The Global Challenge of Diabetes:
Navigating Management Failures and Innovations in Basal Insulin Analogues

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MAT-ZA-2500193-1.0-04/2025

Disclosures

- I have no conflict of interests
- I have spoken for most pharmaceutical companies

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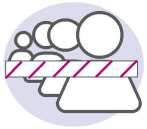
Introduction

Many people 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[1-3]



However, there exists considerable therapeutic inertia to the prompt initiation and optimal titration of BI therapy owing to barriers that include hypoglycaemia[4,5]

Hypoglycaemia is associated with significant morbidity and mortality[6] and hypoglycaemia risk is increased in the frail or elderly and in patients with renal impairment or multiple comorbidities[7,8]

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[9,10]

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

BI, basal insulin; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; T2D, type 2 diabetes

1. Davies MJ, et al. Diabetes Care 2018;41:2669-701.
2. Home P, et al. Diabetes Care 2014;37:1499-508.
3. Harris SB, et al. Diabetes Res Clin Pract 2005;70:90-7.
4. Russell-Jones D, et al. Diabetes Obes Metab 2018;20:488-96.
5. Berard L, et al. Diabetes Obes Metab 2018;20:301-8.
6. Amiel SA et al. BMJ Open.2019;9:e030356.
7. Moen MF, et al. Clin J Am Soc Nephrol 2009;4:1121-7.
8. McCoy RG, et al. JAMA Network Open 2020;3:e1919099-e.
9. Becker RH, et al. Diabetes Care 2015;38:637-43.
10. Heise T, et al. Diabetes, Obesity & Metabolism 2017;19:1032-9.

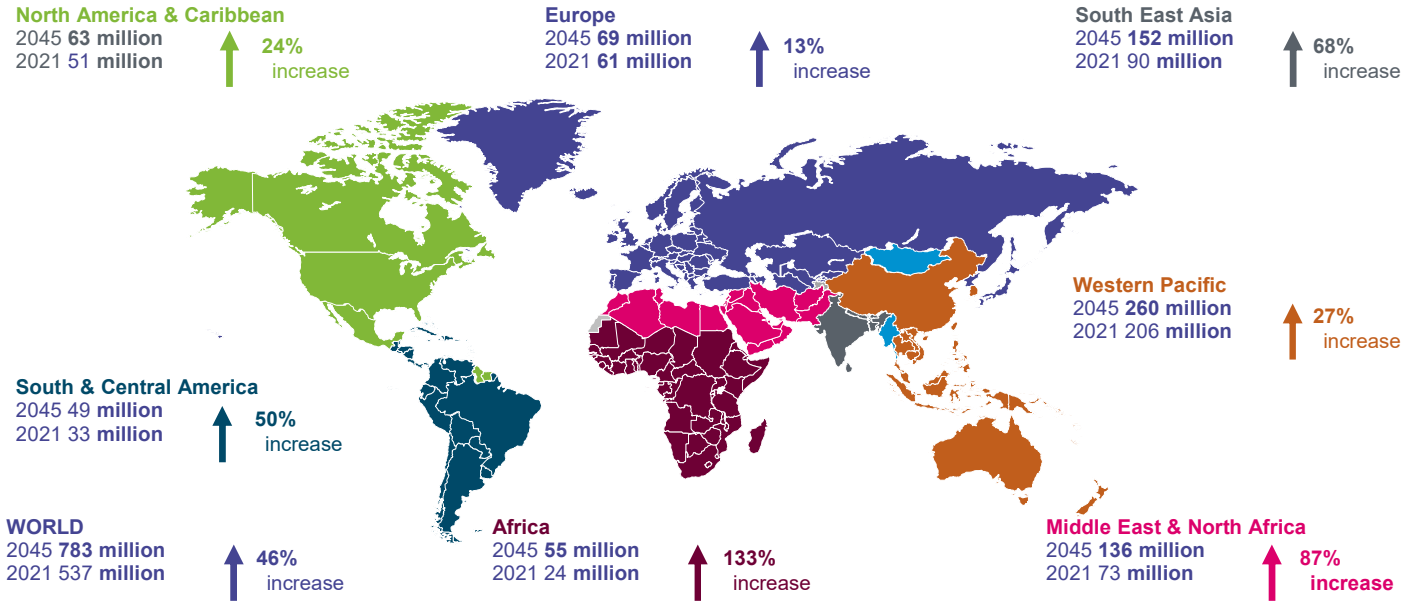
Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

- ~536 million people worldwide had diabetes in 2021
- Prevalence of diabetes is estimated to reach ~783 million

~6.7 million adults died due to diabetes or its complications in 2021*

Total health expenditure on diabetes is estimated at USD 966 billion

Diabetes complications can be prevented by good glycemic control



Data for adults aged 20–79 years
*Excluding mortality risk associated with COVID-19 pandemic

IDF Diabetes Atlas 2021 – 10th Ed. www.diabetesatlas.org

Untreated diabetes can lead to complications and increase the overall risk of mortality

