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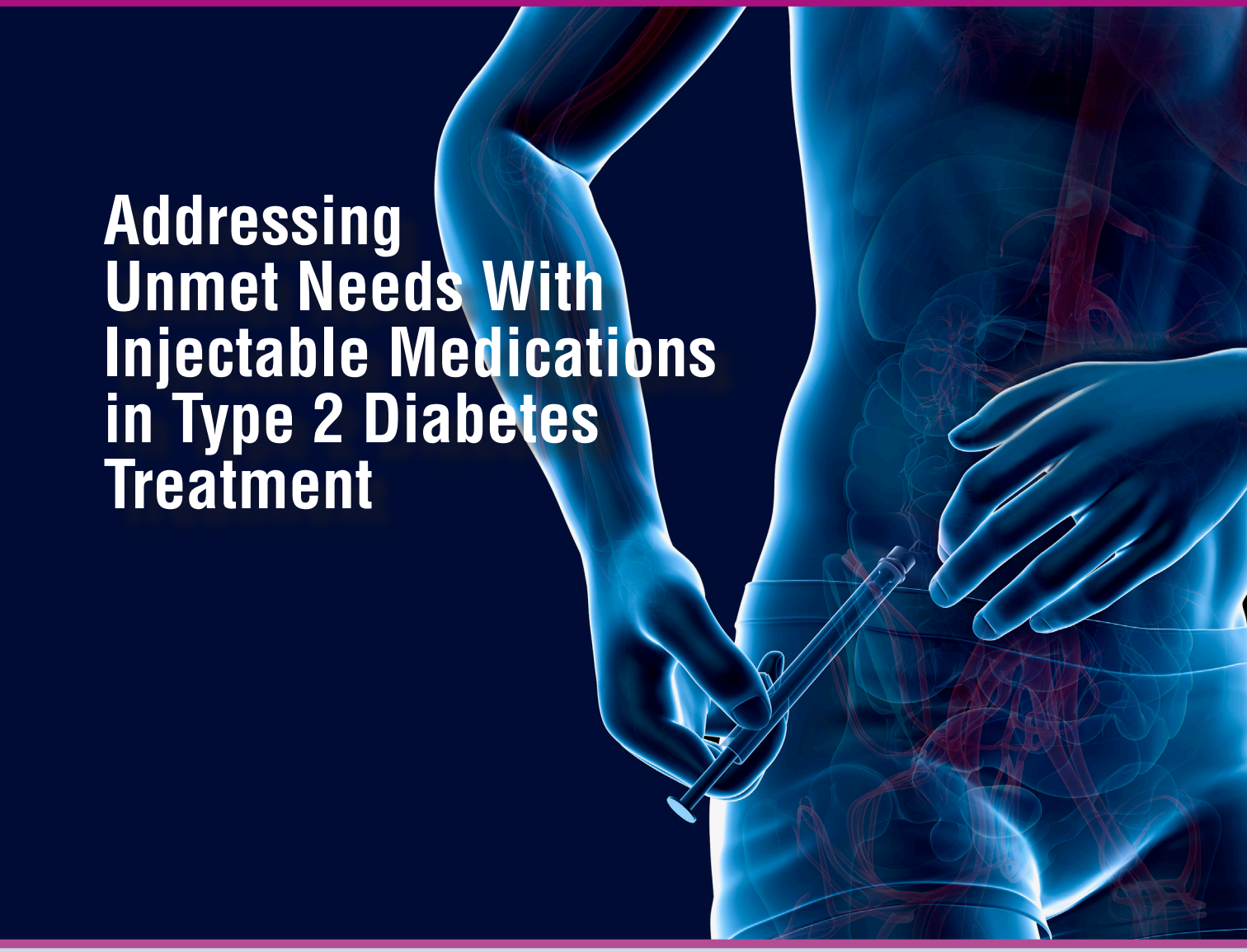
Addressing Unmet Needs With Injectable Medications in Type 2 Diabetes Treatment



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LEARNING OBJECTIVES

- Provide an overview of the unmet needs, with currently available medications for, type 2 diabetes.
- Provide an overview of the rationale and role of basal insulin and glucagon-like peptide-1 receptor agonists as described in current practice guidelines for the management of individuals with type 2 diabetes.
- Describe the efficacy, safety, and tolerability of currently available basal insulin products.
- Describe the efficacy, safety, and tolerability of currently available glucagon-like peptide-1 receptor agonists.
- Describe the efficacy, safety, and tolerability of currently available fixed-ratio combinations of basal insulin and glucagon-like peptide-1 receptor agonists.
- Describe situations in which new injectable products might be used to address unmet patient needs.

Introduction

The percentage of adults with diabetes mellitus (90% to 95% have type 2 diabetes mellitus) who achieved their individualized glycated hemoglobin (HbA1c) target was 64% in 2011-2014.[1] While that's good news, that means 36% were not at their HbA1c target. That's 7.6 million people in the United States with diagnosed diabetes who remained at high risk for retinopathy, nephropathy, cardiovascular events, and nontraumatic amputation, emphasizing the real-world impact and unmet need of suboptimal glucose control.[2] The number not at their glycemic target may be even higher now since the number of people with diabetes rose from 29.1 million in 2012 to 30.3 million in 2015.[3] According to Steven Edelman, MD, Professor of Medicine, University of California, San Diego, "This is frankly shocking, eye-opening information that the health care community needs to confront with new and different therapeutic strategies."[4]

More options are available to treat patients with T2DM. The number of pharmacologic therapies has rapidly expanded over the past decade or so and now includes 12 classes of medications. Complicating matters, however, is poor patient adherence and other barriers to patient self-management that remain as other unmet needs.[4]

Dr. Edelman is one of five diabetes experts who elaborate on the unmet needs of patients with T2DM in this supplement. The experts also provide details about possible solutions to address these unmet needs.

In the first article in this supplement, Edward Shahady, MD, highlights many of the unmet needs of patients with T2DM. Dr. Shahady briefly summarizes patient and provider barriers contributing to suboptimal patient adherence. He also describes limitations of available medications and how differences among classes of medications might be considered in individualizing therapy based on patient needs and characteristics.

In the second article, Eden Miller, DO, focuses on the roles of injectable medications in the treatment of patients with T2DM as recommended in recent treatment algorithms. Dr. Miller describes how the role of insulin has evolved over the past century and how glucagon-like peptide-1 receptor agonists have become an important option as part of dual and triple therapy, including in combination with basal insulin. Dr. Miller summarizes key evidence supporting these roles.

In the third and fourth articles, Pablo Mora, MD, and Steven Edelman, MD, provide greater insight into the evidence and experience concerning newer injectable medications. Dr. Mora focuses on the 2 newest basal insulin analogs, glargine U-300 and degludec U-100 and U-200. Building upon discussion of the pharmacokinetic and pharmacodynamic profiles of these 2 new basal insulins, Dr. Mora discusses their efficacy, safety, and dose timing. Dr. Edelman takes a more clinical approach regarding the GLP-1RAs, summarizing the glycemic and nonglycemic effects and safety and tolerability, noting important differences between the short- and long-acting GLP-1RAs. He also provides a historical overview of the requirement for cardiovascular outcome trials for T2DM medications and highlights the general results of the 10 trials completed, with further discussion of the 2 GLP-1RAs shown to offer cardiovascular benefit vs placebo. Dr. Edelman relates how he considered the characteristics of the GLP-1RAs in providing care to one of his patients.

In the final article, Helen Baron, MD, takes a question-and-answer approach to explain the rationale for and evidence supporting the combined use of basal insulin and a GLP-1RA. Building upon this, Dr. Baron details the evidence and experience of the 2 recently approved fixed-ratio combinations of basal insulin and GLP-1RA, first in comparison to their individual components, then in comparison to combinations of other treatments. Dr. Baron also provides detailed recommendations for initiating and titrating the 2 fixed-ratio basal insulin/GLP-1RA combination products.

Addressing Unmet Needs With Injectable Medications in Type 2 Diabetes Treatment should provide you with insights that help you address unmet patient needs by individualizing basal insulin and GLP-1RAs, including their combination, in the treatment of patients with T2DM. ●

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Medications for Type 2 Diabetes Mellitus: A Work in Progress

Edward Shahady, MD

The near doubling of medication classes for the treatment of patients with type 2 diabetes mellitus (T2DM) over the past decade or so offers greater opportunity to individualize treatment based on patient needs and characteristics. Nonetheless, patient adherence to medications for T2DM is not optimal, ranging from 30% to 93%.[1-6] A recent meta-analysis of 40 studies from 2005 to 2015 showed an adherence rate of 67.9% with oral antihyperglycemic therapy.[7] Adherence with insulin has been reported to range from 51% to 59% at 3 months following initiation, 39% to 48% at 6 months, and 27% to 35% at 12 months.[5]

The importance of medication adherence is demonstrated by a recent report involving 11,272 veterans with T2DM. The report showed a mean decrease in the HbA1c of 0.24% for each 10% increase in the medication possession ratio (MPR) over 5 years of follow up.[8] MPR is the number of days' supply of medication provided to the patient divided by the number of days the patient should take the medication. A MPR of at least 0.80 is generally accepted as indicating good adherence.

Many factors contribute to poor adherence to medications. Some involve the patient, others the health care provider, while others concern limitations with the medications themselves.

PATIENT BARRIERS

Numerous factors contribute to suboptimal patient adherence to medications ranging from lack of awareness and understanding about the consequences of T2DM; inappropriate beliefs that some medications, particularly insulin, may contribute to death; social and cultural beliefs; limited health literacy and/or numeracy; concerns about hypoglycemia and weight gain; treatment complexity; trust in their provider; and medication cost.[9-16] The chronic nature of T2DM and the major impact that self-management plays on patient outcomes[17] necessitate that the individual's barrier(s) be identified and solutions found through collaboration between the patient and provider.[18] Since the barrier(s) may change over time, it is important to ask the patient about barriers and other treatment difficulties at each visit and to collaborate with the patient to find an acceptable solution.[19] In the author's experience, providing a written action plan can help patients feel more in control of their T2DM and help them respond appropriately to adverse events and other concerns that may arise between visits. In addition, providing the patient with diabetes self-management education and support is recommended.[20]

PROVIDER BARRIERS

Health care providers often express frustration in simultaneously managing hyperglycemia while avoiding hypoglycemia in patients with T2DM.[14] This suggests that providers may not be adequately prepared or supported to provide the multifaceted care typically required when managing patients with T2DM.[12-14] Providers may be assuming too much responsibility for outcomes that are primarily determined by the patient's self-management.[17] This situation can lead to clinical inertia wherein the provider avoids modifying therapy despite suboptimal disease control.

While it is true that providers are more knowledgeable than patients about T2DM and its treatments, the patient is more knowledgeable than the provider about many factors that may make it difficult for the patient to self-manage their T2DM. As noted above, a critical role of the provider is to engage the patient in a collaborative, shared decision-making process. This process may involve other members of the diabetes care team.

LIMITATIONS OF AVAILABLE MEDICATIONS

The rapid expansion in the classes of medications approved for the treatment of patients with T2DM is clearly indicative of greater understanding of the pathophysiologic mechanisms contributing to T2DM and greater opportunity to individualize treatment. Yet, each class of medication, indeed each medication, has limitations that have

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the potential to impact patient adherence and glycemic outcomes.

Noninsulin medications have limited effectiveness in lowering fasting and postprandial glucose.[21] Moreover, noninsulin medications often lose their effectiveness in lowering blood glucose over time.[22] Intrapatient and interpatient variability in pharmacokinetics and pharmacodynamics reinforce the need for individualizing the dose, particularly with basal and prandial insulins. Most medications require daily dosing, with some requiring consideration of food intake.

Adverse events remain a concern, including those of newer medications, although risks of hypoglycemia and weight gain are often reduced. The chronic nature of T2DM and the need for long-term treatment emphasize the importance of long-term safety of medications. Yet, developing a clear understanding of long-term safety can be challenging as evidenced by the ongoing uncertainty regarding the possible association of thiazolidinediones with bladder cancer,[23-25] glucagon-like peptide-1 receptor agonists with pancreatitis, pancreatic cancer, and gallbladder disease,[26,27] and sodium glucose cotransporter-2 inhibitors with bone fractures and lower extremity amputations.[28,29] Finally, the higher cost of newer medications can also be a limitation, depending on insurance coverage.

