Clinical Use of Insulin Glargine 300 U/mL in Adults with Type 2 Diabetes: Hypothetical Case Studies

T2D

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Introduction

Many patients with T2D will require insulin treatment for optimal glycaemic control, and intensification of treatment as soon as it is needed is recommended to prevent complications of T2D

However, there exists considerable therapeutic inertia to the prompt initiation and optimal titration of BI therapy owing to barriers that include hypoglycaemia

Hypoglycaemia is associated with significant morbidity and mortality, and hypoglycaemia risk is increased in the frail or elderly and in patients with renal impairment or multiple comorbidities

The second-generation BI analogues Gla-300 and IDeg provide comparable glycaemic control with lower risk of hypoglycaemia compared with the first-generation BI Gla-100

Objective

This review uses hypothetical clinical case studies that are representative of clinical practice to investigate how use of the second-generation BI analogue Gla-300 may lead to beneficial glycaemic outcome in a variety of clinical scenarios

Hypothetical case studies

Joseph

OAD

Age: **52 years** BMI: **32 kg/m²**
Diabetes duration: **6 years**
HbA_{1c}: **8.2 %** (66 mmol/mol)
eGFR: **90 mL/min/1.73m²**

Patient profile

Current medication:

- Metformin
- SGLT2i
- Sulphonylurea
- DPP4i

However, his HbA_{1c} of 8.2 % has not decreased in the past year

He previously tried a GLP-1 RA but discontinued due to GI side effects

He is reluctant to try insulin due to worries about the difficulty and inconvenience of the regimen considering his irregular working hours as a delivery driver

Joseph worries about hypoglycaemia because he experienced an event after starting sulphonylureas

He has hypertension but no established CVD; however, his father had T2D and died of myocardial infarction, so Joseph is worried about potential weight gain with insulin

Research evidence

Gla-300 can be injected up to 3 hours before or after the usual time of once daily administration without affecting its efficacy or safety

The **TAKE CONTROL** RCT showed that self-titration of Gla-300 resulted in superior HbA_{1c} reduction versus physician-led titration, without increased risk of hypoglycaemia

In the **EDITION 3** and **BRIGHT** RCTs, Gla-300 use resulted in comparable glycaemic control to Gla-100 and IDeg, respectively, with less hypoglycaemia during the initial titration periods

In the **DELIVER Naïve** RWE study, initiation of Gla-300 versus Gla-100 was associated with significantly improved glycaemic control without an increase in hypoglycaemia

In the **EDITION 3** and **BRIGHT** trials of people with T2D initiating BI, over 6 months of Gla-300 use, weight only increased by 0.5 kg and 2.0 kg respectively, while HbA_{1c} decreases were 1.4 % and 1.6 %

Possible clinical considerations for Joseph:

1. Joseph's physician could **consider the addition of a BI** alongside a reduction of sulphonylurea dose, with the intent to eventually discontinue the latter
   - A second-generation BI analogue, such as Gla-300, may be considered because of lower hypoglycaemia risk and flexibility of dosing time
2. **Advice on lifestyle and diet modification** should be reiterated, and treatment should be intensified
   - Flash glucose monitoring (FGM) may help Joseph self-manage his glucose measurements
3. **Guidance and training** on performing blood glucose measurements 1–2 times daily, and hypoglycaemia avoidance/management, should be provided, especially given Joseph's occupation as a delivery driver
4. Because Joseph's family history implies high cardiovascular risk, but he is relatively young and has no established CVD, a **HbA_{1c} target of <7 % without hypoglycaemia** should be set to ensure tight glycaemic control

Anna

BI + OAD

Age: **61 years** BMI: **31 kg/m²**
Diabetes duration: **10 years**
HbA_{1c}: **7.5 %** (58 mmol/mol)
eGFR: **92 mL/min/1.73m²**

Patient profile

Current medication:

- Gla-100 (at bedtime)
- SGLT2i
- Metformin
- DPP4i

She is at her individualised temporary HbA_{1c} target of 7.5 % and has no CVD

She had previously tried a fixed-ratio combination of a GLP1-RA and BI but returned to using a BI only due to GI side effects

She has confirmed nocturnal hypoglycaemia with 1–2 episodes every 2–3 weeks resulting in fatigue during the day

Anna is concerned about experiencing severe hypoglycaemia, especially as she lives alone and relies on a car for her work and social life

Because she is at her HbA_{1c} target Anna thinks she does not need to take insulin anymore

Research evidence

In the **DELIVER 2** RWE study people with T2D switching BI to Gla-300 experienced lower incidence of hypoglycaemia compared with other BIs (IDeg, IDet, Gla-100)

In **EDITION 2**, an RCT that included people with T2D uncontrolled on BI + OADs, Gla-300 provided similar glycaemic control to Gla-100 but with less nocturnal and anytime (24 h) hypoglycaemia

The **LIGHTNING** RWE study showed that treatment with Gla-300 was associated with lower rates of severe hypoglycaemia when compared with Gla-100 or IDet in patients switching from another BI

Possible clinical considerations for Anna:

1. Anna should be reminded that **diabetes is a progressive disease** and that glycaemic control does not mean diabetes is in remission
2. As Anna has experienced frequent nocturnal hypoglycaemia, it is important she is **educated about hypoglycaemia self-management** and how to recognise and prevent situations in which hypoglycaemia may occur
3. A **second-generation BI, such as** Gla-300**, may help to reduce the risk of nocturnal hypoglycaemia.** Dose adjustment may be needed and changing administration from evening to morning could be considered
4. When Anna has gained confidence in the safety of her BI therapy, the dose can be further up titrated to reach the general guideline **recommended target of <7 %**

