

Practical Considerations for Use of Insulin/Glucagon-Like Peptide 1 Receptor Agonist Combinations in Older Adults With Type 2 Diabetes

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KEY TAKEAWAYS

- Over 25% of adults ≥ 65 years of age have type 2 diabetes (T2D).
- Individualization of care is important in older adults with T2D, with treatment targets and therapeutic approaches informed by patient-specific medical, psychosocial, functional, and social considerations.
- Fixed-ratio combination injectable products offer unique benefits in older adults, including reduction of both fasting and postprandial glucose, low hypoglycemia risk, lack of weight gain, fewer gastrointestinal side effects, strong durability of effect, and the potential for medication regimen simplification.

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DISCLOSURES

Dr. Champlain serves on the Novo Nordisk speakers bureau and advisory board for Novo Nordisk (diabetes). Joshua Jon Neumiller, PharmD, serves as a paid consultant to Bayer, on the advisory board of Novo Nordisk and Sanofi, and on the speakers bureau of Dexcom.

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INTRODUCTION

According to most recent estimates, more than 37 million individuals currently live with diabetes mellitus (DM) in the United States.¹ The large majority (90%-95%) of these individuals have type 2 diabetes (T2D).¹ T2D is particularly common in older adults. Data indicate that more than 25% of adults ≥ 65 years of age have DM.¹ The American Diabetes Association (ADA) stresses the importance of patient-centered care, inclusive of establishing individualized glycemic targets and treatment approaches developed in partnership with patients through a process of shared decision-making.² Individualized care is of particular importance in older adults who often have medical, psychological, functional, and/or unique social factors that can impact care decisions and priorities.² While glycated hemoglobin A1C (A1C) remains a gold standard measure of glycemic control, the ADA stresses the importance of additional glycemic metrics including fasting plasma glucose (FPG), postprandial glucose (PPG), time in range, and mea-

sures of glycemic variability when evaluating and optimizing glycemic targets and management.² The importance of hypoglycemia prevention is stressed, as is the prevention and treatment of diabetes-related complications through optimized risk-factor management and use of glucose-lowering agents with proven cardiovascular and renal benefits in at-risk individuals.²

Avoidance of therapeutic inertia is important in T2D to maintain optimized, patient-centered care. Therapeutic inertia is not limited to situations of delayed initiation or intensification of therapy, but also includes delays or failure to de-intensify and/or simplify treatment when clinically appropriate.^{2,3} Indeed, the ADA stresses the importance of re-evaluating patient-centered treatment goals and considering de-intensification and/or simplification of medication regimens when clinically indicated, particularly in older adults.² One potential strategy to achieve regimen simplification while maintaining glycemic control is through the use of

fixed-ratio combination (FRC) injectable glucose-lowering products.⁴ This brief review will discuss practical considerations for use of basal insulin/glucagon-like peptide-1 receptor agonist (GLP-1 RA) FRC products and their potential advantages in older adults with T2D.

CASE SCENARIO: PART 1

RJ is a 72-year-old man with T2D presenting to the primary care clinic. RJ was diagnosed with T2D 12 years ago and has a history of hypertension, hypercholesterolemia, and obesity. RJ is currently managed on basal-bolus insulin (BBI) therapy, and reports difficulty managing his insulin regimen, including occasionally forgetting to inject his mealtime insulin. A review of RJ's blood glucose data reveals 4 hypoglycemic events in the previous 14 days, ranging from 51 to 67 mg/dL. RJ reports no hypoglycemia symptoms until his blood glucose is in the "low 50s." RJ additionally experiences frequent PPG spikes >250 mg/dL. In addition to forgetting to administer his mealtime insulin on occasion, RJ also notes difficulty affording his insulin, resulting in insulin rationing at the end of the month.

Lab work: A1C 8.2%, estimated glomerular filtration rate 63 mL/min/1.73m², urinary albumin-to-creatinine ratio 5 mg/g, low-density lipoprotein cholesterol 89 mg/dL, high-density lipoprotein cholesterol 42 mg/dL, and total cholesterol 170 mg/dL

Vitals: Body mass index 34 kg/m², blood pressure 132/88 mmHg in clinic today

Current medications: metformin 1000 mg twice daily, insulin glargine (U-100) 22 units once daily in the morning, insulin lispro (U-100) 6 units three times daily before meals, lisinopril 20 mg once daily, amlodipine 10 mg once daily, atorvastatin 40 mg once daily

Question: What are your goals of therapy for RJ given his presentation and current medication regimen?