CONCLUSION

There have been numerous advances in the medications available for the treatment of patients with T2DM, but limitations remain that have the potential to contribute to barriers to adherence for patients and providers. As discussed in the other articles in this supplement, more informed usage of currently available medications as part of a collaborative decision-making process should help address many of these unmet patient needs. ●

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Role of Injectable Medications in Type 2 Diabetes Treatment

Eden M. Miller, DO

The treatment of patients with diabetes mellitus took a huge leap forward a century ago with the discovery of insulin. Over the next 5 decades, insulin was used primarily in patients with type 1 diabetes mellitus (T1DM). As the supply of insulin grew, and with the advent of human insulin, the use of insulin in patients with type 2 diabetes mellitus (T2DM) became more common. Improving upon earlier insulin formulations, the development of analog insulins shifted the risk:benefit ratio by enabling better targeting of basal and prandial glucose requirements, as well as improved safety and tolerability. The availability of medications, most recently the glucagon-like peptide-1 receptor agonists (GLP-1RAs), as well as oral agents such as the dipeptidyl peptidase-4 inhibitors (DPP-4is) and sodium glucose cotransporter-2 inhibitors (SGLT-2is), also provides opportunities to target treatment.

This article describes the roles of injectable glucose-lowering medications, specifically basal insulin and GLP-1RAs, as recommended in current guidelines and the evidence supporting these recommendations. More detailed discussion of basal insulin and GLP-1RAs can be found later in this supplement.

ROLE OF INSULIN IN T2DM

In 2006, the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) published the first algorithm for the metabolic management of patients with T2DM.[1] This consensus algorithm recommended lifestyle intervention and metformin as first-line therapy with insulin, sulfonylureas, and thiazolidinediones as second-line therapy. Insulin was preferred for patients with glycated hemoglobin (HbA1c) >8.5% or with symptoms secondary to hyperglycemia. Generally similar recommendations were provided in the 2007 guidelines issued by the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) except that insulin should be added in patients with HbA1c 6.5% to 8.5% despite maximally tolerated combination therapy.[2] Despite the recommendation for insulin as second-line therapy, most primary care physicians avoided the use of insulin for patients with T2DM, instead preferring combinations of multiple oral medications.[3,4]

Jump ahead to 2017 and the role of insulin in T2DM has expanded. According to the ADA/EASD algorithm, basal insulin can be used in combination with metformin or as part of triple therapy in combination with metformin and either a sulfonylurea (SU), thiazolidinedione (TZD), DPP-4i, SGLT-2i, or GLP-1RA.[5] Also, insulin in combination with other agents should be considered when hyperglycemia is severe, particularly if the patient is symptomatic or exhibits catabolic features such as weight loss or ketosis. According to the ADA/EASD algorithm, initiating combination insulin injectable therapy should be considered when the blood glucose is ≥300 mg/dL or HbA1c is ≥10% or if the patient has symptoms of hyperglycemia (ie, polyuria, polydipsia).[5] It is important to note that, in contrast to the 2006 ADA/EASD algorithm, there is no recommended HbA1c threshold for the use of insulin in combination with oral therapy in the 2017 algorithm.[5]

The 2017 AACE/ACE algorithm also indicates that insulin can be used as part of dual or triple therapy for patients with HbA1c ≥7.5% (**FIGURE**).[6] In addition, insulin can be used alone or with other glucose-lowering agents for patients with an initial HbA1c >9.0%.

EVIDENCE SUPPORTING A GREATER ROLE OF INSULIN IN T2DM

Much occurred from 2006 to 2017 that contributed to the expanded role of insulin in patients with T2DM. First, T2DM is now recognized as being a progressive disease such that the average patient with T2DM has only approximately 20% of pancreatic ß-cell function remaining at the time of diagnosis.[7] Consequently, treatment intensification is generally required.[5,6] Yet, because many noninsulin medications lower blood glucose by stimulating insulin secretion from the pancreas, glycemic durability is only a few years

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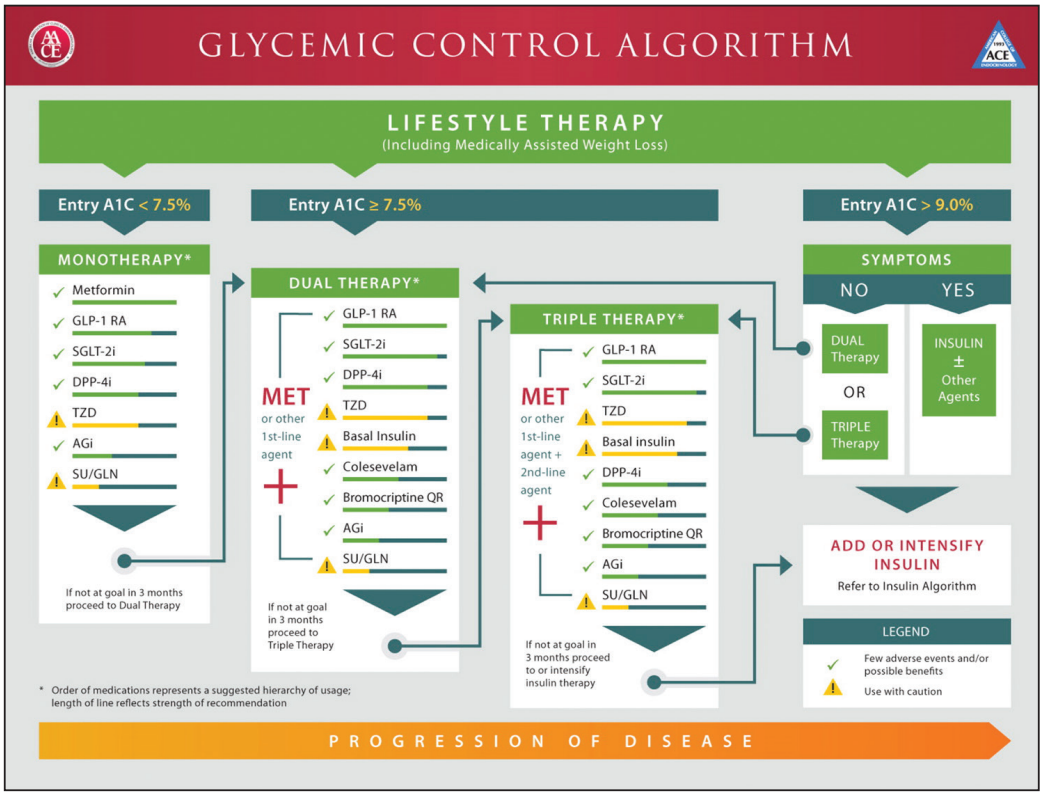
with most noninsulin medications.[8] Moreover, the glycemic-lowering efficacy of oral medications is limited. The addition to metformin of oral medications such as SUs and TZDs results in a maximum additional HbA1c reduction of approximately 1%.[9] Insulin, on the other hand, has no theoretical limit to its glucose-lowering capacity.

Unlike the crude animal-derived formulation first injected into humans, the insulin formulations now available are synthetic and highly purified biologics. This has resulted in more predictable pharmacokinetics and pharmacodynamics enabling once-daily dosing and minimizing the risk of hypoglycemia. Moreover, insulin is a natural hormone and administration of insulin serves to address a pathophysiologic defect in T2DM by offsetting what the body no longer adequately produces. The magnitude of the glucose-lowering effect of insulin is dependent on dose, influenced by insulin resistance, and constrained by the risk of hypoglycemia.

FIGURE 1 AACE/ACE glycemic control algorithm[6]



Abbreviations: AACE/ACE, American Association of Endocrinology/American College of Endocrinology; AGi, alpha-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; GLN, glinide; QR, quick-release; MET, metformin; SGLT-2i, sodium glucose cotransporter-2 inihibitor; SU, sulfonylurea; TZD, thiazolidinedione.

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The early use of insulin has been shown to offer several benefits. In a meta-analysis of 928 patients with a mean HbA1c of 8.69%, the likelihood of achieving the HbA1c target and reducing hypoglycemia risk was significantly greater with the earlier addition of insulin glargine to baseline metformin monotherapy compared with later addition of insulin glargine to metformin plus sulfonylurea (odds ratio (OR), 0.738; 95% confidence interval (CI), 0.218 to 1.258; *P*=.005).[10]

ROLE OF GLP-1RAs IN T2DM

Since the introduction of exenatide twice-daily in 2005, five other GLP-1RAs have been approved for use in the United States: liraglutide, exenatide once-weekly, albiglutide, dulaglutide, and lixisenatide. In the 2009 ADA/EASD algorithm, a GLP-1RA was recommended as a 'less well validated' tier 2 medication as an alternative to a TZD and after metformin, insulin, and an SU.[11] In the 2012 ADA/EASD update, a GLP-1RA was on an equal footing as basal insulin, SU, TZD, and a DPP-4i as one of 5 medication classes recommended for use in combination with metformin.[12] This same algorithm is recommended in the 2017 ADA Standards of Medical Care, with the only exception being an SGLT-2i as another option for use in combination with metformin.[5]

The AACE/ACE 2017 algorithm goes beyond the ADA/EASD 2017 recommendations and lists a GLP-1RA at the top of the 'suggested hierarchy of usage' for use in combination with metformin, while acknowledging the importance of individualizing therapy (**FIGURE**).[6]

Both the 2017 ADA standards and 2017 AACE/ACE recommendations note the cardiovascular benefits of liraglutide

and empagliflozin based on the results of recently published cardiovascular outcomes trials. (See *Gluagon-Like Peptide-1 Receptor Agonists* on page 12.)

EVIDENCE SUPPORTING THE ROLE OF GLP-1RAs IN T2DM

The clinical pharmacology, safety, and efficacy of GLP-1RAs have been investigated in more than 500 trials. The clinical efficacy and safety trials were included in the database of studies used for the systematic review "Diabetes Medications for Adults with Type 2 Diabetes: An Update" prepared for the Agency for Healthcare Research and Quality in 2016.[9] This review reported the following mean outcomes with the combination of a GLP-1RA and metformin compared with metformin monotherapy:

- additional 0.5% to 1.3% HbA1c reduction
- additional 2.0 kg weight reduction
- additional 3.1 mmHg systolic blood pressure reduction.

With respect to hypoglycemia, the systematic review found that the data did not favor either treatment (metformin monotherapy vs metformin + GLP-1RA) for mild, moderate, severe, or total hypoglycemia. This suggests a minimal added risk for hypoglycemia when a GLP-1RA is added to metformin.

GLP-1RAs have been reported to improve various markers of ß-cell function in patients with T2DM, suggesting that GLP-1RAs may remain effective in lowering blood glucose over time.[13,14] A recent meta-analysis estimated ORs for treatment failure with dual therapy in combination with metformin. Using SU as the reference, ie OR=1, the ORs were (least likely to fail to most likely to fail): basal insulin (0.10; 95% CI, 0.01 to 1.89), SGLT-2i (0.68; 95% CI, 0.48 to 0.96), GLP-1RA (0.84; 95% CI, 0.54 to 1.30), TZD (1.18; 95% CI, 0.70 to 1.98), and DPP-4i (1.37; 95% CI, 1.07 to 1.76), indicating that treatment failure with a GLP-1RA is less likely than with several commonly utilized oral medications.[15] Another potential benefit of GLP-1RAs is a reduction in the blood triglyceride level, albeit over a wide range (2 mg/dL to 73 mg/dL).[16-18] Finally, clinical trial data are beginning to demonstrate the cardiovascular safety and, in some cases, cardiovascular benefit, with the GLP-1RAs.[19-21]

CONCLUSION

Current treatment guidelines for patients with T2DM recommend key roles for basal insulin and GLP-1RAs across the spectrum of the disease. These recommendations are based on efficacy and safety data as well as other benefits observed in clinical trials. ●

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Basal Insulins

Pablo F. Mora, MD, FACE, CDE

In healthy humans, the timing and amount of insulin release are exquisitely tied to the body's metabolic demands. Insulin is released at a relatively constant rate over 24 hours to meet the body's basal metabolic needs. In addition, insulin is released in short bursts in response to nutrient intake, as well as in response to changes in peripheral utilization, sensitivity, and endogenous production.[1] To approximate this physiologic state, 2 general types of insulin formulations have been developed. Basal insulins are intended to address the body's basal metabolic needs over 24 hours, and prandial (or bolus) insulins to address the rapid rise in blood glucose in the postprandial state. The quest for a basal insulin with a constant physiologic effect over 24 hours has been challenging, in part because the subcutaneous route of administration remains the most practical, yet physiologically unnatural route for administering insulin (**FIGURE 1**).

