What Primary Care Clinicians Need to Know About Once-Weekly Insulins

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doi: xxxxx

CONTINUING MEDICAL EDUCATION

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of diabetes.

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Initiate basal insulin therapy without unnecessary delays for patients with type 2 diabetes (T2D) for whom insulin treatment is appropriate.
- Review the clinical efficacy and safety data for new and emerging ultra-long-acting, once-weekly insulins.
- Compare and contrast the potential benefits and risks of once-weekly insulins compared with traditional basal insulins.

KEY TAKEAWAYS

- Basal insulin remains an essential and effective glucose-lowering treatment for many patients with T2D.
- Ultra-long-acting, once-weekly insulins may soon be approved and provide an additional option for basal insulin therapy.
- Once-weekly insulins may improve adherence and persistence, increase flexibility in administration time, and reduce glycemic variability compared with once-daily basal insulins.
- Potential concerns with once-weekly insulins may include challenges with dose calculations and concerns about hypoglycemia, which may be resolved as clinicians become more familiar with these insulin formulations.

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Dr. Shubrook serves as a consultant to Abbott Laboratories, Bayer, and Novo Nordisk, and is on the advisory boards of Eli Lilly, Madrigal Pharmaceuticals, and Nevro. Austin Ulrich has no disclosures to report.

SPONSORSHIP

This article is sponsored by Primary Care Education Consortium and the Primary Care Metabolic Group.

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ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, Primary Care Education Consortium.

SUPPORTER

This article is supported by an educational grant from Novo Nordisk.

INTRODUCTION

Type 2 diabetes (T2D) is a chronic and progressive disease characterized by impaired blood glucose control. It is increasingly recognized as a serious public health concern globally.[1] In the United States (US), an estimated 14.7% of adults have diabetes; of these, up to 95% have T2D.[1-3] Patients with T2D often experience significant morbidity due to microvascular and macrovascular complications resulting from elevated blood glucose, and they can also have diminished functional capacity, lower quality of life, and premature death.[4-6]

Primary care clinicians (PCCs) treat at least 90% of patients in the US with T2D and are often the first clinicians to diagnose the disease.[7,8] While some patients with T2D may see an endocrinologist, projections indicate current and future shortages for this medical specialty. Thus, PCCs play a

critical role in the management of patients with T2D, which often involves the use of basal insulin.[8,9]

THE ROLE OF BASAL INSULIN IN T2D

Despite the emergence of newer agents to treat T2D, insulin is still an essential and effective glucose-lowering treatment for many patients.[10] Over the years, insulin therapy has evolved with corresponding advances in molecular biology, chemistry, and technologies for drug delivery. According to current American Diabetes Association guidelines, basal insulin should be considered as the first injectable therapy when a patient with T2D has significant (blood glucose ≥300 mg/dL or glycated hemoglobin [HbA1c] >10%) or symptomatic hyperglycemia or signs of catabolism due to glucotoxicity.[11]

Many patients with T2D do not achieve glycemic control, and few achieve simultaneous control of associated cardiovascular risk factors (glucose, blood pressure, and lipids). Data extrapolated from the National Health and Nutrition Examination Survey (NHANES) 2013-2016 showed that 55.8% of people with T2D were at their target HbA1c level, while only 17.3% reached control of the composite of HbA1c, blood pressure, and blood lipids.[12] Inclusion of body mass index (BMI) targets lowered the finding to <10%.[12] Analysis of NHANES data from 2005 to 2016 showed that the cascade of diabetes care, defined as the composite of diabetes diagnosis, linkage to care, and achievement of individual and combined treatment targets, did not significantly improve over time.[13] Of US adults diagnosed with diabetes, 23% met therapeutic targets from 2005-2008, 25% met targets from 2009-2012, and 23% met targets from 2013-2016.[13]

Recent advances in insulin development have been largely focused on improving ease and convenience for the patient and greater stability in glucose readings. This has led to newer formulations of basal insulins, such as ultra-long-acting, once-weekly insulins, which are nearing US Food and Drug Administration (FDA) approval. Once-weekly basal insulins are predicted to increase treatment adherence, decrease clinical inertia, and improve patient quality of life, provided that potential risks are properly addressed.[10]