Long term complications of T2DM

Microvascular disease

- Nephropathy
- Retinopathy
- Neuropathy

Macrovascular disease

- Peripheral vascular disease
- Coronary artery disease
- Stroke

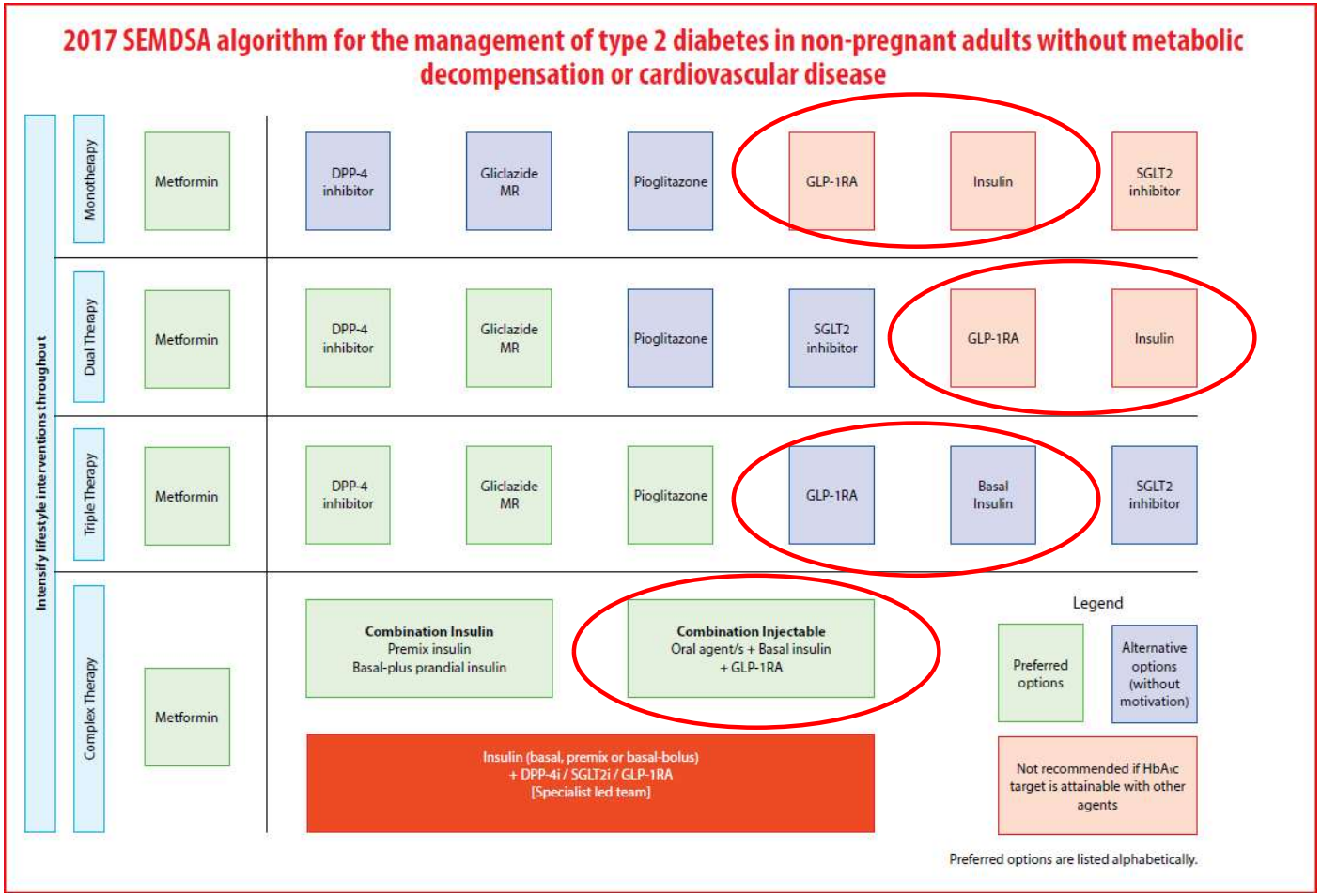
Blood glucose

Metabolic goals to reduce illness

- Blood pressure
- Lipids
- Other risk factors

ADA. Diabetes Care

SEMDSA Guidelines 2017



Fixed dose oral combinations :