Early attempts to develop a basal insulin were aimed at delaying and prolonging insulin absorption from subcutaneous tissues through the addition of protamine (neutral protamine Hagedorn, NPH) or an excess of zinc (Lente, Ultralente) to form suspensions that would slowly dissolve once injected. However, the need for thorough resuspension prior to injection and widely variable interpatient and intrapatient absorption made this approach less than ideal.[2]

Recombinant DNA technology enabled the development of insulin that closely matched the molecular structure of endogenously secreted insulin. However, it was necessary for the insulin to take on a hexameric form in order to have physical stability and an acceptable injection volume.[2] This resulted in a plasma kinetic profile that does not closely resemble either the basal or prandial profile of endogenously secreted insulin.[3]

Further technological advances enabled the design and manufacture of insulin analogs with a protracted and more predictable pharmacodynamic action. One strategy was to modify the amino acid sequence resulting in an insulin with less solubility at physiological pH values. Upon injection into the neutral subcutaneous environment, the insulin microprecipitates into crystals with slow dissolution to provide protracted absorption. This strategy was used to produce insulin glargine (IGlar).[2] A limitation of this strategy is the somewhat unpredictable nature of the formation and redissolution of the crystalline precipitate resulting in some pharmacodynamic variability, including waning of effect over 24 hours in some patients.[4,5]

Another strategy was to develop a pH-neutral formulation that stabilizes self-association of insulin so that it does not precipitate following subcutaneous injection and permits reversible binding to albumin, primarily at the injection site but also in circulation.[6,7] This strategy was used to produce insulin detemir through the addition of fatty acids to the insulin molecule via acylation. Blood glucose variability with detemir is less than with glargine or NPH, but the duration of effect is often less than 24 hours.[4]

These strategies have resulted in less variable metabolic activity over a longer period of time with glargine and detemir than with NPH. Consequently, glargine and detemir provide lower rates of hypoglycemia, particularly nocturnal hypoglycemia.[3,4,8-17] However, the effects are not evenly and consistently distributed throughout the 24-hour period, making these basal insulin analogs less than ideal.

THE NEWEST BASAL INSULIN ANALOGS

The newest basal insulin analogs include IGlar U-300 and insulin degludec (IDeg) U-100 and U-200, approved by the US Food and Drug Administration (FDA) in February 2015 and September 2015, respectively.

Pharmacokinetics and pharmacodynamics

Insulin glargine U-300

IGlar U-300 is a three-fold more concentrated formulation than IGlar U-100. IGlar metabolism in humans is the same for IGlar U-300 and IGlar U-100.[18]

One key difference between IGlar U-300 and IGlar U-100 is that the up-concentration of IGlar U-300 results in formation of 'tighter' crystal precipitates, leading to prolonged

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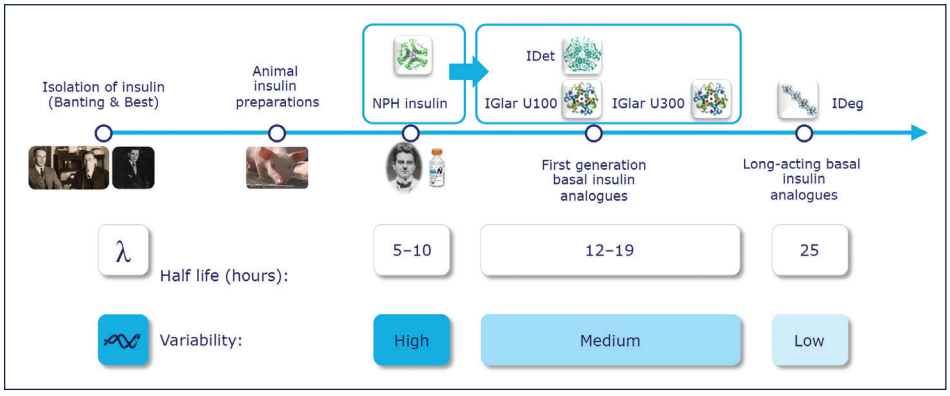
DISCLOSURE

Dr. Mora discloses that he is on the advisory board for Novo Nordisk Inc. and on the speakers' bureaus for AstraZeneca; Novo Nordisk Inc.; and sanofi-aventis U.S. LLC.

FIGURE 1 The quest for the ideal basal insulin



Abbreviations: IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; NPH, neutral protamine Hagedorn.

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absorption with a longer and more stable duration of blood glucose lowering compared with IGlar U-100. In patients with type 1 diabetes mellitus (T1DM) at steady state, the mean half-life was observed to be 13.5 hours for IGlar U-100 and 19.0 hours for IGlar U-300 at a dose of 0.4 units/kg.[19] The glucose-lowering effect of IGlar U-300 was more stable than IGlar U-100 over 24 hours. Tight blood glucose control, ie, blood glucose ≤105 mg/dL, was maintained over a median of 30 hours with IGlar U-300 compared with a median of 25 hours with IGlar U-100.

Another key difference between IGlar U-300 and IGlar U-100 is that the biopotency of IGlar U-300 over the 24-hour dosing period is 27% less than IGlar U-100 at steady state.[19] Consequently, the dose of IGlar U-300 may need to be adjusted accordingly when switching from IGlar U-100. A meta-analysis of clinical trials involving 2496 patients with T2DM showed that, compared with IGlar U-100, a 12% higher dose of IGlar U-300 was required after 6 months.[20]

Insulin degludec

IDeg is an insulin analog in which threonine has been removed at position B30 and position B29 has been acetylated with a 16-carbon fatty diacid with a glutamic acid spacer.[21] Highly stable dihexamers form due to an interaction between one of the fatty diacid side chains of one hexamer and a zinc atom of another. Following injection, the dihexamers adopt an open configuration resulting in formation of multihexamer chains.[22] Diffusion of zinc from each terminal of the chain causes the terminal hexamers to slowly break apart, first forming dimers, then monomers. The insulin monomers are absorbed into the systemic circulation.[22,23]

A comparative study vs IGlar U-100 demonstrated that the molecular structure of IDeg results in important differences between the 2 basal insulin analogs with respect to pharmacokinetics and pharmacodynamics. These differences were observed in patients with type 2 diabetes mellitus (T2DM) in a 26-hour euglycemic clamp study. This technique measures insulin absorption and insulin activity through simultaneous intravenous infusion of insulin and glucose to maintain a constant glucose level. The study showed a mean half-life of 24.4 hours to 26.8 hours for IDeg and a duration of action beyond the 26 hours of the clamp study in all patients over the dose range of 0.4 units/kg to 0.8 units/kg.[24] Steady state was reached after 2 to 3 days of treatment.

A longer duration of action for IDeg was demonstrated in a 42-hour euglycemic clamp study in patients with T1DM.[25] Using the same doses as in the T2DM euglycemic clamp study (0.4, 0.6, or 0.8 units/kg), the glucose-lowering effect of IDeg extended beyond the 42 hours of the clamp study at all 3 doses.

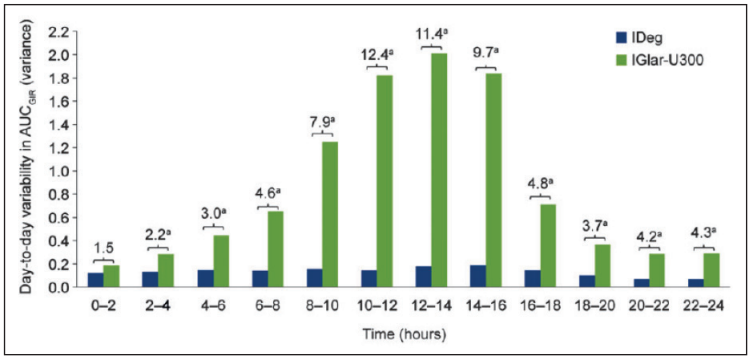
IDeg is available in concentrations of 100 units/mL (U-100) and 200 units/mL (U-200). IDeg U-100 and IDeg U-200 have been shown to be bioequivalent with similar pharmacodynamic profiles at steady state, thereby avoiding the need for dose conversion when switching from U-100 to U-200 or vice-versa.[26] The formation of stable dihexamers enables coformulation of IDeg with the glucagon-like peptide-1 receptor agonist liraglutide and the rapid-acting analog insulin aspart.[5]

Insulin degludec vs insulin glargine U-300

The pharmacodynamics of IDeg have been compared with IGlar U-300 in a double-blind, crossover study in patients with T1DM (N=57).[27] Patients were randomly assigned to 0.4 units/kg of IDeg U-200 or IGlar U-300 once daily for 2 treatment periods lasting 12 days each. Pharmacodynamic variables were assessed at steady state 3 times during each treatment period using a 24-hour euglycemic glucose clamp study.

The day-to-day variability in glucose-lowering effect was consistently low with IDeg over 24 hours, but steadily increased with IGlar U-300 to a maximum between 10 and 14 hours after dosing (**FIGURE 2**).[27] Moreover, the day-to-day variability in glucose-lowering effect was nearly 4 times lower with IDeg than with IGlar U-300 (P<.0001). Within-day variability was 37% lower with IDeg than with IGlar U-300

FIGURE 2 **Day-to-day variability in glucose-lowering effect over 24 hours of degludec vs glargine U-300 at steady state[27]**



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(*P*<.0001). These results are consistent with the significantly lower variability observed with IDeg compared with IGlar U-100 in patients with T1DM.[28]

Efficacy and safety

Insulin glargine U-300

The efficacy and safety of IGlar U-300 were established relative to IGlar U-100 in the EDITION phase 3 program involving patients with T1DM or T2DM.[29-34] The EDITION program showed similar reductions in HbA1c, but generally lower incidences of confirmed, severe, and nocturnal hypoglycemia and less weight gain with IGlar U-300 than IGlar U-100. Details about the EDITION program have been summarized by Anderson.[35] Switching patients from a basal insulin analog to IGlar U-300 has been shown to further reduce the HbA1c and decrease the occurrence of hypoglycemia over 6 months.[36,37]

No studies have been conducted to specifically assess the cardiovascular safety of IGlar U-300. However, a review of safety data by the FDA did not suggest a concerning signal for cardiovascular risk with IGlar U-300 vs U-100.[38] The FDA noted that the development program for IGlar U-300 was not required to rigorously assess cardiovascular risk. The cardiovascular safety of IGlar U-100 was established in the 6-year ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial, showing similar incidences of cardiovascular outcomes with IGlar U-100 compared with standard care.[39]

Insulin degludec

The efficacy and safety of IDeg in patients with T1DM or T2DM were extensively investigated in the phase 3 BEGIN program. In insulin-naïve and insulin-exposed patients with T2DM, basal or basal-bolus therapy with IDeg resulted in similar reductions in HbA1c and similar or significantly greater reductions in FPG compared with IGlar U-100.[40-46] Details about the BEGIN program have been summarized by Philis-Tsimikas.[47]

A lower rate of overall (rate ratio (RR), 0.83; 95% confidence interval (CI), 0.70 to 0.98), nocturnal (RR, 0.64; 95% CI, 0.48 to 0.86), and severe (RR, 0.14; 95% CI, 0.03 to 0.70) hypoglycemia with IDeg compared with IGlar U-100 (*P*<.05 for all) has been shown in a preplanned meta-analysis of 7 phase 3 clinical trials involving patients with T2DM.[48]

Among insulin-naïve patients, significantly lower rates of overall (RR, 0.83; 95% CI, 0.70 to 0.98) and nocturnal (RR, 0.64; 95% CI, 0.48 to 0.86) hypoglycemia with IDeg compared with IGlar U-100 (*P*<.05 for both) have been shown in older adults (age ≥65 years) with T2DM.[49] In older adults with T1DM, overall confirmed hypoglycemia occurred in numerically more patients with IDeg than IGlar U-100 (97.7% vs 94.1%, respectively), while nocturnal confirmed (69.8% vs 82.4%) and severe (9.3% vs 11.8%) hypoglycemia were numerically more common in patients treated with IGlar U-100. In 2 recently completed 64-week crossover trials, severe or confirmed symptomatic overall and severe or confirmed symptomatic nocturnal hypoglycemia occurred in fewer patients with T1DM or T2DM treated with IDeg vs IGlar U-100.[50,51]

The cardiovascular safety of IDeg has been compared with IGlar U-100 in the DEVOTE study in patients with T2DM at high risk of cardiovascular disease (N=7637).[52] After approximately 2 years of treatment, IDeg was noninferior to IGlar U-100 in the primary endpoint (composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (hazard ratio, 0.91; 95% CI, 0.78 to 1.06).