2022 ADA STANDARDS OF MEDICAL CARE IN DIABETES UPDATES

The 2022 ADA *Standards of Medical Care in Diabetes* provide multiple recommendations supporting use of GLP-1 RAs in persons with T2D.² First, GLP-1 RAs with proven benefit are preferentially recommended as an option for patients with, or considered at high risk for, atherosclerotic cardiovascular disease independent of baseline A1C, individualized A1C target, or background glucose-lowering therapy.² For persons with T2D not meeting individualized glycemic targets, use of a GLP-1 RA is recommended as an option when minimization of hypoglycemia and/or promotion of weight loss is desired.² As emphasized within the intensification of injectable therapies algorithm (FIGURE), the ADA preferentially recommends a GLP-1 RA as the first injectable over insulin

when possible. Additionally, the ADA recommends insulin use in combination with a GLP-1 RA for greater efficacy and durability of treatment effect when insulin is required to meet individualized treatment goals.² In older adults with longstanding T2D, however, insulin is often required when oral glucose-lowering therapies are deemed ineffective to maintain individualized glycemic goals.

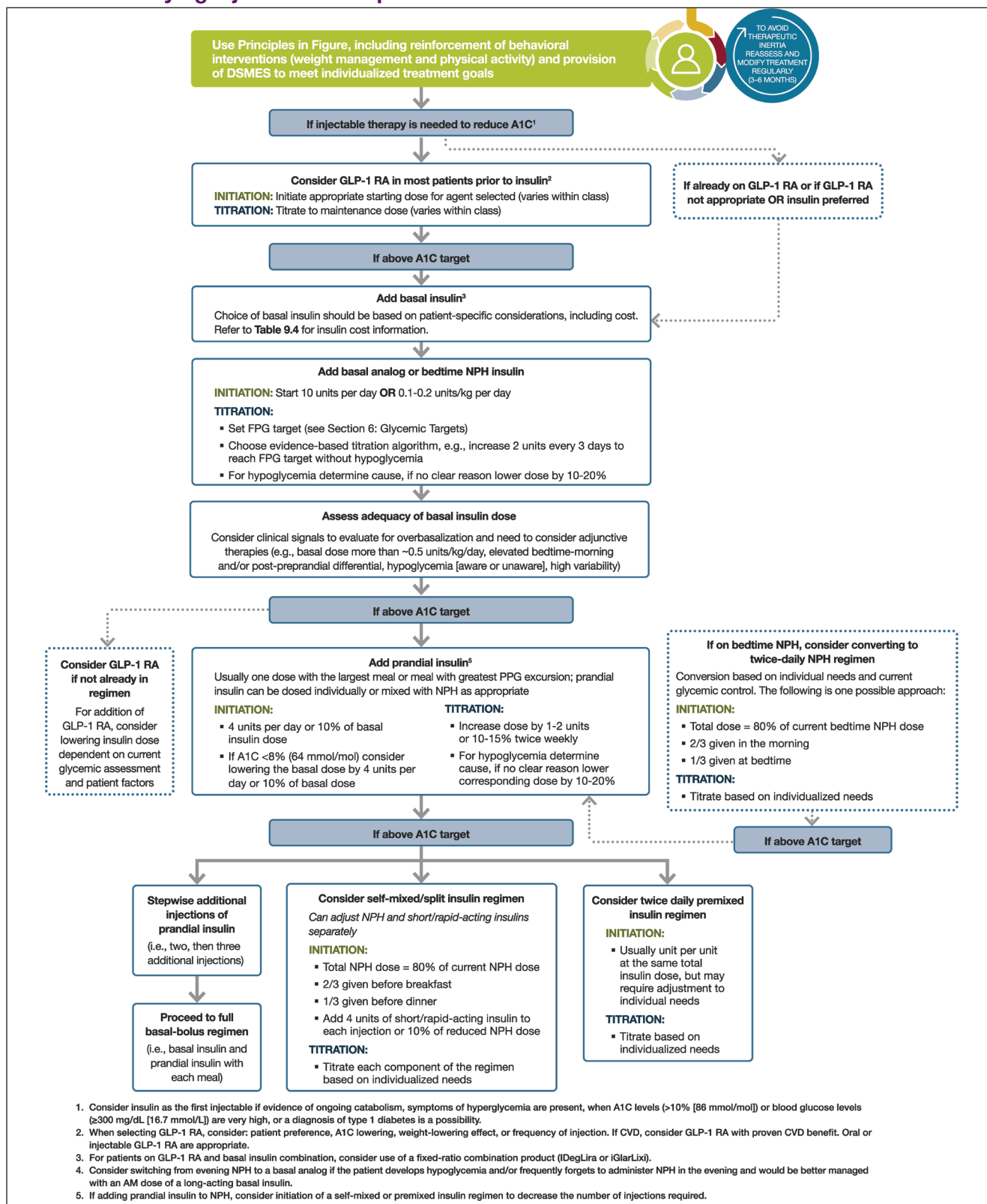
The ADA also provides considerations for management of T2D in older adults and emphasizes the importance of individualized glycemic targets and treatment approaches.² Key factors noted for consideration include assessment of medical, psychological, functional, and social (eg, presence of caregiver, support system) domains, as well as multiple geriatric syndromes that may impact patient care and outcomes.² These factors additionally inform the selection of glucose-lowering therapies and application of general treatment recommendations offered by the ADA. Avoidance of "overtreatment" and hypoglycemia is stressed. Key recommendations regarding individualization of glycemic goals and treatment approaches for older adults with T2D are summarized in TABLE 1.² Overall, based on patient-specific considerations, liberalization of treatment goals, de-intensification of therapy, and/or simplification of the medication regimen may be appropriate to optimize care, minimize hypoglycemia risk, and reduce treatment burden.^{5,6}