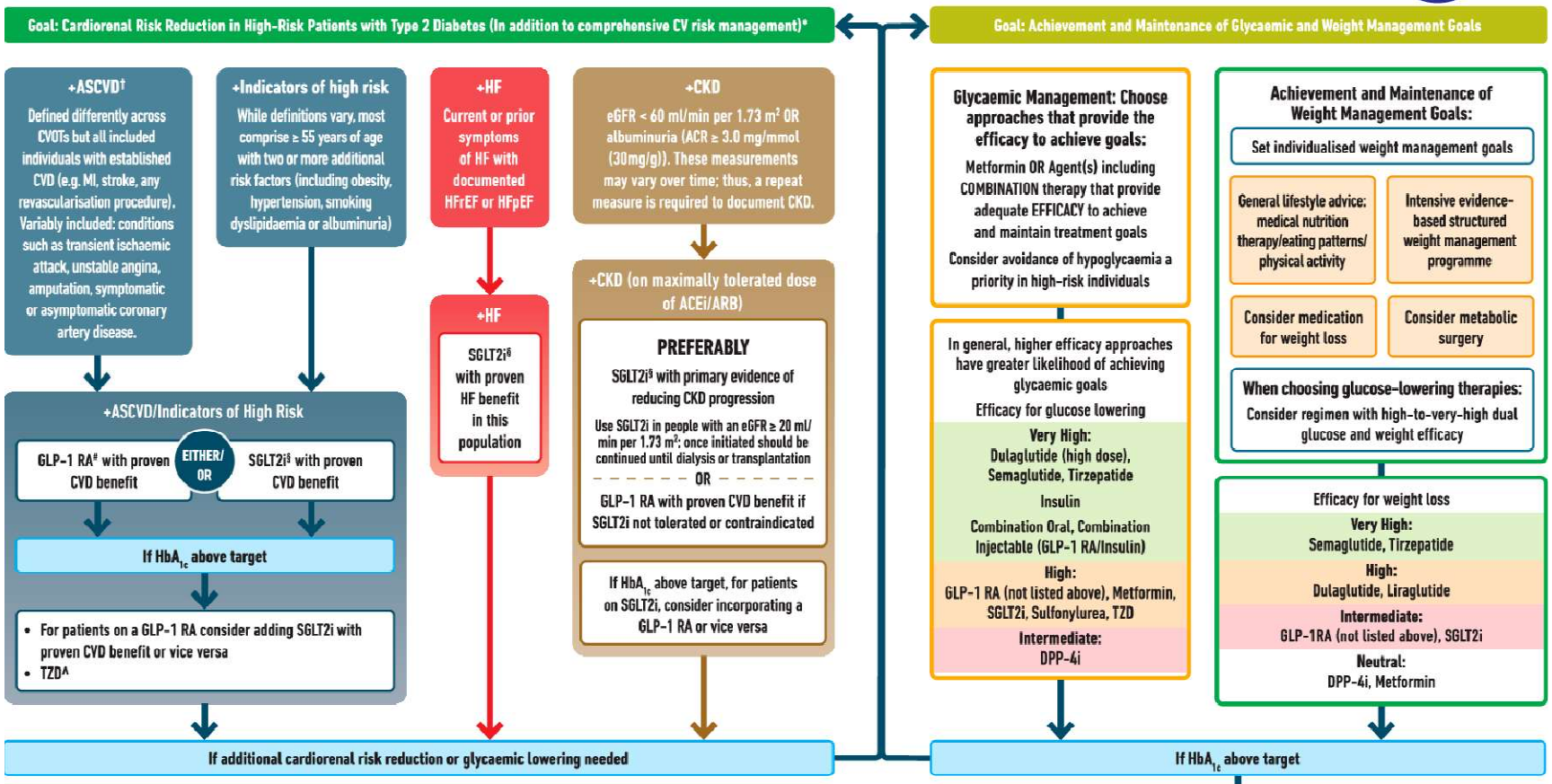
Met - SU
Met - DPP4i
Met - SGLT2i

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2017 ; 22(1) S54 00150685.pdf (mymembership.co.za)

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

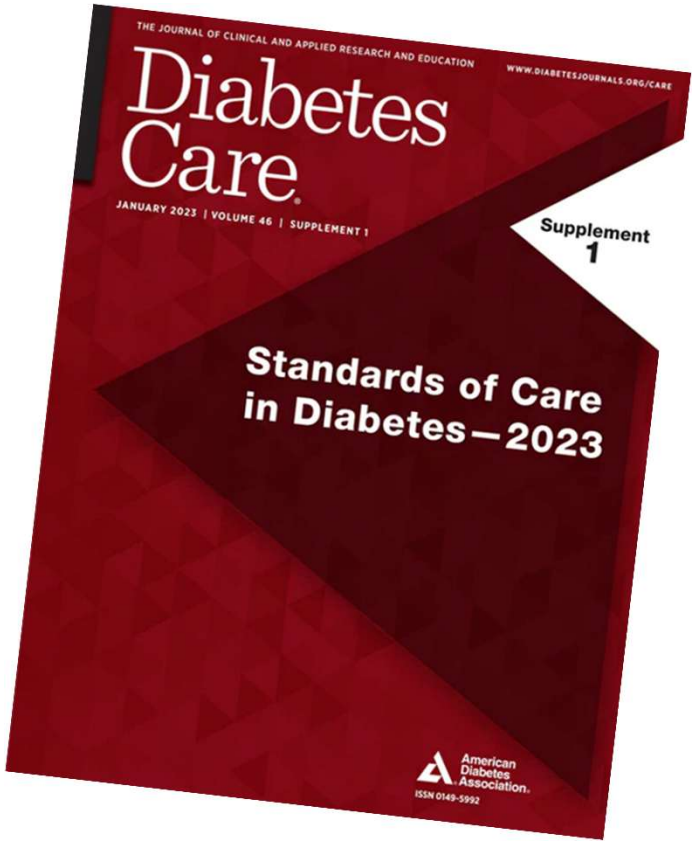


* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

Adapted from Davies MJ, et al. Diabetologia. 2022;45(11):2753–2786.

2023 American Diabetes Association (ADA) SOC Guidelines

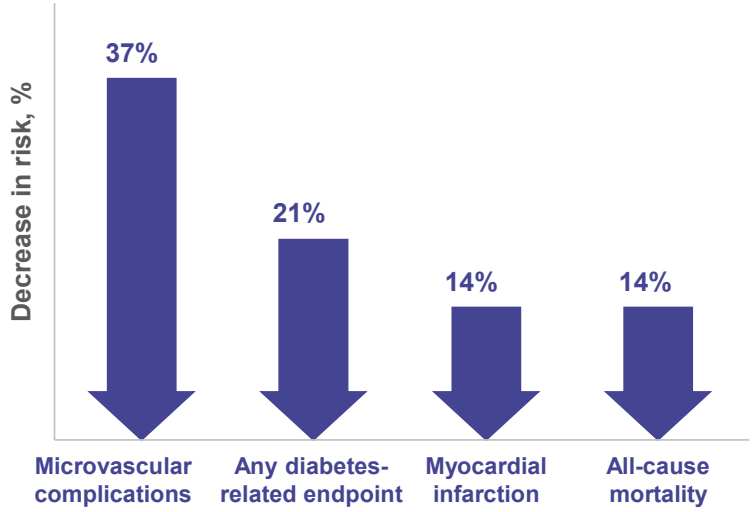
- The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when **A1C levels (>10% [86 mmol/mol]) or blood glucose levels [16.7 mmol/L]) are very high**.