Dose timing

An important barrier to basal insulin therapy for patients is the need to administer the dose at the same time each day.[53-55] The protracted release and longer duration of action with IDeg and IGlar U-300 offer once-daily administration with the possibility of dose time flexibility. However, clinical trial data support dose time flexibility with IDeg but limited flexibility with IGlar U-300, suggesting clinically important differences between their dissimilar mechanisms of protraction.[46,56] Consequently, IDeg can be administered once daily at any time of the day, while IGlar U-300 is administered once daily at the same time each day based on patient preference.[11,15]

The FDA approval for administration of IDeg at any time of the day is based on a study by Meneghini et al.[46] Patients with T2DM were randomized to once-daily treatment for 26 weeks with: (1) IDeg U-100 at the same time each day (IDeg fixed); (2) IDeg U-100 using a forced-alternative dose-timing schedule creating 8-hour to 40-hour dosing intervals (IDeg forced-alternative); or (3) IGlar U-100 at the same time each day.[46] At the end of the study, noninferiority of IDeg forced-alternative was confirmed relative to IGlar U-100. Reductions in the HbA1c were 1.07%, 1.28%, and 1.26%, for IDeg fixed, IDeg forced-alternative, and IGlar, respectively. The respective rates of overall (3.6 vs 3.6 vs 3.5 episodes/patient-year) and nocturnal (0.6 vs 0.6 vs 0.8 episodes/patient-year) hypoglycemia were similar among the 3 groups.

Patient-reported outcomes

Both IDeg and IGlar U-300 are only available for administration using a pen device. IDeg was shown to improve several patient-reported outcomes versus comparators in the BEGIN trials involving patients with T2DM. These included physical functioning, vitality, and bodily pain.[44,57,58] There were no differences in overall mental health or in the domains of social functioning or emotional health. Patients also expressed a high level of satisfaction with the FlexTouch pen in ease in learning and confidence in using the pen, ease in holding the pen stable or seeing the dose scale while self-injecting, pushing down the injection button, and selecting the correct dose.[59]

IGlar U-300 also has been shown to improve treatment satisfaction similar to IGlar U-100 in the EDITION program, although health-related quality of life was unchanged from baseline.[29,30,34] Patient concerns about hypoglycemia, including perceived frequency of hypoglycemia, improved similarly with IGlar U-300 and U-100.[29-32]

SUMMARY

The newest basal insulin analogs IDeg (U-100 and U-200) and IGlar U-300 address several barriers and unmet needs with previously available insulin formulations, thus continuing a favorable shift in the risk:benefit ratio of basal insulins. These include a protracted release of insulin with subcutaneous administration that results in pharmacodynamic properties that more closely mimic endogenous basal secretion of insulin over 24 hours with less variability in glucose-lowering effect. As a result, a higher percentage of patients achieve the HbA1c goal <7.0% without hypoglycemia, particularly nocturnal hypoglycemia. In addition, IDeg offers flexibility with dose timing as it can be administered at any time of the day. ●

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Glucagon-Like Peptide-1 Receptor Agonists

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INTRODUCTION

Observations that oral glucose provokes a greater insulin secretory response than the same amount of glucose injected into a vein,[1] coupled with isolation of an extract from the upper intestine that produces a fall in blood glucose,[2,3] led to recognition that the incretin system plays a role in glucose homeostasis. Subsequent investigation identified glucagon-like peptide-1 (GLP-1) as the key gut hormone producing this insulinotropic response. Although the level of GLP-1 in persons with type 2 diabetes mellitus (T2DM) was found to be lower than healthy controls, the role of GLP-1 via subcutaneous administration was shown to be limited due to its rapid inactivation by dipeptidyl peptidase-4 (DPP-4). Investigation aimed at overcoming this rapid inactivation by DPP-4 led to the discovery that the saliva of the lizard *Heloderma suspectum* includes exendin-4, a peptide closely related to GLP-1, that is resistant to DPP-4. Synthetic exendin-4 was approved as exenatide for twice-daily injection by the US Food and Drug Administration (FDA) in 2005, becoming the first GLP-1 receptor agonist (GLP-1RA).[4]

Since 2005, four new GLP-1RAs (liraglutide, albiglutide, dulaglutide, and lixisenatide) and a once-weekly formulation of exenatide were approved for the treatment of persons with T2DM. Another GLP-1RA, semaglutide, is under review by the FDA, as is exenatide administered via an osmotic mini-pump.

Overview of clinical effects of GLP-1RAs

GLP-1RAs have multiple effects to improve glycemic control and reduce weight. They lead to insulin secretion and glucagon suppression, both in a glucose-dependent manner.[3,5,6] This translates into stimulating insulin and inhibiting glucagon in the postprandial state only if the glucose levels are abnormal, thereby protecting against hypoglycemia. The GLP-1RAs also normalize or slow gastric emptying to limit the rate of nutrients leaving the stomach and entering the small intestine. This also serves to reduce the postprandial glucose levels and, in conjunction with activation of the central nervous system, induce satiety leading to reduced food intake and weight loss.[6]

Glycemic and nonglycemic effects of long- and short-acting GLP-1RAs

The GLP-1RAs exert a variety of glycemic and nonglycemic effects, with clinically important differences among the class based on whether the GLP-1RA is classified as short-acting (exenatide twice-daily, lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide once-weekly, liraglutide) based on duration of the glucose-lowering effect (**TABLE**).[7,8]

A key difference is that the short-acting GLP-1RAs slow gastric emptying, resulting in a pronounced effect on the postprandial glucose (PPG) level, particularly related to the meal following dosing. In contrast, the long-acting GLP-1RAs have a transient effect on gastric emptying, but more of an effect on stimulating insulin secretion and inhibiting glucagon secretion, both in a glucose-dependent manner. The result is a more sustained effect on the entire 24-hour glucose level, including fasting plasma glucose (FPG), generally resulting in greater reduction of the glycated hemoglobin (HbA1c) with the long-acting GLP-1RAs.[9-18] As a class, the GLP-1RAs provide an additional 0.5% to 1.3% HbA1c reduction when added to metformin.[19]

The addition of a GLP-1RA to metformin results in nonglycemic benefits, including a 1.3 kg to 2.7 kg weight loss compared with metformin monotherapy.[19] While not indicated for weight loss, a GLP-1RA may be especially useful in patients with T2DM with overweight or obesity or patients treated with another class of medication that causes weight gain. Although the studies are not directly comparable, weight loss appears to be greater with long-acting vs short-acting GLP-1RAs, with liraglutide providing the greatest weight loss among the long-acting GLP-1RAs.[9-18] Another

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DISCLOSURE

Dr. Edelman discloses that he is on the advisory boards and speakers' bureaus for AstraZeneca; Dexcom, Inc.; Eli Lilly and Company; Johnson & Johnson; MannKind Corporation; Merck & Co., Inc.; Novo Nordisk Inc.; and sanofi-aventis U.S. LLC. He is a board member for Senseonics.

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TABLE Comparison of short- vs long-acting GLP-1RAs[7,8]

Effects	Short-acting[a]	Long-acting[b]
HbA1c	↓	↓↓
Fasting glucose	↓	↓↓
Postprandial glucose	↓↓	↓
Fasting insulin secretion	↑	↑↑
Postprandial insulin secretion	↑	↑
Glucagon secretion	↓	↓↓
Intestinal glucose absorption	↓	↔
Gastric emptying rate	↓	↓(transient)
Appetite	↓	↓
Hypoglycemia[c]	Modest	Modest

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin.

[a]Exenatide twice-daily, lixisenatide.

[b]Albiglutide, dulaglutide, exenatide once-weekly, liraglutide.

[c]If used with sulfonylureas and/or insulin.

benefit is a mean 3.1 mm Hg reduction in systolic blood pressure but no significant reduction in diastolic blood pressure.[19] Head-to-head trials between GLP-1RAs have shown no significant differences in reduction of systolic blood pressure.[9-16,18] GLP-1RAs also lower the triglyceride level (range 2 mg/dL to 73 mg/dL).[20-22]

Safety and tolerability

The incidence of hypoglycemia is low, occurring in <5% of patients treated with the addition of a GLP-1RA to metformin monotherapy.[19] Head-to-head trials show minor hypoglycemia to be similarly or less frequent with long-acting than short-acting GLP-1RAs.[9-18] Severe hypoglycemia is rare, likely due to the glucose-dependent actions of GLP-1RAs. Gastrointestinal (GI) adverse events (ie, nausea and vomiting) are one of the most common adverse events, with nausea having the most impact on patients. GI adverse events are less common with long-acting than short-acting GLP-1RAs, perhaps due to the gradual increase in plasma drug levels with the long-acting GLP-1RAs compared with the rapid rise to a peak blood level with the short-acting GLP-1RAs.[9-18] Injection site reactions appear to be more common with long-acting GLP-1RAs, particularly albiglutide and exenatide once-weekly.[9-18]

GLP-1RAs have been reported as being associated with an increased risk of pancreatitis and pancreatic cancer. However, a 2014 review by the US Food and Drug administration (FDA) and European Medicines Agency concluded that "a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with current data. …Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available."[23] Subsequent to this review, 2 studies of health records from European and North American countries showed no evidence of an associated between incretin drugs and an increased risk of pancreatitis (N=1,532,513) or pancreatic cancer (N=972,384) compared with other glucose-lowering drugs.[24,25]

CLINICAL PHARMACOLOGY

The GLP-1RAs are synthetic peptides with homology for native GLP-1 ranging from 50% for lixisenatide to 97% for liraglutide.[8] The peptide nature of GLP-1RAs generally results in antibody formation to the GLP-1RA in 1% to 9% of study subjects, but may be as high as 70% with lixisenatide.[26-31] Antibody formation to the GLP-1RA has little observable effect on glycemic lowering or safety with albiglutide, dulaglutide, or liraglutide, but may attenuate glycemic lowering with the short-acting GLP-1RAs.[26-28,30-32] In clinical practice, these issues are uncommon with all formulations and rarely affect patient care.

Cardiovascular outcomes

Amidst concerns regarding the cardiovascular safety of

medications for lowering blood glucose,[33] in 2008 the FDA initiated the requirement that new medications used to treat patients with T2DM be shown not to pose an unacceptable increase in cardiovascular risk compared to placebo as part of standard care.[34] To demonstrate this, a clinical trial is required that includes patients with T2DM at higher risk of cardiovascular events (eg, those with advanced disease, advanced age, or renal impairment) and be at least 2 years in duration to allow assessment of longer-term risks. The events to be assessed are major adverse cardiovascular events (MACE), including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The new glucose-lowering medication is found to be noninferior, ie, similar, to placebo regarding cardiovascular safety if the upper bound of the two-sided 95% confidence interval for the estimated risk ratio is less than 1.8. If the upper bound of the two-sided 95% confidence interval for the estimated risk ratio is less than 1.0, the cardiovascular safety of the new glucose-lowering medication is found to be superior to placebo, ie, it offers a cardiovascular benefit.

Twenty trials have been initiated in accordance with the FDA requirement. The study design, statistical methods, including the number and demographics of subjects, are not similar among the trials; however, all but one involved primarily adults with T2DM and pre-existing or at high risk of cardiovascular disease. Ten trials have been completed, with all demonstrating noninferiority of the glucose-lowering medication compared to placebo, thereby excluding an unacceptable level of cardiovascular risk. Moreover, of the 5 completed trials involving a GLP-1RA, only liraglutide and semaglutide (investigational) demonstrated statistical superiority, ie, cardiovascular benefit, vs placebo. The results for liraglutide, lixisenatide, and semaglutide have been published.[35-37]

Exploratory analyses in these trials suggested that the risks of microvascular events and nephropathy were significantly reduced with liraglutide.[36] For semaglutide, the risks of nonfatal stroke, need for revascularization, and new or worsening nephropathy were significantly reduced, but risk of retinopathy was increased.[37] The difference between groups in retinopathy was observed early and the majority in both groups (83% to 84%) had pre-existing retinopathy at baseline, which may be important; however, this unexpected side effect is being investigated further.