BRIEF REVIEW OF CLINICAL EVIDENCE AND POTENTIAL BENEFITS OF FRC THERAPIES

While basal insulin may be sufficient to achieve FPG targets, additional agents are often needed to manage PPG excursions when the A1C remains above goal (FIGURE),² especially in older adults who often experience significant postprandial hyperglycemia.⁷ While the addition of prandial insulin is one approach, FRC agents offer an alternative strategy with potential advantages (TABLE 2).⁸⁻¹⁴

Treatment with FRC agents has demonstrated greater A1C reductions when compared to intensification of basal insulin or GLP-1 RAs alone in persons with T2D that is inadequately controlled on their current glucose-lowering regimen.⁴ Participants randomized to FRC agents characteristically achieve greater A1C reductions without an increase in hypoglycemia or weight gain when compared to basal insulin alone, and with fewer gastrointestinal adverse events when compared to GLP-1 RA treatment alone.⁴ A post hoc analysis of data from 2 trials with the insulin glargine/lixisenatide FRC product reported that enrolled participants ≥65 years of age derived similar benefit as participants <65 years of age.⁸ Importantly, data show that treatment with the FRC agent iDegLira results in longer durability of treatment effect (defined as time after medication initiation until treat-

FIGURE. Intensifying injectable therapies in T2D²



Abbreviations: DSMES, diabetes self-management education and support; NPH, neutral protamine hagedorn insulin.

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TABLE 1. **Key ADA recommendations related to treatment of older adults with T2D²**

- Consider the assessment of medical, psychological, functional (self-management abilities), and social domains in older adults to provide a framework to determine targets and therapeutic approaches for DM management
- Screen for geriatric syndromes (ie, polypharmacy, cognitive impairment, depression, urinary incontinence, falls, persistent pain, and frailty) in older adults, as they may affect diabetes self-management and diminish quality of life
- In older adults with T2D at increased risk for hypoglycemia, medication classes with a low risk of hypoglycemia are preferred
- Overtreatment of DM is common in older adults and should be avoided
- Deintensification (or simplification) of complex regimens is recommended to reduce the risk of hypoglycemia and polypharmacy, if it can be achieved within the individualized A1C target
- Consider costs of care and insurance coverage rules when developing treatment plans to reduce risk of cost-related nonadherence

TABLE 2. **Potential advantages of FRC agents in older adults with T2D**

- Regimen simplification (basal insulin + GLP-1RA in single injection) to improve medication compliance/persistence^{8,13,14}
- Reductions in both FPG and PPG¹²
- Lack of weight gain^{10,11}
- Decreased gastrointestinal side effects when compared to GLP-1 receptor agonists alone⁸
- Low hypoglycemia risk when compared to basal-bolus insulin therapy¹⁰
- Non- β -cell reliance with preserved efficacy in patients with longstanding T2D⁸
- Durability of glycemic benefit⁹

TABLE 3. **Currently available FRC agents^{15,16}**

	Insulin glargine/lixisenatide FRC	Insulin degludec/liraglutide FRC
Indication	Adjunct to diet and exercise to improve glycemic control in adults with T2D	Adjunct to diet and exercise to improve glycemic control in adults with T2D
Initial recommended dosing	<p><i>Naïve to basal insulin or to a GLP-1 RA, currently on a GLP-1 RA, or currently on <30 units of basal insulin daily:</i></p> <ul style="list-style-type: none"> • Discontinue therapy with current basal insulin or GLP-1 RA • Initiate at 15 units (15 units of insulin glargine/5 mcg lixisenatide) subcutaneously once daily <p><i>Currently on 30-60 units of basal insulin daily, with or without a GLP-1 RA:</i></p> <ul style="list-style-type: none"> • Discontinue therapy with current basal insulin or GLP-1 RA • Initiate at 30 units (30 units of insulin glargine/10 mcg lixisenatide) subcutaneously once daily 	<p><i>Naïve to basal insulin or a GLP-1 RA:</i></p> <ul style="list-style-type: none"> • Initiate at 10 units (10 units of insulin degludec/0.36 mg liraglutide) subcutaneously once daily <p><i>Currently on basal insulin or a GLP-1 RA:</i></p> <ul style="list-style-type: none"> • Discontinue therapy with current basal insulin or GLP-1 RA • Initiate at 16 units (16 units of insulin degludec/0.58 mg liraglutide) subcutaneously once daily
Recommended titration	<p>Titrate based on FPG:</p> <ul style="list-style-type: none"> • Above target range: Increase dose by 2 to 4 units • Within target range: No change • Below target range: Decrease dose by 2 to 4 units 	<p>Titrate based on FPG:</p> <ul style="list-style-type: none"> • Above target range: Increase dose by 2 units • Within target range: No change • Below target range: Decrease dose by 2 units
Maximum dose^a	60 units	50 units