Lorenzo

OAD

Age: **80 years** BMI: **27 kg/m²**
Diabetes duration: **16 years**
HbA_{1c}: **8.9 %** (47 mmol/mol)
eGFR: **64 mL/min/1.73m²**

Patient profile

Current medication:

- Metformin
- SGLT2i
- DPP4i

He suffers from:
Mild renal impairment, pre-proliferative retinopathy, peripheral neuropathy, dementia

His hypertension and lipids are well managed with treatment

Family caregivers are unsure about whether Lorenzo's glycaemic control is adequate, but are also concerned about the impact of hypoglycaemia

They are concerned for Lorenzo's safety, worried about the complexity of BI treatment, and Lorenzo is reluctant to start injectable therapy

Research evidence

In the **SENIOR** RCT, Gla-300 demonstrated good efficacy and safety in older people with T2D, particularly in those of advanced age (≥75 years of age), in which rates of documented symptomatic hypoglycaemia and severe hypoglycaemia were lower with **Gla-300** versus Gla-100

A post hoc analysis of the **EDITION 1–3** RCTs showed that Gla-300 provided similar glycaemic control to Gla-100, with a lower incidence of nocturnal hypoglycaemia, irrespective of age (<65 years or ≥65 years)

In a post hoc analysis of the **BRIGHT** RCT, Gla-300 was associated with greater HbA1c reductions versus IDeg-100, without an increase of hypoglycaemia, in people with T2D who were ≥70 years of age and initiating BI

Possible clinical considerations for Lorenzo:

1. Lorenzo needs better glycaemic control because his **raised blood glucose levels** will be **detrimental to his neuropathy and retinopathy**
2. Lorenzo's physician may **consider the addition of a BI** with a simple titration algorithm, as recommended in ADA guidelines
3. **A second-generation BI** analogue such as Gla-300 could provide a relatively simple treatment regimen that would help him to improve glycaemic control, with a lower risk of hypoglycaemia compared with the first-generation BI, Gla-100
4. Lorenzo and his carers should receive education to enable them to manage Lorenzo's diabetes, using a **pragmatic HbA_{1c} target of <8 %** and home glucose monitoring

Christina

OAD

Age: **68 years** BMI: **30 kg/m²**
Diabetes duration: **20 years**
HbA_{1c}: **8.8 %** (73 mmol/mol)
eGFR: **40 mL/min/1.73m²**

Patient profile

Current medication:

- Metformin
- SGLT2i
- DPP4i
- ARB
- Calcium channel blocker
- Atorvastatin

She suffers from:
Hypertension, stable stage 3A CKD and her urine ACR is 10 mg/mmol

She has previously tried a GLP-1 RA but could not tolerate the GI side effects

Her hypertension is managed with current treatment, but she suffers from background diabetic retinopathy

Christina worries about glycaemic control as she has never reached her target since being diagnosed

She is particularly worried about the effect of poor glycaemic control on her CKD and eye disease

Research evidence

A post hoc analysis of the **EDITION 1–3** RCTs showed that glycaemic control with Gla-300 was comparable to that with Gla-100, but with lower rates of hypoglycaemia, in people with T2D and mild-to-moderate renal impairment

The **DELIVER HIGH RISK** study found that in people with T2D and mild-to-moderate renal impairment, switching from another BI to Gla-300 resulted in similar HbA_{1c} reductions and less hypoglycaemia than a switch to a first-generation BI

A post hoc analysis of the **BRIGHT** RCT found that Gla-300 use was associated with greater reductions in HbA_{1c} than IDeg use, without increased hypoglycaemia, in people with T2D and impaired renal function

Possible clinical considerations for Christina:

1. **Glycaemic control is essential to avoid the progression of CKD** and as Christina is already using metformin and an SGLT2i and could not tolerate a GLP-1 RA, the **next step could be a BI** such as Gla-300
2. Christina should receive **education on diabetes self-management,** managing hypoglycaemia risk, and how to deal with hypoglycaemic events
3. Christina should be given **recommendations for medication use on days she is not feeling well.** If a BI is initiated, she may benefit from continued insulin treatment on such days but with increased blood glucose monitoring, and adjustment of her insulin dose if needed
4. A pragmatic **HbA_{1c} target of 7.0–7.5 %** may be most appropriate

Conclusions

Many people with T2D will eventually require a basal insulin to achieve or maintain glycaemic control

Second-generation BI analogues, such as Gla-300 and IDeg, represent a suitable BI option for people needing intensification of their antihyperglycaemic regimens to meet individualised glycaemic targets

Improved communication between HCPs and patients, along with appropriate educational tools and support, may increase patient confidence in the administration and titration of BI dose, ultimately improving glycaemic management

Abbreviations
ACR, urine albumin to creatinine ratio; ADA, American Diabetes Association; ARB, angiotensin II receptor blocker; BI, basal insulin; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HCP, healthcare professional; IDeg, insulin degludec; IDet, insulin detemir; OAD, oral antihyperglycaemic drug; RCT, randomised controlled trial; RWE, real-world evidence; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; U, units.

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