FASTING AND POSTPRANDIAL GLUCOSE AS CARDIOVASCULAR RISK FACTORS

The pharmacologic management of patients with T2DM is generally approached with sequential addition of medications aimed at lowering the HbA1c to a target level, generally HbA1c <7.0%.[38] Metformin, which is utilized as initial therapy in most patients with T2DM, is effective in reducing primarily the FPG. The use of metformin may not achieve the target HbA1c level in all patients, but this depends on many other factors such as baseline HbA1c, duration of diabetes, etc. Additionally, T2DM is a progressive disease, generally necessitating the addition of other diabetes medication to metformin over time. The PPG and FPG contribute almost equally to HbA1c when it is in the range of 7.3% to 8.4%.[39] PPG is the principal determinant of HbA1c when it is less than 7.3% and FPG is the principal determinant of HbA1c when it is more than 8.4%. Consequently, add-on therapy to metformin that significantly lowers PPG may be considered when the HbA1c remains above the target of <7.0% and the FPG is within the normal range. Medications that produce a moderate/marked reduction of the PPG are rapid- and short-acting GLP-1RAs, prandial insulins, and pramlintide.

Beyond its importance in contributing to HbA1c, the PPG level is important to consider in the management of patients with T2DM since it has been shown to be an independent risk factor for cardiovascular disease, although this remains controversial.[40-43] The Honolulu Heart Program showed that the risk of a fatal coronary event increased progressively with rising 1-hour postprandial glucose,[44] while the Baltimore Longitudinal Study of Aging showed a dramatic rise in all-cause mortality for 2-hour PPG >200 mg/dL.[45] Among the 3 meals in a typical day, the 2-hour PPG level following lunch is the strongest risk factor for a cardiac event and all-cause mortality.[46] In addition, there is the suggestion that lowering PPG levels may improve cardiovascular function.[47-49]

CASE SCENARIO/SUMMARY

Pam is a 35-year-old African-American female with a 3-year history of T2DM. Despite maximally tolerated doses of metformin, sulfonylurea, and DPP-4i, her HbA1c is 8.7%. Her mean FPG and PPG levels over the past 2 weeks have been 177 mg/dL and 269 mg/dL, respectively. Her past medical history includes hypertriglyceridemia, hypertension, central obesity (body mass index 43 kg/m^2), and renal dysfunction (estimated glomerular filtration rate 45 mL/min/1.73 m2). What are the benefits and limitations of initiating a GLP-1RA in Pam?

Answer: A GLP-1RA, with the expected effects to lower both FPG and PPG, as well as promote weight loss, would be an excellent choice. The addition of a GLP-1RA would be expected to lower her HbA1c to achieve her target of 7.0% or less. The DPP-4i should be discontinued due to the overlapping effects on the incretin system with the GLP-1RA, while the combination of a sulfonylurea and GLP-1RA substantially increases the risk of hypoglycemia. Given Pam's medical history, a GLP-1RA would

be a good choice since a GLP-1RA lowers the triglyceride level, as well as provides a modest reduction of the systolic blood pressure. A major benefit of adding a GLP-1RA is that it promotes weight loss in most patients with T2DM. Improvements in various markers of pancreatic ß-cell function have been reported in patients with T2DM, which suggest, although not proven, that a GLP-1RA may have long durability of response.[50,51] The need for injection may be a limitation, although an easy to use pen to administer the GLP-1RA and patient education is usually effective in addressing this issue. Adverse events, principally nausea, are a barrier to patient adherence to GLP-1RA therapy, which is why starting at a low dose and titrating slowly to avoid this gastrointestinal side effect is important.

Although Pam has moderate renal impairment, any of the GLP-1RAs can be given without adjusting the dose; however, caution is advised when initiating or escalating doses of a GLP-1RA in patients with renal impairment.[26-31] Renal function should be monitored in patients with renal impairment taking albiglutide, dulaglutide, or lixisenatide who report severe adverse gastrointestinal reactions.[26,29,30]

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Using Combinations of a Basal Insulin and a Glucagon-Like Peptide-1 Receptor Agonist

Helen L. Baron, MD

CASE SCENARIO

Steve is a 53-year-old male diagnosed with type 2 diabetes mellitus (T2DM) 8 years ago. He is relatively new to your practice due to changes in his employer's insurance carrier.

Yesterday morning, his wife observed him to be confused after getting out of bed; he fell shortly after. Random blood glucose level in the emergency department was 54 mg/dL.

Over the first 5 years following diagnosis, Steve was treated with several combinations of metformin-based oral therapy. Three years ago, his glycated hemoglobin (HbA1c) was 7.9%, so his oral medications except metformin were discontinued and basal insulin once daily with dinner was initiated. His HbA1c was reduced to 6.7% within several months. Since starting basal insulin, he has gained 16 pounds (current body mass index [BMI] 36.4 kg/m^2). Over the past year, he has experienced numerous episodes of hypoglycemia, which he admits cause him to not take his insulin several times per month. Review of his blood glucose log shows wide fluctuations in his blood glucose levels over the past month, ranging from 82 mg/dL to 168 mg/dL for fasting glucose (FPG) and from 148 mg/dL to 244 mg/dL for postprandial glucose (PPG).

Physical exam: blood pressure 144/92 mm Hg, mild retinopathy with exudates, faint tingling in his feet.

Laboratory: HbA1c 7.8%, low density lipoprotein cholesterol (LDL-C) 164 mg/dL, triglycerides 410 mg/dL, estimated glomerular filtration rate (eGFR) 48 mL/min/1.73 m^2, mild proteinuria.

Current medications: metformin 1000 mg twice daily, basal insulin 76 units (0.72 units/kg) with dinner, hydrochlorothiazide 25 mg once daily, lisinopril 20 mg once daily, simvastatin 40 mg once daily, aspirin 81 mg once daily.

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DISCLOSURE

Dr. Baron discloses that she is on the advisory boards and speakers' bureaus for Novo Nordisk Inc. and sanofi-aventis U.S. LLC. She is on the advisory board for Intarcia Therapeutics, Inc.

Given Steve's history and need for modifying the treatment plan, you narrow your discussion with Steve to consideration of the options for intensifying once-daily basal insulin. These are switching to twice-daily basal insulin, adding prandial insulin, adding a glucagon-like peptide-1 receptor agonist (GLP-1RA), or adding a sodium glucose cotransporter-2 inhibitor (SGLT-2i). You consider that switching to twice-daily basal insulin would allow splitting the total daily dose of insulin in half, which may lower the risk of hypoglycemia, particularly during the night and early morning. Although reduction of his FPG is likely, it is unlikely that he will reach the HbA1c target of <7.0% since basal insulin is unlikely to normalize his PPG. Moreover, further weight gain is possible.

Addition of prandial insulin, with corresponding reduction of his basal insulin dose, would lower his PPG, but would have little effect on FPG. In addition, further weight gain is likely and concern about hypoglycemia would remain.

Addition of an SGLT-2i is reasonable as it would lower his FPG, while providing modest reduction of his PPG, with an expected reduction of his HbA1c of 0.5% to 1.4% with minimal risk for hypoglycemia.[1-7] Other benefits with the addition of an SGLT-2i to metformin would be reductions of his weight by 1.5 kg to 2.5 kg and systolic blood pressure by 2 mm Hg to 9 mm Hg. Reevaluation of his diuretic therapy would be appropriate to avoid volume depletion-related adverse events.[7-9] A small dose-dependent increase in LDL-C would be expected,[1,2,4] although the importance of this is unclear since canagliflozin and empagliflozin have been shown to produce significant reductions in major adverse cardiovascular events compared with placebo.[10,11]

A limitation of SGLT-2i therapy is that canagliflozin and empagliflozin should not be initiated in a patient with an eGFR <45 mL/min/1.73 m^2 and dapagliflozin in a patient with an eGFR <60 mL/min/1.73 m^2. Canagliflozin and empagliflozin should be discontinued if the eGFR falls below 45 mL/min/1.73 m^2.[12-14] Moreover, canagliflozin is associated with an increased risk of bone fractures and lower extremity amputations.[15,16]

The remainder of this article will present the rationale and data for combining a basal insulin with a GLP-1RA, including as fixed-ratio products.

GLP-1RA IN COMBINATION WITH BASAL INSULIN

For decades, a rapid- or short-acting insulin was added for patients with inadequate glycemic control with optimized basal insulin. As new classes of medications have been approved and experience with them gained, some of these new classes of medications are now recommended to intensify treatment beyond basal insulin. The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) algorithm recommends a GLP-1RA as the alternative to prandial insulin, while the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) algorithm recommends a GLP-1RA as the preferred alternative to prandial insulin, with a SGLT-2i or dipeptidyl peptidase-4 inhibitor (DPP-4i) as possible alternatives.[17,18] Both algorithms emphasize that the selection of medication for intensifying basal insulin depends on patient needs and characteristics.[17,18]

What is the rationale for combining a GLP-1RA with basal insulin?

The rationale for combining a GLP-1RA with basal insulin is predicated on their complementary mechanisms of glucose-lowering and improvement in safety and tolerability compared with basal insulin alone.[17] GLP-1RAs increase pancreatic insulin secretion and decrease glucagon secretion, both in a glucose-dependent manner. They decrease both FPG and PPG, with short-acting GLP-1RAs having a greater effect on PPG and longer-acting GLP-1RAs a greater effect on FPG. GLP-1 RAs promote modest weight loss in most patients and are associated with a low rate of hypoglycemia. In contrast, administration of basal insulin increases the level of circulating insulin in a dose-dependent but glucose-independent manner. Basal insulin effectively lowers HbA1c and FPG, but has little effect on PPG. Basal insulin is associated with weight gain and carries the highest risk of hypoglycemia of available glucose-lowering medications.[19]

What evidence supports combining a GLP-1RA with basal insulin?

Results from numerous trials demonstrate the efficacy and safety of combining a GLP-1RA with basal insulin. Nineteen of these randomized trials involving 7053 patients with T2DM were analyzed in a recent meta-analysis.[20] The meta-analysis combined trials with different treatment regimens, including trials of fixed-ratio as well as free-dose combinations of GLP-1RA and basal insulin. Some trials included stable insulin dosing, while others included insulin titration. The meta-analysis also pooled basal insulin-only trials with trials of basal insulin plus prandial insulin.

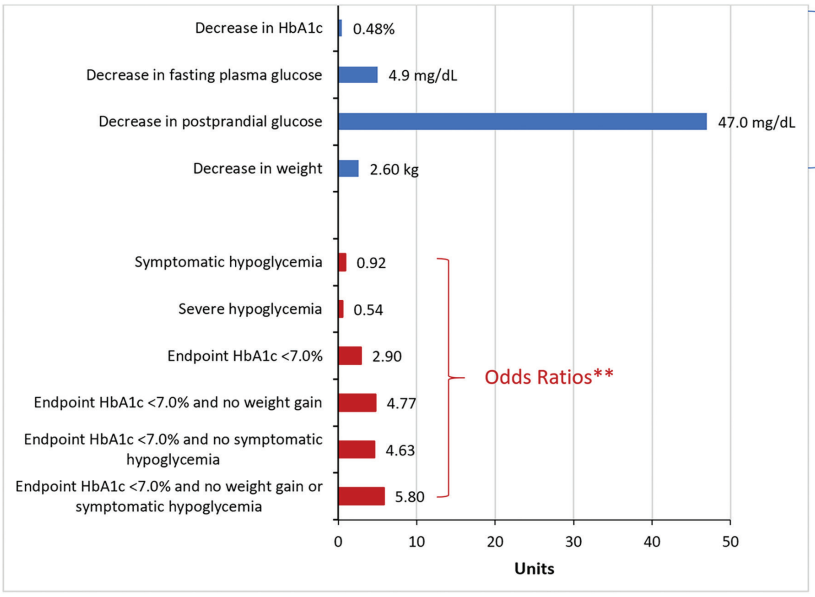
In the 19 trials included in the meta-analysis, the mean duration of T2DM ranged from 6.7 years to 17.7 years, mean baseline HbA1c ranged from 7.2% to 8.8%, and mean BMI ranged from 25.2 kg/m^2 to 42.6 kg/m^2.[20] The meta-analysis showed significant benefits with the addition of a GLP-1RA to basal insulin vs basal insulin with or without prandial insulin for several glycemic endpoints and weight effects, including several composite endpoints (**FIGURE 1**).[20] There was, however, no significant difference between the 2 groups regarding symptomatic or severe hypoglycemia, with odds ratios (95% confidence interval [CI]) of 0.92 (0.68 to 1.23) and 0.54 (0.21 to 1.38), respectively.