An estimated 7.4 million Americans with diabetes use one or more form of insulin to manage their condition.[14] The goals of insulin therapy are to replicate as closely as possible a normal glycemic profile without unacceptable weight gain or hypoglycemia. For patients with T2D, initiating insulin therapy should start with basal insulin with a preference for basal insulin analogs.[11] However, acceptability of insulin is still low among patients with T2D, leading to reluctance to initiate and continue insulin therapy.[15] Moreover, a large proportion of people interrupt or discontinue treatment shortly after initiation.[16,17] According to 1 analysis, only 20% of people initiating basal insulin continued with insulin treatment within the year after initiation.[16]

Clinical inertia in reaching T2D treatment goals

A retrospective cohort study of more than 80,000 patients showed that median time to treatment intensification with insulin was longer than 7 years for those who were not meeting glycemic goals on oral antihyperglycemic medications alone.[18] In another study, clinicians waited for an average of 9 years before insulin initiation, at which point the average HbA1c was 9.5% and diabetic complications had emerged. Even after insulin initiation, the clinicians did not intensify therapy adequately, and average HbA1c remained at 7.9% after 4 years.[19]

Clinical inertia is characterized by lack of treatment initiation or intensification resulting in failure to achieve glycemic goals and is a common reason for poor glycemic control.[20] Unfortunately, clinical inertia is very prevalent in clinical settings in the US. One study showed that fewer than 50% of patients with T2D and a high HbA1c had their treatment appropriately intensified.[21] Another study showed that clinical inertia was seen in more than 26% of patients who had an HbA1c of ≥7%, and more than 18% of patients with an HbA1c of ≥8%—with failure to intensify the medication regimen over a median 4.2 years of follow-up.[22] Additionally, clinical inertia has resulted in inadequate glycemic control in 40% to 60% of patients with T2D.[23,24] These findings are remarkable considering the focus of guidelines on the importance of glycemic control, indicating that increased attention is needed to achieve glycemic targets in patients with T2D.

CASE SCENARIO

A 59-year-old woman with a 20-year history of T2D presents to her primary care clinic for a follow-up visit 3 months after starting basal insulin once daily, despite her hesitation to use an injectable medication. After about 1 month of titrating her basal insulin dose via twice-weekly phone appointments, she had reached a dose of 45 units of insulin glargine once daily (0.5 units/kg), with a fasting glucose level ranging from 130 mg/dL to 140 mg/dL over a week of measurements and no hypoglycemic episodes. Since then, she says that she has had a difficult time remembering to do her daily injections on her own. She also doesn't like having to give herself an injection every day.

Her fasting blood glucose in clinic today is 195 mg/dL and her HbA1c is 9.6%, which is improved from her HbA1c of 10.3% measured 3 months ago. Her other antihyperglycemic medications include metformin 2000 mg daily and oral semaglutide 14 mg once daily. She states that she would like to try to work on her diet and exercise to get her HbA1c lower, toward her goal of <7%.

The patient in this case scenario originally responded well to basal insulin therapy, with fasting blood glucose values that indicated improvement in overall glucose control. However,

after she was no longer under close follow-up, she began to miss doses and is at risk for clinical inertia, raising her chances of complications that can result from hyperglycemia. This patient may be a good candidate for receiving a once-weekly basal insulin and more support to improve her adherence and overall glucose control.

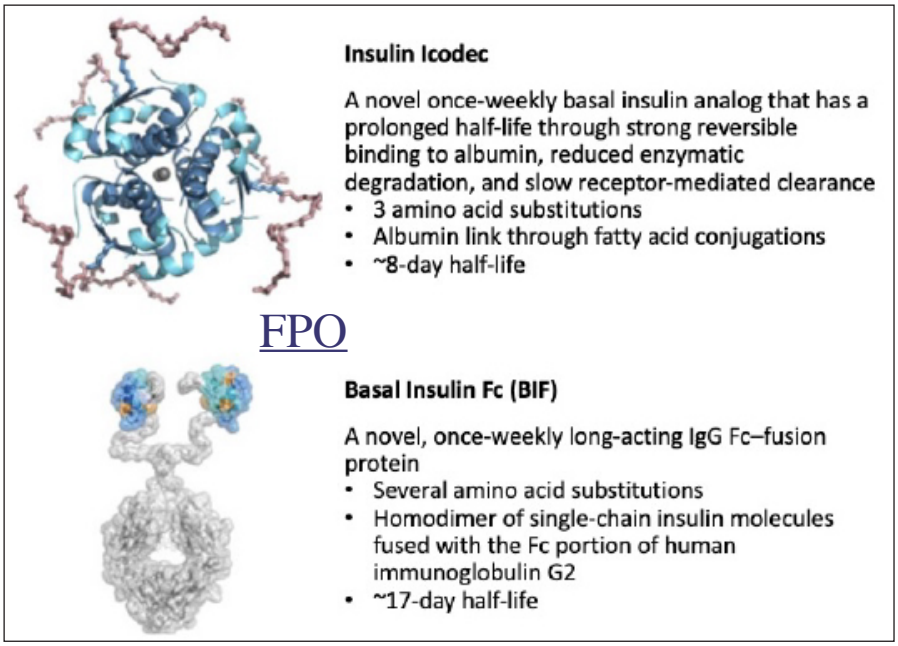
NEW AND EMERGING ONCE-WEEKLY BASAL INSULINS

