24 units
- D. 45 units

ACE recommends weight-based dosing based on the level of hyperglycemia (A1C) (Figure 2).⁴ One important point is that a starting dose of insulin is never likely to be the dose on which a patient should remain. Patients can easily be taught to self-titrate their insulin doses based on the results of self-monitoring of blood glucose levels; several studies have shown that patients are capable of doing this safely and effectively.¹⁰⁻¹²

Based on Claudia’s weight of 174 lb (~79 kg) and an A1C level of 9.1%, a starting dose between 16 and 24 units is indicated. A dose of 20 units is chosen for simplicity, with instructions to titrate every 2-3 days by adding 2 U to reach an FBG level between 80 and 110 mg/dL. Claudia is to call the office with any concerns and is counseled about the signs, symptoms, and correction measures for hypoglycemia. Figure 3 shows other titration options, as well as what to do should hypoglycemia occur.⁴

Claudia titrated her therapy throughout the first month and 1-month followup is a good idea to prevent overdoing the basal insulin dose. At her follow-up appointment in 1 month, Claudia is feeling much better. She has titrated her basal insulin dose to 40 units every night. Her meter download shows fasting glucose levels between 100 and 110 mg/dL for the past several days. Her most recent blood glucose reading taken 2 hours after lunch is 190 mg/dL. Her A1C level is 8%. She has regained some of the weight she had lost when she was severely

Algorithm for Adding Basal (Long-acting) Insulin

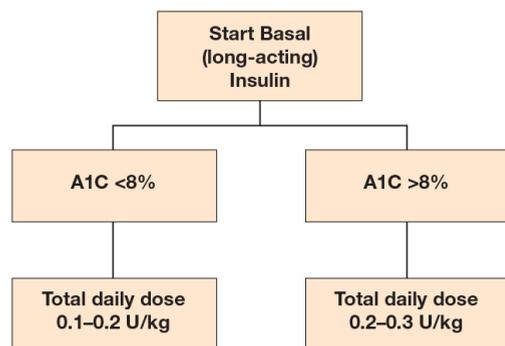


Figure 2. Algorithm for Adding Basal (Long-acting) Insulin. From AACE Comprehensive Diabetes Management Algorithm 2013. Endocr Pract. Mar-Apr 2013;19(2):327-336.

Algorithm for Titrating Basal (Long-acting) Insulin

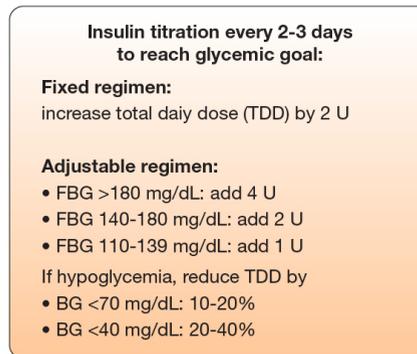


Figure 3. Algorithm for Titrating Basal (Long-acting) Insulin. From AACE Comprehensive Diabetes Management Algorithm 2013. Endocr Pract. Mar-Apr 2013;19(2):327-336.

hyperglycemic (current weight is 190 lb). Patients with severe hyperglycemia often will lose weight as they will become catabolic and lose calories through glucosuria. Claudia is feeling less tired and is more willing to pursue her lifestyle modification efforts. She has joined a local gym and is taking some strength-training classes.

Current medications:

- Lisinopril 20 mg/day x 8 years
- Metformin/pioglitazone 850/30 mg daily (switched to combination product at last visit)
- Insulin long-acting basal analog 40 units

Question 4:

What would be your recommendation for Claudia now?

- Add a dipeptidyl peptidase -4 (DPP-4) inhibitor
- Add a GLP-1 RA
- Add prandial insulin
- Any of the above are reasonable choices

Any one of the above is a reasonable choice for intensifying therapy when patients are achieving FBG goals but are not at A1C goals while on basal insulin therapy. The AACE algorithm suggests that prandial control can be provided by either of the incretin-based treatment options (DPP-4 inhibitors or GLP-1 RAs) or by intensification of insulin therapy with prandial insulin. If choosing a prandial insulin, the total daily dose of insulin (prandial and basal) will be 0.3-0.5 U/kg, divided approximately evenly between basal analog and prandial analog insulins.

DPP-4 inhibitors inhibit breakdown of endogenous incretin hormones. Clinical trial data on the use of insulin with DPP-4 inhibitors suggest that an A1C reduction of between 0.4% and 0.7% can be achieved when the oral agent is added to insulin after 6 months of therapy.¹³⁻¹⁶ This may not be quite enough to bring Claudia to an A1C level <7%. Weight change was similar for placebo and DPP-4 inhibitor arms in these trials.¹³⁻¹⁶ The risk of hypoglycemia is low with addition of DPP-4 inhibitors and their tolerability profiles are good.