What has contributed to the change in recommendations for intensifying basal insulin?

A key factor has been the widely recognized challenges encountered with prandial insulin in clinical practice. These include weight gain, risk for hypoglycemia, dose time inflexibility, and need for frequent monitoring and dose adjustment.[17,21] Another factor supporting the recommendation for using a GLP-1RA for intensifying basal insulin is the results from head-to-head trials.[22-26] Twenty-six of these trials lasting 12 to 52 weeks involving 11,425 patients with T2DM were included in a recent meta-analysis.[27] The meta-analysis compared the addition of a GLP-1RA to various regimens of basal insulin and prandial insulin, including basal-plus (adding one main-meal prandial insulin to basal insulin once daily) or full basal-bolus (4 insulin injections daily). In the 2 basal-plus and 5 basal-bolus studies, the HbA1c reduction and percentage of patients who achieved HbA1c <7.0% were similar in the GLP-1RA and basal-plus groups. However, in both the basal-plus and basal-bolus trials, the change in weight and the risk of hypoglycemia favored the addition of a GLP-1RA.[27]

Other differences between the addition to basal insulin of a GLP-1RA vs prandial insulin were observed in the 12-week 4B trial by Diamant et al in patients with inadequate glycemic control with glargine and metformin.[22] The addition to basal insulin of exenatide twice daily vs mealtime lispro thrice-daily provided similar reductions in the HbA1c, but addition of exenatide resulted in greater reduction in FPG. Breakfast and dinner PPG levels were similar between the 2 groups, but lispro provided greater reduction in the lunch PPG level. The addition of exenatide resulted in fewer daytime hypoglycemic episodes but more gastrointestinal (GI) adverse events than the addition of lispro. The addition of exenatide to basal insulin resulted in weight loss compared to weight gain with the addition to basal insulin of lispro.

FIGURE 1 **Meta-analysis of studies comparing basal insulin plus a GLP-1RA vs basal insulin with or without prandial insulin[20]**



Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin.
Note: Number of studies per endpoint ranged from 6 to 17.
Note: Data are presented as basal insulin plus GLP-1RA vs basal insulin with or without prandial insulin.
*Data are difference in means (95% confidence interval):
decrease in HbA1c: -0.48% (-0.67 to -0.30)
decrease in fasting plasma glucose: -4.9 mg/dL (-8.8 to -0.9)
decrease in postprandial glucose: -47.0 mg/dL (-67.0 to -27.2)
decrease in weight: -2.60 kg (-3.32 to -1.89).
**Data are odds ratio (95% confidence interval):
symptomatic hypoglycemia: 0.92 (0.68 to 1.23)
severe hypoglycemia: 0.54 (0.21 to 1.38)
endpoint HbA1c <7.0%: 2.90 (1.97 to 4.25)
endpoint HbA1c <7.0% and no weight gain: 4.77 (2.92 to 7.80)
endpoint HbA1c <7.0% and no symptomatic hypoglycemia: 4.63 (2.94 to 7.29)
endpoint HbA1c <7.0% and no weight gain or symptomatic hypoglycemia: 5.80 (3.48 to 9.67).

How does the cost-effectiveness of adding a GLP-1RA to basal insulin compare with adding prandial insulin?

Analysis of the 4B trial showed the addition to basal insulin of a GLP-1RA to be cost-effective compared with the addition of prandial insulin.[28] Cost-effectiveness analyses compare the relative costs and outcomes of different treatments or other interventions. Exenatide was associated with a cost per quality-adjusted life-year of approximately US$2200, which is within conventional limits of cost-effectiveness.[28]

COMBINATION OF BASAL INSULIN AND GLP-1RA AS FIXED-RATIO COMBINATION PRODUCTS

Comparison with individual components

The use of multiple classes of medications for many chronic diseases often results in reduced patient adherence to medications. Studies show that patient adherence declines when patients move from treatment with one medication to more than one medication. The decline is smaller in moving from one medication to a combination product.[29-31] When moving from treatment with 2 individual medications to a combination product, patient adherence improves.[29,30,32]

Which fixed-ratio combination products have been approved for T2DM?

In 2016, the US Food and Drug Administration (FDA) approved 2 products that combine a basal insulin with a GLP-1RA. Similar to premixed insulins, these 2 new products are titratable, fixed-ratio combination products. The first fixed-ratio combination product approved in the United States combines insulin glargine U-100 and the GLP-1RA lixisenatide (iGlarLixi). iGlarLixi can be titrated over a range of 15 to 60 units where 1 unit of iGlarLixi equals 1 unit of glargine and 0.33 mcg of lixisenatide. The second fixed-ratio combination product approved combines insulin degludec U-100 and the GLP-1RA liraglutide (IDegLira). IDegLira can be titrated over a range of 10 to 50 units where 1 unit of IDegLira contains 1 unit of degludec and 0.036 mg of liraglutide.

To achieve the glycemic target, titration of iGlarLixi and IDegLira is based on the insulin component, thereby allowing for a slow increase in the dose of the GLP-1RA to minimize the frequency and severity of some of the GI adverse events.

How do the efficacy and safety of the fixed-ratio of glargine and lixisenatide compare with the individual components?

iGlarLixi and IDegLira have been compared with their individual components in prospective randomized clinical trials (**TABLE 1**).[33-35] The efficacy and safety of iGlarLixi were

TABLE 1 Studies of fixed-ratio combinations of insulin glargine/lixisenatide and insulin degludec/liraglutide vs individual components

Trial description	Endpoints/outcomes			
Insulin glargine/lixisenatide				
LixiLan-O[35]		**MET + iGlarLixi**[a] **(n=469)**	**MET + glargine**[a] **(n=467)**	**MET + lixisenatide 20**[b] **mcg/d (n=234)**
R, OL, PG, MC; 30 wks MET ± 1 OAD Screening: HbA1c: 8.2%-8.3% 4-week run-in metformin optimization; other OADs stopped Baseline at randomization: Diabetes duration: 8.7-8.9 y HbA1c: 8.1% FPG: 176-178 mg/dL PPG: 263-274 mg/dL N=1170	ΔHbA1c, %	-1.6	-1.3	-0.9
	ΔFPG, mg/dL	-63	-59	-27
	ΔPPG, mg/dL	-103	-59	-83
	Δ2-h PPG excursion, mg/dL	-42	-3	-58
	% HbA1c <7.0%	74	59	33
	% HbA1c <7.0% w/o weight gain	43	25	28
	ΔWeight, kg	-0.3	1.1	-2.3
	Symptomatic hypoglycemia,[c] events/patient-year	1.4	1.2	0.3
	Severe hypoglycemia, events/patient-year	0	<0.01	0
	Total daily dose of insulin at study end, units	39.8	40.3	N/A

continued

compared with the individual components in patients with T2DM inadequately controlled with metformin with or without a second oral agent in the LixiLan-O trial.[35] At the end of 30 weeks, which included a 4-week run-in to optimize metformin and stop other glucose-lowering agents, greater reduction in HbA1c was achieved with iGlarLixi compared with glargine or lixisenatide (**TABLE 1**). More patients achieved HbA1c <7% with iGlarLixi than glargine or lixisenatide. The reduction in FPG was similar in the iGlarLixi and glargine groups and smaller with lixisenatide, while the reduction in PPG was significantly greater with iGlarLixi than glargine, but significantly less than with lixisenatide. Body weight decreased with iGlarLixi and lixisenatide, but increased with glargine.

The incidence of documented symptomatic hypoglycemia was similar with iGlarLixi and glargine and lower with lixisenatide. Nausea (9.6% vs 24%) and vomiting (3.2% vs 6.4%) occurred less frequently with iGlarLixi than lixisenatide, respectively. The final daily dose of basal insulin was similar in the iGlarLixi and glargine groups. Baseline HbA1c, disease duration, and BMI had no impact on glycemic outcomes.[36]

Except for the lower frequency of GI adverse events with iGlarLixi, the safety profiles of the medications were as expected. Most adverse events were considered mild or moderate in intensity. An adverse event leading to treatment discontinuation occurred in 2.6% of patients treated with iGlarLixi, 1.9% of patients treated with glargine, and 9.0% of patients treated with lixisenatide.[35] The lower incidence of GI adverse events with iGlarLixi vs lixisenatide is likely due to the slow increase in lixisenatide dose that occurs as the insulin dose is titrated to achieve glycemic control.

A major adverse cardiovascular event was observed in 2 patients in the iGlarLixi group (one cardiovascular death and one unstable angina), 7 in the glargine group (2 cardiovascular deaths, 2 heart failure hospitalizations, and one each for nonfatal stroke, unstable angina, and coronary revascularization), and 2 in the lixisenatide group (one cardiovascular death and one nonfatal stroke). No events were adjudicated as pancreatitis in any group, while one patient in the glargine group had pancreatic cancer.

How do the efficacy and safety of the fixed-ratio of degludec and liraglutide compare with their individual components?

The efficacy and safety of IDegLira have been assessed in the DUAL clinical trial program. The 26-week DUAL-I trial with 26-week extension compared IDegLira with degludec U-100 or liraglutide in insulin-naïve patients uncontrolled on metformin with or without pioglitazone.[33,34] Over the first 26 weeks, treatment with IDegLira resulted in a significantly greater reduction in HbA1c than degludec or liraglutide, thereby meeting the noninferiority criteria to degludec and superiority to liraglutide.[33,34] In addition, a significantly higher proportion of patients achieved an HbA1c <7% with IDegLira than degludec or liraglutide. The proportion of

TABLE 1 **Studies of fixed-ratio combinations of insulin glargine/lixisenatide and insulin degludec/liraglutide vs individual components (*continued)***

Trial description	Endpoints/outcomes			
Insulin deguldec/liraglutide				
DUAL-I[33]		**MET ± PIO + IDegLira[d] (n=833)**	**MET ± PIO + degludec[d] (n=413)**	**MET ± PIO + liraglutide 1.8[e] mg/d (n=414)**
R, OL, PG, MC; 26 wks MET ± PIO Diabetes duration: 6.6-7.2 y HbA1c: 8.3% FPG: 162-169 mg/dL N=1660	ΔHbA1c, %	-1.9	-1.4	-1.3
	ΔFPG, mg/dL	-65	-65	-32
	% HbA1c <7.0%	81	65	60
	% HbA1c <7.0% w/o weight gain	46	21	54
	ΔWeight, kg	-0.5	1.6	-3
	Confirmed hypoglycemia,[f] events/patient-year	1.8	2.6	0.2
	Severe hypoglycemia,[f] %	0.4	0.5	0
	Total daily dose of insulin at study end, units	38	53	N/A
DUAL-1 extension[34] 26-week extension of DUAL-1 N=1311	ΔHbA1c,[g] %	-1.8	-1.4	-1.2
	ΔFPG,[g] mg/dL	-62	-61	-30
	% HbA1c <7.0%[g]	78	63	57
	% HbA1c <7.0% w/o weight gain[g]	45	19	48
	ΔWeight,[g] kg	-0.4	2.3	-3
	Confirmed hypoglycemia,[f] events/patient-year	1.8	2.8	0.2
	Severe hypoglycemia, %	0.4	0.5	0.5
	Nocturnal hypoglycemia,[h] events/patient-year	0.2	0.4	0.02
	Total daily dose of insulin at study end, units	39	62	N/A

Abbreviations: DB, double-blind; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IDegLira, insulin degludec/liraglutide; iGlarLixi, insulin glargine/lixisenatide; MC, multicenter; MET, metformin; N/A, not applicable; OAD, oral antidiabetic drug; OL, open-label; PG, parallel group; PIO, pioglitazone; PPG, postprandial glucose; R, randomized.

[a]Titrated to achieve an FPG of 80-100 mg/dL while avoiding hypoglycemia to a maximum of 20 mcg/d of lixisenatide (if applicable) and 60 units/d of glargine.

[b]Initial dose of 10 mcg/d for 2 weeks, then 20 mcg/d.

[c]Hypoglycemia defined as typical symptoms with self-measured blood glucose ≤70 mg/dL.