Innovative insulin formulations and delivery systems have resulted in an expansion of choices that include basal insulins, rapid-acting insulins, and intermediate-acting formulations.[25] Now, once-weekly basal insulin formulations are in late-stage development, with insulin icodec receiving a recommendation for marketing approval in Europe and an FDA decision expected soon.[26,27] Insulin icodec is a novel once-weekly basal insulin analog that has a prolonged half-life through strong reversible binding to albumin, reduced enzymatic degradation, and slow receptor-mediated clearance.[28] Basal insulin Fc (BIF) is a novel, once-weekly, long-acting IgG Fc–fusion protein that is currently being assessed for diabetes treatment.[29] While these once-weekly insulins are not yet clinically available, evidence supports their comparable efficacy and safety in patients with T2D[10] (**FIGURE 1**).

Both insulin icodec and BIF have been investigated in late-stage trials (**TABLE 1**), with overall positive results.[30-35] Results of the phase 3 ONWARDS trials evaluating insulin icodec are summarized in **TABLE 2**.[36] As a whole, the ONWARDS trials showed noninferiority of insulin icodec compared to basal insulin analogs (insulin glargine and insulin degludec) for HbA1c reduction.[30-34] In ONWARDS 2 and ONWARDS 5, insulin icodec also demonstrated superiority compared to other basal insulins in reducing HbA1c from baseline.[31,34] In ONWARDS 1 and ONWARDS 3, more patients receiving insulin icodec (10% more and 15% more, respectively) achieved target HbA1c without significant hypoglycemia.[30,32] In all ONWARDS trials, the rates of hypoglycemia were similar between insulin icodec and other basal insulins.

As of the time of this publication, all phase 3 QWINT trials evaluating BIF are still ongoing, with no results reported. As clinical data continue to emerge for once-weekly insulins, their potential role in clinical practice will be further clarified.

FIGURE 1. Key considerations for new and emerging once-weekly insulins with late-stage trial data[40]



Source: Trevisan R, Conti M, Ciardullo S. Once-weekly insulins: a promising approach to reduce the treatment burden in people with diabetes. *Diabetologia*. Published online April 29, 2024. doi:10.1007/s00125-024-06158-9. Figure licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction. The license can be viewed at this link: https://creativecommons.org/licenses/by/4.0/legalcode

LOOKING TO THE FUTURE: ONCE-WEEKLY INSULINS IN CLINICAL PRACTICE

As once-weekly insulin formulations become available, PCCs will be at the forefront of providing practical strategies for the integration of these formulations into clinical practice. Indications for once-weekly insulin are likely to be similar to those for once-daily insulin, but treatment adherence and quality of life may be important considerations, especially for patients who frequently miss doses of antihyperglycemic medications. New insulin titration strategies will be needed because glucose-lowering will not achieve a steady state for several weeks after initial dosing. Clinicians will need to learn these approaches and educate patients on how to manage dosing and concomitant preprandial insulin.[10] Though these strategies are not yet well defined, they will become clearer in the coming years with the potential approval of once-weekly insulin products in the US.