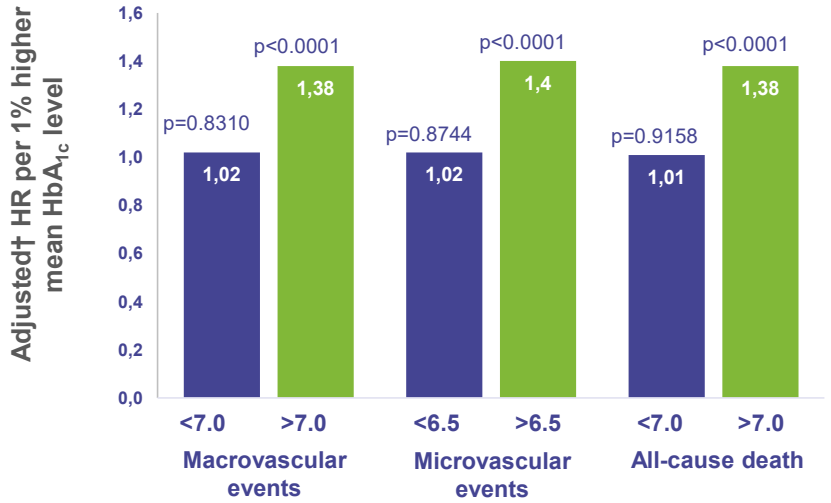
Diabetes Care 2023;46(Supplement_1):S267–S278; https://diabetesedstore.net/products/ada-2023-standards-of-care-book

Importance of glycemic control to prevent long-term complications of T2D

UKPDS Trial[1]:
Each 1% reduction in HbA_{1c} is associated with



ADVANCE Trial[2]:
Association of HbA_{1c} levels with vascular complications and deaths in people with T2D



†Adjusted for age, sex, randomised BP and glucose treatment (excluded in randomised treatment subgroup analyses), mean UACR, mean eGFR, mean SBP, mean triacylglycerol, mean LDL-cholesterol, mean HDL-cholesterol, mean BMI and the additional baseline covariates of currently treated hypertension, history of macrovascular disease, history of microvascular disease, smoking, drinking, ECG abnormality (left ventricular hypertrophy, Q-wave, atrial fibrillation) and duration of diabetes.
BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; T2D, type 2 diabetes; UACR, urine albumin-creatinine ratio; UKPDS, United Kingdom Prospective Diabetes Study.
1. Stratton IM, et al. BMJ. 2000;321:405-412. **2.** Zoungas S, et al. Diabetologia. 2012;55:636-643.

Evolution of basal insulin development from 1st to 2nd generation basal insulin analogs: overcoming limitations

Insulin glargine 100 U/mL (Gla-100) and insulin detemir (IDet) were developed to overcome some limitations of early basal insulins such as NPH insulin, with less variable absorption and longer duration of action[1,2]

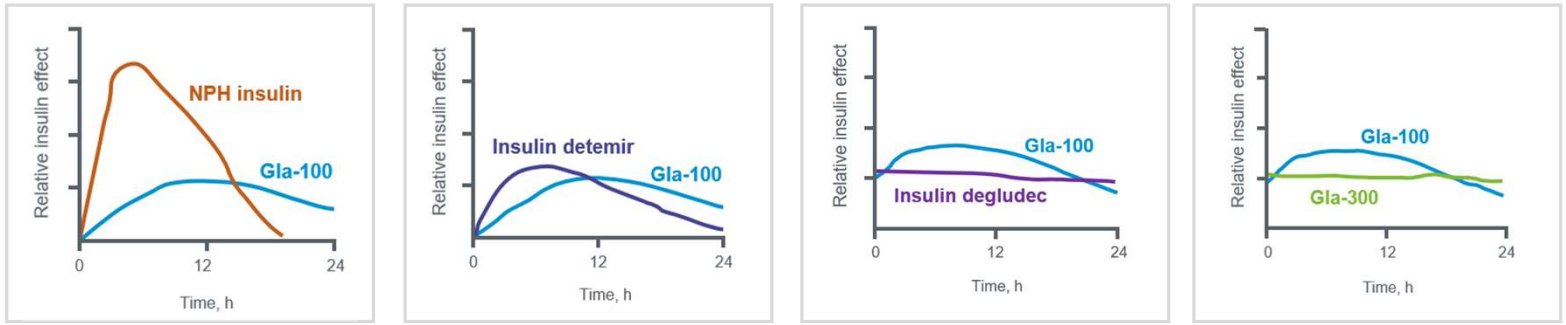
Longer-acting basal insulins, **insulin glargine 300 U/mL (Gla-300)** and insulin degludec (IDeg), have since been developed with less variability and more prolonged durations of action (>24 h)[1,2]

Timeline

- **NPH**[3,4] 1982/1991
- **Gla-100**[5] 2000
- **IDet**[6] 2005
- **Gla-300**[8] 2015
- **IDeg**[7] 2015