[d]Titrated to achieve an FPG of 72 mg/dL to 90 mg/dL. The initial dose of IDegLira and degludec was 10 units; the maximum daily dose of IDegLira was 50 units of degludec and 1.8 mg of liraglutide; there was no limit to the dose of degludec.

[e]Liraglutide initiated at 0.6 mg/day and increased by 0.6 mg per week to a maximum of 1.8 mg/d.

[f]Hypoglycemia requiring assistance (severe) or episodes in which self-measured blood glucose was <56 mg/dL with or without symptoms.

[g]Changes from baseline (week 0) to week 52.

[h]Hypoglycemia occurring between 0001 and 0559 h.

patients who achieved HbA1c <7% without weight gain or without hypoglycemia was significantly higher with IDegLira than degludec. More patients treated with liraglutide than IDegLira achieved HbA1c <7% without weight gain or without hypoglycemia. Body weight increased with degludec, but decreased with IDegLira and liraglutide. The daily dose of insulin was lower in the IDegLira group vs degludec group at study end.

Three-quarters (78.8%) of patients continued into the 26-week extension phase. From week 26 to week 52 of DUAL-I, the daily dose of IDegLira increased by 1 unit to a final mean daily dose of 39 units/day (39 units insulin degludec and 1.4 mg liraglutide), whereas the degludec dose continued to increase as would be expected due to disease progression, with a mean daily dose of 62 units at 52 weeks. The liraglutide arm remained unchanged on the 1.8 mg dose. The slight weight loss with IDegLira versus weight gain with degludec was likely due to liraglutide, as well as the lower insulin dose. The lower insulin dose with IDegLira also contributed to a lower incidence of hypoglycemia than observed with degludec.[34] In addition, a substudy of DUAL-I showed that, at week 26, IDegLira produced a significantly greater decrease from baseline in mean PPG increment than insulin degludec.[37] The decrease in PPG increment was similar with

IDegLira and liraglutide despite IDegLira patients receiving a mean liraglutide dose of approximately 1.4 mg/d compared with 1.8 mg/d in the liraglutide arm. The PPG reductions with IDegLira were similar over all 3 main meals.

Over the 26 weeks of DUAL-I and the 26-week extension, the most frequently reported adverse events were headache, nausea, diarrhea, vomiting, nasopharyngitis, and upper respiratory tract infection, most of which were mild and not treatment-related.[34] An adverse event leading to treatment discontinuation occurred in 1.7% of patients treated with IDegLira, 2.2% of patients treated with degludec, and 6.3% of patients treated with liraglutide. Liraglutide was associated with a higher incidence of discontinuation due to the higher frequency of GI adverse events occurring shortly after initiating treatment. The lower incidence of GI adverse events with IDegLira vs liraglutide is likely due to the slow increase in liraglutide dose that occurs as the IDegLira dose is titrated based on the degludec component to achieve glycemic control.

Six major adverse cardiovascular events occurred, 4 with IDegLira (2 myocardial infarctions and 2 cardiovascular deaths) and one (myocardial infarction) in each of the degludec and liraglutide groups. One of the 2 cardiovascular deaths with IDegLira was due to sudden death of unknown reasons and the other due to cardiopulmonary arrest caused by sepsis. Over the 52 weeks, 5 cases of pancreatitis or suspected pancreatitis and 16 adverse events of increased lipase and/or amylase were reported; two were adjudicated to be treatment-emergent pancreatitis. Both were in the liraglutide group, but judged by the investigators as unlikely to be treatment-related. No medullary thyroid carcinomas were reported.

How does the cost-effectiveness of a fixed-ratio basal insulin/GLP-1RA combination compare with basal-bolus therapy?

A recent report from an analysis of the DUAL VII study suggests that IDegLira is cost-effective compared to basal-bolus therapy from a US health care payer perspective in patients with inadequate glycemic control on insulin glargine U-100 (20-40 units) and metformin.[38] The percentage of patients achieving glycemic control was similar in the 2 groups after 26 weeks, but a greater proportion of patients receiving IDegLira achieved glycemic targets without weight gain and/or hypoglycemia. For example, 52.9% of IDegLira patients and 23.2% of basal-bolus insulin patients achieved HbA1c <7.0% without confirmed hypoglycemia. The annual cost of control for all endpoints was lower with IDegLira than basal-bolus insulin, with greater differences when weight gain and hypoglycemia were included. For example, the annual cost per patient achieving HbA1c <7.0% without confirmed hypoglycemia was $19,033 for IDegLira and $46,317 for basal-bolus insulin.

COMPARISON OF FIXED-RATIO BASAL INSULIN AND GLP-1RA COMBINATIONS WITH OTHER TREATMENTS

The efficacy and safety of iGlarLixi and IDegLira have been compared with various combinations of glucose-lowering agents in randomized, prospective clinical trials (**TABLE 2**).[39-42]

How do the efficacy and safety of iGlarLixi compare with increasing the dose of glargine, both in combination with oral therapy?

LixiLan-L compared iGlarLixi with up-titrated glargine U-100 in patients with inadequate glycemic control with glargine U-100 15-40 units/day in combination with ≤2 oral agents.[39] Doses of iGlarLixi and up-titrated glargine U-100 were capped at 60 units/day. At 30 weeks, patients treated with iGlarLixi experienced significantly greater HbA1c reduction despite a similar mean final insulin dose (47 units in both groups). Although the mean change in FPG was similar in the 2 groups, iGlarLixi resulted in significantly greater improvement in postprandial glycemic control after a standardized meal. The postprandial benefit was due to the lixisenatide component at a titrated mean dose of 17 mcg/day. More patients treated with iGlarLixi achieved several composite endpoints that included glycemic control, no weight gain, and/or no hypoglycemia. These benefits were independent of baseline HbA1c, BMI, and duration of diabetes.[43]

The proportion of patients who experienced confirmed symptomatic hypoglycemia was similar in the 2 groups. GI adverse events were more common with iGlarLixi than glargine, were generally mild, and led to discontinuation in 1.1% of patients. A major adverse cardiovascular event occurred in low and similar percentages of patients in both groups. There were no cases of pancreatitis or pancreatic cancer reported.

How do the efficacy and safety of IDegLira compare with degludec, both in combination with metformin?

DUAL-II evaluated the contribution of the liraglutide component of IDegLira by comparing the efficacy and safety of IDegLira with degludec, both once daily with a maximum insulin dose of 50 units. Eligible patients had inadequate glycemic control with basal insulin 20-40 units/day plus metformin with or without a sulfonylurea or glinide; the latter 2 were discontinued at randomization.[40] After 26 weeks, the mean degludec dose was 45 units/day in both groups. IDegLira provided significantly greater reductions in HbA1c and FPG, as well as a smaller rise in postprandial glucose, than degludec.

TABLE 2 Additional studies of fixed-ratio combinations of insulin glargine/lixisenatide and insulin degludec/liraglutide

Trial description	Endpoints/outcomes		
Insulin glargine/lixisenatide			
LixiLan-L[39]		**MET + iGlarLixi[a] (n=367)**	**MET + glargine[a] (n=369)**
R, OL, PG, MC; 30 wks Basal insulin (15-40 units/d) ± OADs Screening: HbA1c: 8.5% FPG: 142-144 mg/dL 6-week run-in: metformin and basal insulin optimization; other OADs stopped Baseline: Diabetes duration: 12-12.1 y HbA1c: 8.1% FPG: 131-133 mg/dL N=736	ΔHbA1c, %	-1.1	-0.6
	ΔFPG, mg/dL	-7	-9
	ΔPPG, mg/dL	-85	-25
	Δ2-h PPG excursion, mg/dL	-70	-9
	% HbA1c <7.0%	55	30
	% HbA1c <7.0% w/o weight gain	34	13
	ΔWeight, kg	-0.7	0.7
	Symptomatic hypoglycemia,[b] events/patient-year	3	4.2
	Severe hypoglycemia, events/patient-year	0.02	<0.01
	Total daily dose of insulin at study end, units	47	47
Insulin degludec/liraglutide			
DUAL-II[40]		**MET + IDegLira[c] (n=199)**	**MET + degludec[c] (n=199)**
R, DB, PG, MC; 26 wks Basal Insulin (20-40 units/d) + MET ± SU/GLIN; SU/GLIN stopped at randomization Diabetes duration: 10-11 y HbA1c: 8.7%-8.8% FPG: 173-175 mg/dL N= 398	ΔHbA1c, %	-1.9	-0.9
	ΔFPG, mg/dL	-62	-46
	2-h PPG excursion, mg/dL	40	43
	% HbA1c <7.0%	60	23
	% HbA1c <7.0% w/o weight gain	51	12
	ΔWeight, kg	-2.7	0
	Confirmed hypoglycemia,[d] events/patient-year	1.5	2.6
	Severe hypoglycemia, %	0.5	0
	Nocturnal hypoglycemia,[e] events/patient-year	0.22	0.32
	Total daily dose of insulin at study end, units	45	45

continued

Body weight decreased with IDegLira, but remained stable with degludec. More patients treated with IDegLira achieved several composite endpoints that included glycemic control, no weight gain, and/or no hypoglycemia. Rates of confirmed and nocturnal hypoglycemia were similar in both groups. Nausea occurred in 6.5% and 3.5% of IDegLira and degludec patients, respectively. A patient in each group experienced a myocardial infarction; one patient in the degludec group experienced a stroke. One case of metastatic pancreatic cancer was reported in the degludec group. There were no cases of pancreatitis, medullary thyroid cancer, or thyroid cancers confirmed. The study results showed that liraglutide, at a titrated dose averaging less than 1.8 mg/day, significantly improved glycemic control, but did not increase the safety risk.

How do the efficacy and safety of IDegLira compare with exenatide twice-daily or liraglutide, both in combination with oral therapy?

DUAL-III involved insulin-naïve patients with inadequate glycemic control on a GLP-1RA and ≥1 oral agents.[41] Patients were randomized to IDegLira or to continue on their exenatide twice-daily or liraglutide unchanged, with both groups

TABLE 2 Additional studies of fixed-ratio combinations of insulin glargine/lixisenatide and insulin degludec/liraglutide (*continued*)

Trial description	Endpoints/outcomes		
DUAL-III[41]		**MET ± PIO ± SU + IDegLira[f] (n=292)**	**MET ± PIO ± SU + GLP-1RA[g] (n=146)**
R, OL, PG, MC; 26 wks Diabetes duration: 10.4 y MET ± PIO ± SU + GLP-1RA HbA1c: 7.7%-7.8% FPG: 162-169 mg/dL N= 438	ΔHbA1c, %	-1.3	-0.3
	ΔFPG, mg/dL	-54	-11
	% HbA1c <7.0%	75	36
	ΔWeight, kg	2	-0.8
	Confirmed hypoglycemia,[d] events/patient-year	2.82	0.12
	Severe hypoglycemia, %	0.3	0
	Nocturnal hypoglycemia,[e] events/patient-year	0.45	0.015
	Total daily dose of insulin at study end, units	43	N/A
DUAL-V[42]		**MET + IDegLira[h] (n=278)**	**MET + glargine[h] (n=279)**
R, OL, PG, MC; 26 wks Diabetes duration: 11.3-11.6 y MET + Glargine (20-50 units/d) HbA1c: 8.2%-8.4% FPG: 160-161 mg/dL N= 557	ΔHbA1c, %	-1.8	-1.1
	ΔFPG, mg/dL	-51	-50
	% HbA1c <7.0%	72	47
	% HbA1c <7.0% w/o weight gain	50	20
	ΔWeight, kg	-1.4	1.8
	Confirmed hypoglycemia,[d] events/patient-year	2.23	5.05
	Severe hypoglycemia	0	0.4
	Nocturnal hypoglycemia,[e] events/patient-year	0.22	1.23
	Total daily dose of insulin at study end, units	41	66

Abbreviations: DB, double-blind; FPG, fasting plasma glucose; GLIN, glinide; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; IDegLira, insulin degludec/liraglutide; iGlarLixi, insulin glargine/lixisenatide; MC, multicenter; MET, metformin; OAD, oral glucose-lowering drug; OL, open-label; PG, parallel group; PIO, pioglitazone; PPG, postprandial glucose; R, randomized; SU, sulfonylurea.

[a]Titrated to achieve a fasting plasma glucose of 80-100 mg/dL with no hypoglycemia to a maximum of 20 mcg/d of lixisenatide (if applicable) and 60 units/d of glargine.

[b]Hypoglycemia defined as typical symptoms with self-measured blood glucose ≤70 mg/dL.