Potential candidates for receiving once-weekly insulins, if approved, include patients with T2D who are inadequately controlled on multiple glucose-lowering agents and require basal insulin therapy.[37] Patients who prefer flexibly in dose timing and those who have difficulty with adherence to daily injections may also be good candidates, as they may benefit from a reduced injection burden and attenuated consequences of missing a dose.[37]

TABLE 1. Phase 3 trials evaluating the once-weekly insulins icodec and BIF in patients with T2D[35]

Trial	Design	Patients (with T2D)	Comparator	Baseline treatment	Duration (weeks)
Insulin icodec					
ONWARDS 1[30]	Open label	Insulin-naïve N = 984	Glargine U100	Any noninsulin drugs	78
ONWARDS 2[31]	Open label	Insulin-treated N = 526	Degludec	Basal insulins ± noninsulin glucose-lowering agents	26
ONWARDS 3[32]	Double blind	Insulin-naïve N = 588	Degludec	Any noninsulin drugs	26
ONWARDS 4[33]	Open label	Insulin-treated N = 582	Glargine U100	Multiple daily insulin injections ± noninsulin drugs	26
ONWARDS 5[34]	Open label	Insulin-naïve N = 1085	Glargine U100/300 and degludec	Any noninsulin drugs	52
BIF					
QWINT-1 NCT05662332	Open label	Insulin-naïve N = 670	Glargine U100	At least 1 glucose-lowering medication	52
QWINT-2 NCT05362058	Open label	Insulin-naïve N = 912	Degludec	At least 1 glucose-lowering medication	52
QWINT-3 NCT05275400	Open label	Insulin-treated N = 986	Degludec	Basal insulins ± up to 3 noninsulin drugs (except SUs)	78
QWINT-4 NCT05462756	Open label	Insulin-treated N = 670	Glargine U100	Multiple daily insulin injections	26

Abbreviation: SU, sulfonylurea.

Adapted from Trevisan R, Conti M, Ciardullo S. Once-weekly insulins: a promising approach to reduce the treatment burden in people with diabetes. *Diabetologia*. Published online April 29, 2024. doi:10.1007/s00125-024-06158-9

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Compared to once-daily basal insulins, once-weekly basal insulins have a variety of potential benefits, including improved adherence and persistence, flexibility in time of administration, and reduced glycemic variability (**FIGURE 2**).[37] Potential concerns include lack of familiarity, challenges with dose calculations, and hypoglycemia.[37]

Potential benefits of once-weekly insulins

T2D regimens are complex for a large proportion of affected individuals and include dietary management, physical exercise, receiving multiple antihyperglycemic medications, and blood glucose monitoring. Injection burden is a major barrier to insulin adherence as prescribed and results in one-third of those prescribed insulin not being adherent or persistent in treatment.[38] Fewer injections may reduce this burden and improve the likelihood of treatment adherence. Once-weekly insulins may provide an option to improve convenience, adherence, and quality of life as compared to once-daily basal insulins.[28]

Once-weekly insulins may provide more flexibility in dose timing and provide better glucose coverage in the case of missed doses.[37] When once-weekly insulins reach steady state, a missed dose does not result in immediate loss of efficacy due to the agent's long half-life. Additionally, due to the flatter pharmacokinetic profile of once-weekly insulins, a decrease in day-to-day glycemic variability is expected.

Potential concerns about once-weekly insulins

Because clinicians are less familiar with once-weekly insulins, they may have concerns such as worry over a "large dose" of insulin injected at once and hypoglycemia management.[37] As such, there is a need for education about the pharmacokinetics of weekly insulins. As with any insulin, a potential safety concern with once-weekly insulins is the risk for hypoglycemia. A meta-analysis of 7 randomized trials found an increased risk for hypoglycemic events with insulin icodec compared to once-daily basal insulins (risk ratio 1.24; 95% CI, 1.02-1.50; $P = .03$) and a numerically decreased risk for severe hypoglycemia (risk ratio 0.81; 95% CI, 0.31-2.08).[39]

To manage hypoglycemia that occurs while a patient is receiving once-weekly insulin, the fundamental principles are similar to treating typical hypoglycemia episodes, as