1990 — 2000 — 2010 — 2020

Profile comparisons

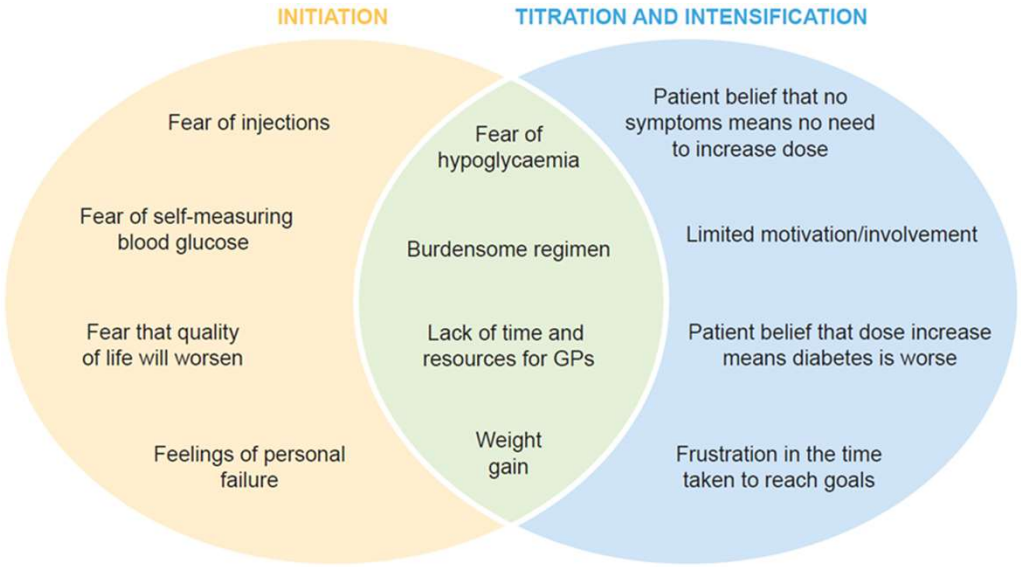


Comparison of action after a single dose for NPH and Gla-100 and for Gla-100 and insulin detemir; Comparison at steady state for Gla-100 and Gla-300 and for Gla-100 and insulin degludec. NPH, neutral protamine Hagedorn. IDet, insulin detemir. IDeg, insulin degludec.

1. Eliaschewitz FG, Barreto T. Diabetol Metab Syndr. 2016;6;8:2; **2.** Pettus J et al. Diabetes Metab Res Rev. 2016;32(6):478–496.; 3. INSULIN ISOPHANE [PI] https://pi.lilly.com/us/INSULIN ISOPHANE-USPI.pdf; **4.** INSULIN ISOPHANE[PI] https://www.novo-pi.com/insulinisophanelinn.pdf; 5. INSULIN GLARGINE U-100 [PI] https://products.sanofi.us/insulin glargine u-100/insulin glargine u-100.html; **6.** INSULIN DETEMIR [PI] https://www.novo-pi.com/insulin detemir.pdf; **7.** INSULIN DEGLUDEC [PI] https://www.novo-pi.com/insulin degludec.pdf;
8. INSULIN GLARGINE U-300 [PI] https://products.sanofi.us/insulin glargine u-300.pdf

Therapeutic inertia in initiating and titrating insulin treatment is common

Barriers to insulin initiation, optimal titration, and intensification



- Prompt and ongoing treatment intensification is recommended to prevent diabetes complications[1-3]
- However, there exists considerable therapeutic inertia to the prompt initiation and optimal titration of BI therapy owing to barriers that include hypoglycaemia[4,5]

BI, basal insulin; GP, general practitioner; HCP, healthcare professional.

1. Davies MJ, et al. Diabetes Care 2018;41:2669-701.
2. Home P, et al. Diabetes Care 2014;37:1499-508.
3. Harris SB, et al. Diabetes Res Clin Pract 2005;70:90-7.
4. Russell-Jones D, et al. Diabetes Obes Metab 2018;20:488-96.
5. Berard L, et al. Diabetes Obes Metab 2018;20:301-8.
Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

Hypoglycaemia is a major barrier to optimal T2D management

Study	Hypoglycaemia	Severe hypoglycaemia
Hypoglycaemia Assessment Tool (HAT)[1]	19.2 events per patient-year	2.5 events per patient-year
Brod M, et al. 2011[2]	28% experience non-severe hypoglycaemia at least once/week	Not reported
Canadian InHypo-DM study[3]	28 events per patient year	2.5 events per-patient year

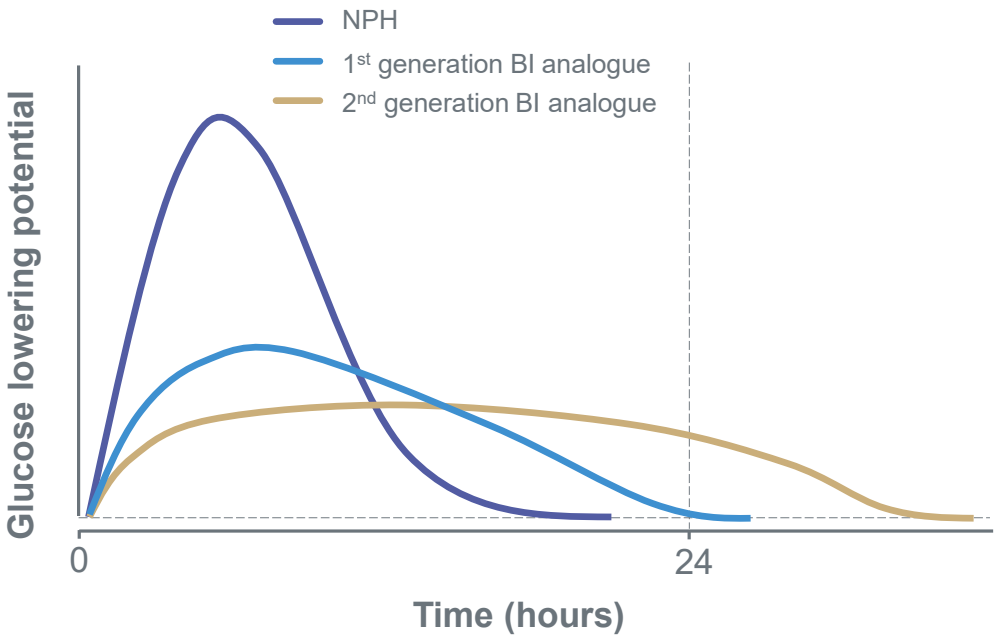
- Hypoglycaemia is common and underreported in people with T2D,[1-3] and is a barrier to achieving glycaemic control[4]
- Mild-to-moderate hypoglycaemia can increase the risk of injury from falls or accidents[5]
- Recurrent hypoglycaemia, especially severe episodes, is strongly associated with CV events[6-8]
- Hypoglycaemia risk is higher in the elderly or frail, and those with renal impairment or multiple comorbidities[9,10]

CV, cardiovascular; T2D, type 2 diabetes.