GLP-1RAs act directly on GLP-1 receptors to increase insulin release and suppress glucagon secretion in a glucose-dependent manner, thus providing glycemic control with a low incidence of hypoglycemia. GLP-1RAs also promote weight loss, and have beneficial effects on markers of beta-cell function, lipid levels, BP, and cardiovascular risk markers.¹⁷ The combination of a GLP-1RA and insulin is effective for optimizing glucose control, working on complementary aspect of diabetes pathophysiology.¹⁸ GLP-1RAs also ameliorate some of the adverse effects typically associated with insulin. Data from clinical studies support the therapeutic potential of GLP-1RA/insulin combination therapy, typically showing beneficial effects on glycemic control and body weight, with a low incidence of hypoglycemia and, in patients on established insulin therapy, facilitating reductions in insulin dose.¹⁹

Minimizing the risk of hypoglycemia is a priority for physicians and patients alike and should influence treatment choices as a matter of safety, patient

adherence, and ultimately an influence on healthcare costs. Minimizing risk of weight gain is also a priority in terms of safety, adherence, and cost.⁴

A patient-centered discussion with Claudia considers the risk of hypoglycemia, risk of weight gain, and the risk of diabetes-related complications from uncontrolled hyperglycemia. It is decided that she will start a longer-acting GLP-1 RA.

Question 5:

In addition to the notation in Claudia's original medical history that she has no history of pancreatitis, what else should be documented before prescribing a longer-acting GLP-1 RA?

- A. No history of bone marrow dysplasia
- B. No history of hepatitis C
- C. No family history of medullary thyroid carcinoma (MTC)
- D. No history of systemic lupus erythematosus

Cases of pancreatitis have been described in connection with the use of exenatide, liraglutide, and other GLP-1 RAs, although no causal relationship has been established.²⁰ Patients should know the signs and symptoms of pancreatitis and stop taking incretin-based therapies if severe abdominal pain and vomiting occur. If pancreatitis is confirmed, therapy should not be restarted. Diabetes in and of itself is associated with a higher risk of pancreatitis.²¹ If a history of pancreatitis is noted in a patient's record, another class of drugs should be considered.

There is no link between the use of GLP-1 RAs and hepatitis C, bone marrow dysplasia, or systemic lupus erythematosus.

Both of the longer-acting GLP-1 RAs, liraglutide and exenatide once weekly, are contraindicated in patients with a personal or family history of MTC or multiple endocrine neoplasia type 2 (MEN-2). Documentation of a negative family or personal history of MTC or MEN-2 is recommended before prescribing GLP-1 RAs. No special monitoring (eg, calcitonin or ultrasound) is required when starting or maintaining a GLP-1 RA.

Claudia starts on liraglutide 0.6 mg one daily in the evening. Exenatide once-weekly is not approved for use with basal insulin.

Question 6:

Adding a GLP-1 RA to basal insulin therapy may have what effect on the basal insulin dosage requirements?

- A. Decrease in insulin dose
- B. Increase in insulin dose
- C. No effect on insulin dose

A recent review analyzed the latest randomized controlled clinical trials of insulin/GLP-1 RA combination therapy and results from "real-world" use of these regimens as reported through observational and clinical practice studies.¹⁹ The most common finding across all types of studies was that combination therapy improved glycemic control without weight gain or an increased risk of hypoglycemia.¹⁹ Many studies reported weight loss and a reduction in insulin use when a GLP-1 RA was added to existing insulin therapy.¹⁹ Thus, it would seem important to closely monitor blood glucose levels and adjust basal insulin levels downward as needed to avoid hypoglycemia. Should hypoglycemia occur, reduce the total daily dose of insulin by 10%-20% if the blood glucose level is <70 mg/dL or by 20%-40% if the level is <40 mg/dL (personal experience).

It is important that when adding combination therapy that Claudia knows the signs and symptoms of hypoglycemia and that she and her family know how to treat hypoglycemia should it occur.

Claudia does well on her regimen of metformin, a single injection of a long-acting basal insulin analog, and a single injection of a GLP-1 RA. She generally chooses to inject both medications in the evening at different injection sites, often one in each thigh. She loses approximately 5 lbs over the next 3 months and her A1C level decreased to 6.9%. She has continued to monitor her blood glucose levels and is able to self-titrate her insulin dose down to 10 units. She has up-titrated the liraglutide to the maximal glucose-lowering dose of 1.8 mg with the ability to tolerate the transient gastrointestinal side effects (ie, nausea) by eating very slowly and acknowledging the satiety effect.

Return visit 3 months: Current medications:

- Lisinopril 20 mg/day x 8 years
- Metformin/pioglitazone 850/30 mg daily
- Insulin glargine 30 units
- Liraglutide 1.8 mg

Summary

The progressive nature of T2DM, with its changing pathophysiological features, mandates physicians to change therapy as the nature of the disease changes in order to maintain glycemic control. In patients with long-standing diabetes, beta-cell function is likely to be at a minimum, making agents that rely on insulin secretion (secretagogues like sulfonylureas) less useful. The ADOPT trial demonstrated the durability of thiazolidinediones and metformin in terms of maintenance of glycemic control compared to sulfonylureas. Eventually, most patients will require insulin therapy. Basal insulin therapy is relatively easy to use to meet background insulin requirements. Prandial glucose control can be achieved with addition of GLP-1 RAs, which not only increase insulin secretion but suppress glucagon-mediated hyperglycemia. They do this without increasing the risk of hypoglycemia or increasing the risk of weight gain, in contrast to adding prandial insulin injections.

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