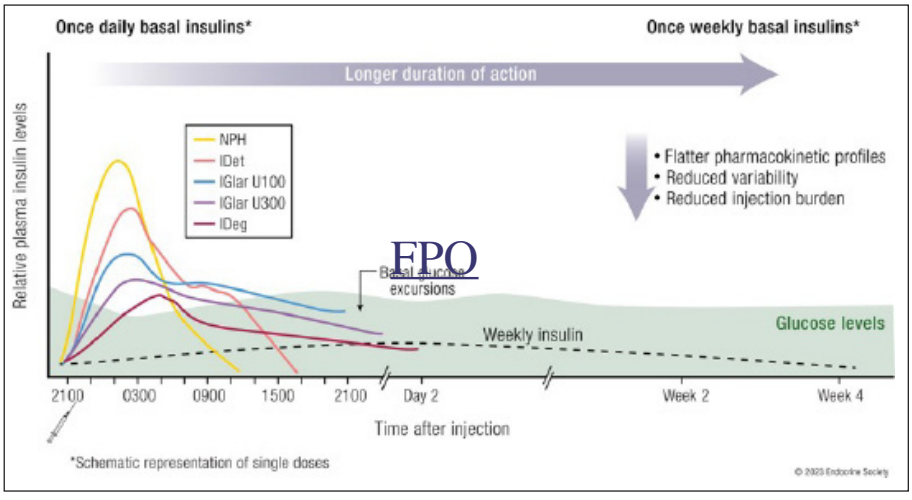
TABLE 2. Key results and hypoglycemic events of the phase 3 ONWARDS trials evaluating insulin icodec in patients with T2D[36]

Trial	Main results	Hypoglycemic events
ONWARDS 1[30]	Icodec compared to glargine: • HbA1c reduction: –0.2% • Increase in patients at target HbA1c without significant hypoglycemia: 10% • TIR: increased 4.3%	Icodec: 226 episodes in 61 patients (12.4%); 1 severe episode Glargine: 114 episodes in 66 patients (13.4%); 7 severe episodes
ONWARDS 2[31]	Icodec demonstrated noninferiority and superiority to degludec in reducing HbA1c from baseline	No significant differences in hypoglycemia rates
ONWARDS 3[32]	Icodec compared to degludec: • HbA1c reduction: –0.2% • Increase in patients at target HbA1c without significant hypoglycemia: 15%	Icodec: 53 episodes in 26 patients (9%); 0 severe episode Degludec: 23 episodes in 17 patients (6%); 2 severe episodes
ONWARDS 4[33]	Icodec compared to glargine: • Mean change in HbA1c: –1.16% in the icodec group (baseline 8.29%); –1.18% in the glargine group (baseline 8.31%)	Icodec: 35 episodes in 22 patients (8%) Glargine: 33 episodes in 25 patients (9%)
ONWARDS 5[34]	Icodec in conjunction with the dosing guide app demonstrated noninferiority and superiority compared with basal insulin analogs in reducing mean HbA1c from baseline	No significant differences in hypoglycemia rates

Abbreviations: TIR, time in range.

insulin icodec has a similar counterregulatory hormone response and recovery compared with insulin glargine.[37] Principles for treating hypoglycemia in patients with T2D typically include advising the patient to consume 15 g of glucose (or other fast-acting carbohydrate) for a blood glucose value of ≤70 mg/dL and recheck the blood glucose 15 minutes afterward.[40] If blood glucose remains at or near 70 mg/dL (or less), or if glucose is not rising, an additional 15 g of fast-acting carbohydrates should be consumed, repeating the process until glucose rises. In the case of continual ongoing hypoglycemia, the patient should seek additional care.

FIGURE 2. Comparison of once-daily and once-weekly basal insulins[37]



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

Source: Rosenstock J, Juneja R, Beals JM, Moyers JS, Ilag L, McCrimmon RJ. The basis for weekly insulin therapy: evolving evidence with insulin icodec and insulin efsitora alfa. *Endocr Rev*. 2024;45(3):379-413. Figure licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction. The license can be viewed at this link: https://creativecommons.org/licenses/by/4.0/legalcode

Patient case revisited

Revisiting the case scenario, use of a once-weekly insulin would likely help the patient be more adherent to her regimen, because she prefers to avoid daily injections. With improved adherence to her basal insulin regimen, her blood glucose would likely improve, lowering her risk for cardiometabolic complications associated with hyperglycemia.

Advice when talking to patients:

- Assess interest in once-weekly insulin injections
- Discuss the timing action curves for ultra-long-acting insulin
- Remind patients that the dose given will have a long 7-day time of action
- Base titrations on prescribing instructions and the patient's blood glucose values

CONCLUSION

PCCs manage most patients with T2D in the US, including many who receive or are appropriate candidates for basal insulin therapy. Despite insulin's long history in treating diabetes, clinical inertia routinely occurs due to a variety of factors, resulting in treatment delays and suboptimal glucose management. New and emerging once-weekly insulins offer additional approaches for basal insulin therapy in T2D that may reduce clinical inertia and improve treatment adherence and patient outcomes. ●

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