1. Aronson R, et al. Diabetes Res Clin Pract 2018;138:35-43.
2. Brod M, et al. Value in Health 2011;14:665-71.
3. Ratzki-Leewing A, et al. BMJ Open Diabetes Res Care 2018;6:e000503.
4. Cryer PE. Diabetes 2008;57:3169-76.
5. Seaquist ER, et al. Diabetes Care 2013;36:1384-95.
6. Cryer PE. Diabetes Care 2012;35:1814-6.
7. Zoungas S, et al. N Engl J Med 2010;363:1410-8.
8. McCoy RG, et al. Diabetes Care 2012;35:1897-901.
9. Moen MF, et al. Clin J Am Soc Nephrol 2009;4:1121-7.
10. McCoy RG, et al. JAMA Network Open 2020;3:e1919099-e.

Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

Second-generation basal insulin analogues can minimise the risk of hypoglycaemia

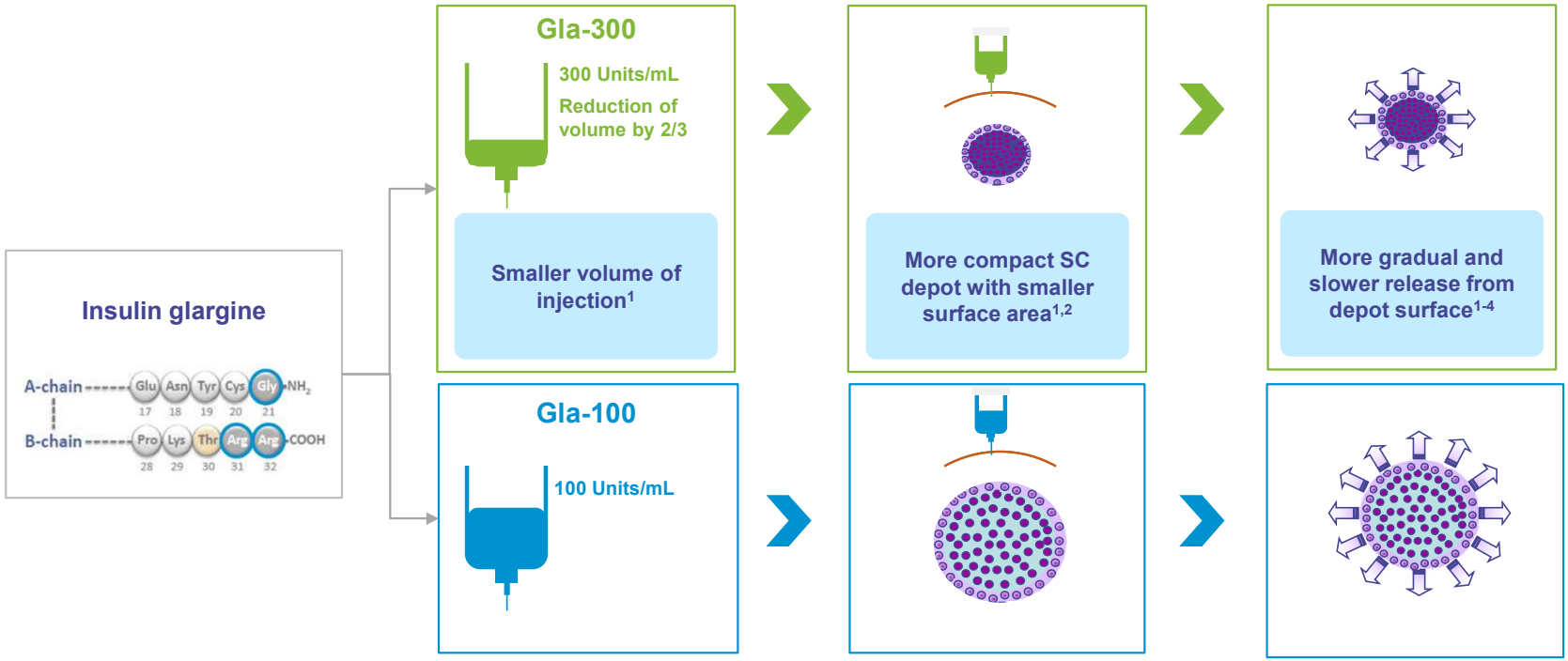


- Guidelines recommend BI analogues, due to a lower risk of hypoglycaemia vs NPH insulin[1-3]
- The ideal BI has PK/PD profile with low variability and a long duration of action
- The improved PK/PD profiles of the 2nd-generation BI analogues (Gla-300 and IDeg) are associated with a lower risk of hypoglycaemia vs the 1st-generation BI analogues[4,5]

BI, basal insulin; Gla-300, insulin glargine 300 U/mL; IDeg, insulin degludec; NPH, neutral protamine Hagedorn; PD, pharmacodynamic; PK, pharmacokinetic.