[c]Titrated to achieve an FPG of 72 mg/dL to 90 mg/dL; the maximum daily dose of IDegLira was 50 units of degludec and 1.8 mg of liraglutide (if applicable).

[d]Hypoglycemia requiring assistance (severe) or episodes in which self-measured blood glucose was <56 mg/dL with or without symptoms.

[e]Hypoglycemia occurring between 0001 and 0559 h.

[f]Titrated to achieve an FPG of 72 mg/dL to 90 mg/dL; the initial daily dose was 16 units of degludec and 0.58 mg liraglutide and the maximum daily dose was 50 units of degludec and 1.8 mg of liraglutide.

[g]Maximum tolerated dose of liraglutide once daily or exenatide twice daily.

[h]Titrated to achieve an FPG of 72 mg/dL to 90 mg/dL; the initial daily dose was 16 units of degludec and 0.58 mg liraglutide and the maximum daily dose was 50 units of degludec and 1.8 mg of liraglutide; there was no limit to the dose of glargine.

continuing baseline oral treatment. The mean daily dose of exenatide twice-daily was 18.4 mcg and of liraglutide 1.7 mg. After 26 weeks, the mean IDegLira dose was 43 units of degludec and 1.5 mg of liraglutide. At 4 weeks, greater reductions in HbA1c and FPG were observed with IDegLira vs unchanged exenatide twice-daily or liraglutide, thereby demonstrating no deterioration in blood glucose when switching from a GLP-1RA to IDegLira. After 26 weeks, IDegLira provided significantly greater HbA1c, FPG, and 9-point self-monitored blood glucose reductions than continued treatment with a GLP-1RA. Patients treated with IDegLira experienced a significant increase in body weight and were significantly more likely to experience confirmed or nocturnal hypoglycemia, both likely due to the initiation of degludec in insulin-naïve patients. The most frequently reported adverse events were nasopharyngitis, upper respiratory tract infection, increased

lipase, headache, and diarrhea. Nausea occurred in more patients treated with unchanged GLP-1RA. Two patients in the IDegLira group experienced a stroke. Three neoplasms were confirmed by adjudication, 2 with IDegLira and one with unchanged GLP-1RA therapy. No medullary thyroid cancer, thyroid-related adverse events, or pancreatitis were reported. Patient-reported health outcomes and satisfaction were significantly greater with IDegLira than unchanged GLP-1RA. Patients treated with IDegLira indicated a higher perceived frequency of hypoglycemia and a lower perceived frequency of hyperglycemia, both findings in keeping with the clinical outcomes of the trial.

How do the efficacy and safety of IDegLira compare with increasing the dose of glargine, both in combination with metformin?

DUAL-V compared IDegLira with up-titrated glargine U-100 in patients with inadequate glycemic control with glargine U-100 20-50 units/day plus metformin.[42] After 26 weeks, patients treated with IDegLira experienced a significantly greater HbA1c reduction than patients treated with up-titrated glargine U-100, while there was no difference in FPG. Patients treated with IDegLira lost weight, while those who uptitrated glargine U-100 gained weight. Significantly more patients treated with IDegLira achieved several composite endpoints that included glycemic control, no weight gain, and/or no hypoglycemia. Adverse events, primarily GI in nature, were more common with IDegLira. However, no more than 4% of patients experienced nausea with IDegLira at any given week during the trial. There were significantly fewer confirmed hypoglycemic episodes with IDegLira than glargine U-100. One major adverse cardiovascular event occurred in each group. One case of metastatic pancreatic cancer in the IDegLira group was positively adjudicated, but considered by the investigator as unlikely to be treatment-related. Two thyroid disease events and a single event of pancreatitis were reported but not confirmed by the adjudication committee. Improvements in patient-reported outcomes with IDegLira were generally due to greater improvement in treatment burden and diabetes management.

SUMMARY OF KEY FINDINGS FROM CLINICAL TRIALS OF FIXED-RATIO BASAL INSULIN/GLP-1RA PRODUCTS

Insulin glargine U-100/lixisenatide

The fixed-ratio combination iGlarLixi provided significantly better glycemic control, while reducing key adverse events associated with basal insulin and GLP-1RA therapy in insulin-naïve and insulin-treated patients. iGlarLixi was not insulin-sparing, providing comparable FPG reduction as glargine U-100. However, iGlarLixi provided significantly greater PPG reduction than glargine U-100. More patients treated with iGlarLixi achieved composite endpoints that included glycemic control, no weight gain, and/or no hypoglycemia than glargine U-100 or lixisenatide. Weight effects with iGlarLixi were intermediate between glargine U-100 and lixisenatide in insulin-naïve patients. The rates of confirmed symptomatic hypoglycemia were similar to glargine U-100 in insulin-naïve and insulin-treated patients. The overall adverse event profile parallels the profiles of the individual components. The low incidence of GI adverse events was likely due to the slow increase in lixisenatide dose that occurs as the glargine dose is titrated to achieve glycemic control. Adjudicated major cardiovascular events occurred in a low percentage of patients treated with iGlarLixi. There were no cases of adjudicated pancreatitis, pancreatic cancer, or medullary thyroid cancer with iGlarLixi.

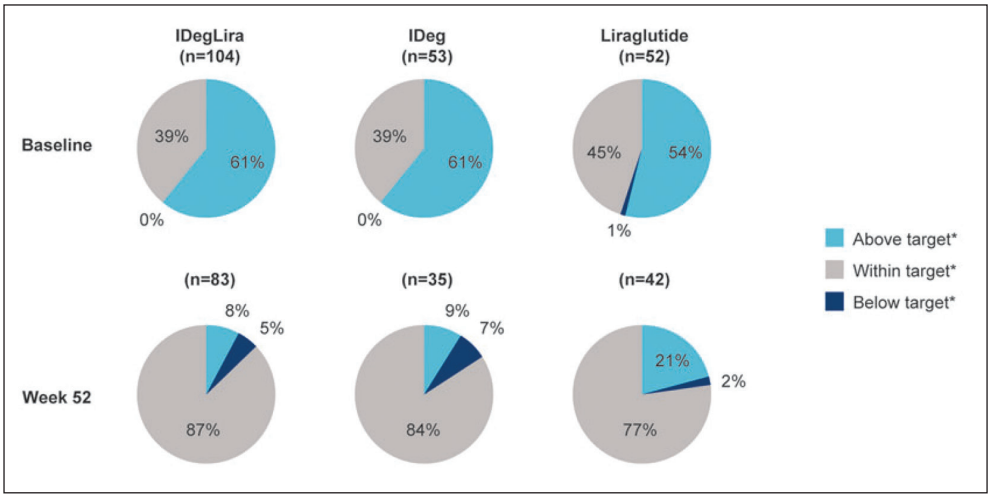
Insulin degludec/liraglutide

The DUAL clinical trial program showed that IDegLira provides significantly better glycemic control, while reducing key adverse events associated with basal insulin and GLP-1RA therapy in insulin-naïve and insulin-treated patients, as well as GLP-1RA-treated patients. IDegLira was insulin-sparing, resulting in significantly greater HbA1c reductions at a lower total daily insulin dose than degludec. IDegLira effectively lowered HbA1c independent of baseline HbA1c, disease duration, or previous insulin dose.[44] More patients treated with IDegLira achieved composite endpoints that included glycemic control, no weight gain, and/or no hypoglycemia. Further, a post hoc sub-study analysis of the DUAL-I trial using continuous glucose monitoring showed that IDegLira reduced glycemic excursions. Patients treated with IDegLira spent a greater proportion of the day within the target range of 70 to 162 mg/dL than degludec or liraglutide alone for all pre- and postprandial levels over the 24-hour period (**FIGURE 2**).[45]

Weight effects with IDegLira were intermediate between degludec and liraglutide, resulting in weight loss when switching from basal insulin and no weight gain when switching from oral agents. Across the DUAL trials, the rate of confirmed hypoglycemia was low and was consistently lower vs basal insulin comparators; however, concomitant use of IDegLira with a sulfonylurea appears to increase the rate of hypoglycemia. Rates of nausea with IDegLira were higher than with insulin comparators but lower than with liraglutide, occurring in no more than 4% of patients per week in the DUAL program. The low rate of nausea is likely due to the slow increase in the liraglutide dose that occurs with titration of IDegLira based on the degludec component.

A major adverse cardiovascular event was infrequently reported. There were no cases of adjudicated, treatment-related pancreatitis, pancreatic cancer, or medullary thyroid cancer with IDegLira. IDegLira was associated with greater improvement than comparators in patient-reported health outcomes and treatment satisfaction, generally due to greater improvement in treatment burden and diabetes management.

FIGURE 2 Proportion of time within the interstitial glucose target range with fixed-ratio degludec/liraglutide[45]



Abbreviations: IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide.

*Above (interstitial glucose ≥162 mg/dL), within (interstitial glucose 70-161 mg/dL), and below (interstitial glucose <70 mg/dL)

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RECOMMENDATIONS FOR INITIATING AND TITRATING FIXED-RATIO BASAL INSULIN/GLP-1RA PRODUCTS

Recommendations for initiating iGlarLixi and IDegLira are provided in **TABLE 3**.[46,47] It is necessary that basal insulin and GLP-1RA therapy be discontinued prior to initiation of iGlarLixi or IDegLira.[46,47]

How should iGlarLixi and IDegLira be initiated and titrated?

For iGlarLixi, the recommended initial dose is 15 units (15 units of insulin glargine and 5 mcg of lixisenatide) or

TABLE 3 Recommendations for initiating fixed-ratio insulin glargine/lixisenatide and insulin degludec/liraglutide[46,47]

	Insulin degludec and liraglutide (Xultophy 100/3.6)	Insulin glargine and lixisenatide (Soliqua 100/33)
Prior to initiating	Discontinue basal insulin, GLP-1RA	
How supplied	Each mL contains: 100 units degludec and 3.6 mg liraglutide	Each mL contains: 100 units glargine and 33 mcg lixisenatide
Dosing	Based on insulin component	
Initial dose	16 units	If inadequately controlled with <30 units basal insulin or lixisenatide: 15 units If inadequately controlled with 30-60 units basal insulin: 30 units
When to administer	Once daily at same time each day with or without food	Once daily within the hour prior to the first meal of the day
Dose range delivered per injection	10 to 50 units	15 to 60 units
Maximum dose	50 units (50 units degludec/1.8 mg liraglutide)	60 units (60 units glargine/20 mcg lixisenatide)
Route of administration	Subcutaneously only	
Injection site	Thigh, upper arm, abdomen	

30 units (30 units of insulin glargine and 10 mcg of lixisenatide) based upon prior insulin dose or lixisenatide use. The dosage should be titrated upwards or downwards by 2 to 4 units every week.[46] For IDegLira, the recommended initial dose is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide), the dosage should be titrated upwards or downwards by 2 units every 3 to 4 days.[47] For both products, titration is based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal until the desired fasting plasma glucose is achieved. The dosage is between 15 to 60 units for iGlarLixi[46] and between 10 to 50 units for IDegLira.[47] To minimize the risk of hypoglycemia or hyperglycemia, additional titration of both products may be needed with changes in physical activity, meal patterns (ie, macronutrient content or timing of food intake), or renal or hepatic function; during acute illness; or when used with other medications, eg, a thiazolidinedione, anti-adrenergic drug, or those that affect glucose metabolism.[46,47]

When should the dose of iGlarLixi and IDegLira be administered?

iGlarLixi should be administered once daily within the hour prior to the first meal of the day.[46] IDegLira should be administered at the same time each day with or without food.[47]

What should be done if the patient does not achieve glycemic control despite treatment with the maximum recommended dose of iGlarLixi or IDegLira?

Alternative treatment should be used if a patient requires a dose of iGlarLixi over 60 units[46] or over 50 units for IDegLira.[47] If the patient is not at the FPG target, adding a medication that targets FPG such as basal insulin should be considered. If the patient is at the FPG target but not the PPG target, adding a medication that targets PPG such as prandial insulin should be considered.

What should the patient do if he or she misses a dose of iGlarLixi or IDegLira?

For both products, patients who miss a dose should be instructed to resume the once-daily regimen with the next scheduled dose and to not administer an extra dose or increase the dose.[46,47] For IDegLira, if more than 3 days have elapsed since the last dose, patients should be instructed to reinitiate therapy at the starting dose as this will mitigate GI symptoms.[47]

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