^a Dosing of FRC agents is based on units of the basal insulin component.

ment intensification is required to maintain glycemic targets) when compared with basal optimization alone.⁹

In persons with T2D that is inadequately controlled on basal insulin, switching to IDegLira therapy is associated with comparable glycemic efficacy to intensification with BBI therapy, with more favorable effects on hypoglycemia rates and body weight.¹⁰ Likewise, intensification to a once-daily insulin glargine/lixisenatide product has also been shown to be at least as effective as intensification to a twice-daily premixed insulin (70/30) regimen in basal insulin-treated T2D, with the FRC treatment resulting in weight benefit and less hypoglycemia.¹¹

Trials evaluating the benefits of a GLP-1 RA added on to BBI and transitioning from a BBI to an FRC regimen highlight the potential benefits of FRC therapies. First, the addition of a GLP-1 RA (albiglutide) in persons with T2D on background BBI therapy resulted in decreased prandial insulin needs while also facilitating medication regimen simplification, promoting weight loss, and reducing hypoglycemia events.¹² Similarly, trials transitioning persons with T2D from BBI to a once-daily FRC agent reported similar or better glycemic control, a need for fewer injections, and less hypoglycemia following transition to the FRC agent.^{13,14} Notably, Taybani and colleagues tested this approach in an older population of persons with T2D (mean baseline age = 64 years) and a mean baseline A1C of 6.42%.¹⁴ In this trial, transitioning participants from BBI to FRC resulted in reductions in A1C (mean, -0.3%; $P < 0.0001$) and body weight (mean, 3.11 kg; $P < 0.0001$), indicating that clinical benefits can be realized even in persons with T2D with “good” glycemic control by transitioning from BBI to an FRC agent.¹⁴

CURRENTLY AVAILABLE INSULIN/GLP-1 RA FRC PRODUCTS

Based on the evidence discussed above supporting the efficacy of FRC agents in the treatment of T2D, 2 products have received US Food and Drug Administration approval and are currently available in the United States.^{15,16} A summary of key product information is provided in **TABLE 3**.^{15,16}

CASE SCENARIO: PART 2

Question: Based on the information just covered, what changes would you consider for RJ? How would you work with RJ to implement these changes and maximize his success? As previously presented, RJ is a 72-year-old man with T2D, hypercholesterolemia, and obesity. RJ has voiced challenges managing a complex regimen that includes BBI therapy in addition to financial challenges affording his medications. RJ's A1C (8.2%) is above his individualized goal of 7.0% (**TABLE 4**). He is experiencing notable glycemic variability, including frequent hypoglycemic events and postprandial hyperglycemia.

TABLE 4. Framework for considering treatment goals for glycemia

Patient Characteristics/ Health Status	Rationale	Reasonable A1C Goal, % (mmol/mol)‡
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0–7.5 (53–58)
Complex/intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0 (64)
Very complex/poor health (LTC or end-stage chronic illnesses or moderate-to-severe cognitive impairment or 2+ ADL impairments)	Limited remaining life expectancy makes benefit uncertain	Avoid reliance on A1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia

Abbreviations: ADL, activities of daily living; LTC, long-term care.

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While there are many issues that would need to be addressed with RJ, his current glucose-lowering regimen is not meeting his needs. To reach his glycemic goal, minimize his hypoglycemia risk, and simplify his regimen, RJ's BBI regimen was discontinued, and he was transitioned to treatment with an insulin/GLP-1 RA FRC product. Given RJ's financial challenges, he was assisted in taking advantage of the Medicare Part D Senior Savings Model where he was able to obtain his FRC product at a maximum copay of \$35/month.¹⁷ De-intensification of therapy from a BBI regimen to an insulin/GLP-1 RA FRC product resulted in reduced glycemic variability, elimination of his hypoglycemic events, improvements in his PPG and A1C levels, and simplification of his regimen.

SUMMARY AND CONCLUSIONS

It is important to consider the unique needs of older adults with T2D when determining patient-centered glycemic goals

and treatment plans. Insulin/GLP-1 RA FRC products offer key advantages that may allow for regimen simplification while maintaining glycemic control and minimizing hypoglycemia risk. ●

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