1. Davies MJ, et al. Diabetes Care 2018;41:2669-701.
2. Garber AJ, et al. Endocr Pract 2020;26:107-39.
3. American Diabetes Association. Diabetes Care 2020;43:S98-S110.
4. Becker RH, et al. Diabetes Care 2015;38:637-43.
5. Heise T, et al. Diabetes, Obesity & Metabolism 2017;19:1032-9.
Harris SB, Parente EB, Karalliedde J. *Diabetes Ther.* 2022. [Epub ahead of print]

Compact depot formation results in more gradual insulin release with Gla-300 vs Gla-100



No differences in potency between Gla-100 and Gla-300 on a unit to unit base

For illustrative purposes only.

1. Pettus J, et al. Diabetes Metab Res Rev. 2016;32(6):478–496;
2. Adapted from Sutton G, et al. Expert Opin Biol Ther. 2014;14(12):1849–1860;
3. Steinstraesser A, et al. Diabetes Obes Metab. 2014;16(9):873–876;
4. Becker RH, et al. Diabetes Care. 2015;38(4):637–643.

Case 1: Andile
Insulin initiation – uncontrolled on multiple oral agents

Andile

Age: 47 years **BMI:** 33 kg/m^2

Diabetes duration: 6 years

eGFR: 90 mL/min/1.73 m^2

HbA$_{1c}$: 8.2% (66 mmol/mol)

Current medication

Metformin
SGLT2i
Sulphonylurea
DPP4i

Tried a GLP-1 RA but discontinued due to GI side effects

HbA$_{1c}$ of 8.2 % has not decreased in the past year

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

Hypoglycaemia concerns because he experienced an event after starting a sulphonylurea

Has hypertension, but no established CVD. His father had T2D and died of MI, so Andile is worried about **potential weight gain** with insulin

BMI, body mass index; CVD, cardiovascular disease; DPP4i, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HbA$_{1c}$, glycated hemoglobin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MI, myocardial infarction; OAD, oral antihyperglycaemic drug; SGLT2i, sodium/glucose cotransporter-2 inhibitor; T2D, type 2 diabetes.

Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

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[1]
- 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[2]
- 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[3,4]
- 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[5]
- In the **EDITION 3** and **BRIGHT** trials[3,4] 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 %

BI, basal insulin; HbA_{1c}, glycated hemoglobin; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg, insulin degludec; RCT, randomized control trial; RWE, real world evidence, T2D, type 2 diabetes

1. Riddle MC, et al. Diabetes Technol Ther. 2016;18:252-7.
2. Russell-Jones D, et al. Diabetes Obes Metab. 2019;21:1615-24.
3. Bolli GB, et al. Diabetes Obes Metab. 2015;17:386-94.
4. Rosenstock J, et al. Diabetes Care 2018;41:2147-54.
5. Bailey TS, et al. Diabetes Obes Metab. 2019;21:1596–605.
Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

Clinical considerations for Andile

Consider adding a BI and reducing the SU dose (with intent to eventually discontinue the SU):

- A second-generation BI analogue may offer relatively low hypoglycaemia risk and dosing flexibility

Advice on lifestyle and diet modification should be reiterated, and treatment should be intensified

Guidance and **training on performing BG measurements** 1–2 times/daily, and hypoglycaemia avoidance/management, especially as he is a delivery driver

Family history implies high **CV risk**:

- Relatively young and no established CVD
- HbA_{1c} target of <7 % without hypoglycaemia should be set to ensure tight glucose control

BG, blood glucose; BI, basal insulin; CV, cardiovascular; CVD, cardiovascular disease; Gla-300, insulin glargine 300 U/mL; SU, sulphonylurea

Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

Case 2: Ella
Hypoglycaemia concerns with first-generation BI

Ella

Age: 61 years **BMI:** 31 kg/m^2

Diabetes duration: 10 years

eGFR: 92 mL/min/1.73 m^2

HbA$_{1c}$: 7.5% (58 mmol/mol)

Current medication

First-generation BI analogue (bedtime)
Sulphonylurea

SGLT2i
DPP4i

At her individualised HbA$_{1c}$ target of 7.5 % (58 mmol/mol) and has no CVD

Tried a fixed-ratio combination of GLP-1 RA + BI but discontinued due to GI side effects

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

Concerned about being unaware of hypoglycaemia and having a **severe event**, particularly as she lives alone & drives to work and for social life

Because she is at her HbA1c target, **Ella intends to stop her insulin**

Confirmed nocturnal hypoglycaemia is a hypoglycaemic event occurring during sleep that is subsequently confirmed with a blood glucose reading of <70 mg/dL
BI, basal insulin; BMI, body mass index; CVD, cardiovascular disease; DPP4i, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HbA$_{1c}$, glycated hemoglobin; OAD, oral antihyperglycaemic drug; SGLT2i, sodium/glucose cotransporter-2 inhibitor.
Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

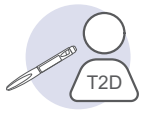
Research evidence

- 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)[1]
- 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[2]
- 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[3]

BI, basal insulin; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg, insulin degludec; IDet, insulin detemir; OAD, oral antihyperglycaemic drug; RCT, randomized control trial; RWE, real world evidence, T2D, type 2 diabetes

1. Zhou FL, et al. Diabetes Obes Metab. 2018;20:1293-7.
2. Yki-Ja¨rvinen H, et al. Diabetes Care. 2014;37:3235-43.
3. Pettus J, et al. Diabetes Ther. 2019;10:617-33.
Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

Clinical considerations for Ella



She should be reminded that **T2D is progressive**, and that glycaemic control does not mean she is in remission

Due to **frequent nocturnal hypoglycaemia**, she needs education about hypoglycaemia self-management, and recognising/preventing situations in which hypoglycaemia may occur

Second-generation BI analogues may help to reduce the risk of nocturnal hypoglycaemia

- Dose might need adjusting upon switching, and changing administration from evening to morning should be considered

Once confident with her BI therapy, the dose can be titrated to reach the **recommended target of <7%**

BI, basal insulin; T2D, type 2 diabetes

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Case 3: Jabavu
Basal insulin treatment in older people with T2D

Jabavu

Age: 80 years **BMI:** 27 kg/m^2

Diabetes duration: 16 years

eGFR: 64 mL/min/1.73 m^2

HbA$_{1c}$: 8.9% (74 mmol/mol)

Current medication

Metformin DPP4i
SGLT2i

- Mild renal impairment
- Pre-proliferative retinopathy
- Peripheral neuropathy
- Dementia
- His hypertension and lipids are well managed with treatment

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

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

BI, basal insulin; BMI, body mass index; DPP4i, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; HbA$_{1c}$, glycated hemoglobin; OAD, oral antihyperglycaemic drug; SGLT2i, sodium/glucose cotransporter-2 inhibitor; T2D, type 2 diabetes

Harris SB, Parente EB, Karalliedde J. *Diabetes Ther.* 2022. [Epub ahead of print]

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[1]
- 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)[2]
- In a post hoc analysis of the **BRIGHT** RCT, Gla-300 was associated with greater HbA_{1c} reductions versus IDeg-100, without an increase of hypoglycaemia, in people with T2D who were ≥70 years of age and initiating BI[3]

BI, basal insulin; HbA_{1c}, glycated hemoglobin; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg, insulin degludec; RCT, randomized control trial; T2D, type 2 diabetes

1. Ritzel R, et al. Diabetes Care. 2018;41:1672-80.
2. Yale JF, et al. Diabetes Metab. 2020;46(2):110-18.
3. Bolli GB, et al. Diabetes Obes Metab. 2021;23(7):1588-93.
Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

Clinical considerations for Jabavu

Jabavu needs better glycaemic control because his **raised BG levels will be detrimental to his neuropathy and retinopathy**

- Hypoglycaemia may also **worsen his dementia**

May consider the **addition of a BI with a simple titration algorithm**, as recommended by the ADA

Second-generation BI analogues may provide a relatively simple regimen that would help to **improve glycaemic control**, with a risk of hypoglycaemia that could be lower than the first-generation BI analogues

Jabavu and his carers should receive education to enable them to manage his diabetes, using a **pragmatic HbA_{1c} target of <8% (64 mmol/mol) and home glucose monitoring**

ADA, American Diabetes Association; BG, blood glucose; BI, basal insulin.

Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

Case 4: Rolene

Insulin in people with comorbidities + increased hypoglycaemia risk

Rolene

Age: 68 years **BMI:** 30 kg/m^2

Diabetes duration: 20 years

eGFR: 40 mL/min/1.73 m^2

HbA$_{1c}$: 8.8% (73 mmol/mol)

Current medication

Metformin
SGLT2i
DPP4i
ARB
Atorvastatin
Calcium channel blocker

Tried a GLP-1 RA but could not tolerate GI side effects

- Hypertension
- Stable stage 3A CKD
- Background diabetic retinopathy

Rolene 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**

ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; DPP4i, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HbA$_{1c}$, glycated hemoglobin; SGLT2i, sodium/glucose cotransporter-2 inhibitor

Harris SB, Parente EB, Karalliedde J. *Diabetes Ther*. 2022. [Epub ahead of print]

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[1]
- 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[2]
- 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[3]

BI, basal insulin; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; HbA_{1c}, glycated hemoglobin; IDeg, insulin degludec; RCT, randomized control trial; T2D, type 2 diabetes

1. Escalada FJ, et al. Diabetes Obes Metab. 2018;20:2860-8.
2. Sullivan SD, et al. Poster 133-LB presented at ADA 2019, San Francisco, CA, June 7-11 2019.
3. Haluzik M, et al. Diabetes Obes Metab. 2020;22(8):1369-77.
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Clinical considerations for Rolene

Glycaemic control is essential to **avoid CKD progression**

- Rolene is already on metformin + SGLT2i and did not tolerate GLP-1 RA, so the next step could be a BI analogue

Should receive **education on diabetes self-management**, managing hypoglycaemia risk, and dealing with hypoglycaemic events

Should receive recommendation for medication use on days she is unwell

- If BI is initiated, Rolene may benefit from continued treatment on such days with **increased BG monitoring**, and adjustment of dose if needed

A **pragmatic HbA_{1c} target of 7.0–7.5%** (53–58 mmol/mol) may be most appropriate

BI, basal insulin; BG, blood glucose CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; SGLT2i, sodium/glucose cotransporter-2 inhibitor

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Background and rationale

- Between 2013 and 2019 CGM was used in 11% of clinical trials for BIs[1]
- Despite wide use of second-generation BI analogues and increasing usage of CGM in people with T1D in clinical practice, **InRange is the first RCT to compare the two second-generation BI analogues with TIR as the primary endpoint**

Objective

The **primary objective** of **InRange** (NCT04075513) was to demonstrate non-inferiority of Gla-300 versus IDeg-100 on **glycaemic control,** as measured by **TIR** and **variability, using blinded CGM in adults with T1D**

BI, basal insulin; CGM, continuous glucose monitoring; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; RCT, randomised controlled trial; T1D, type 1 diabetes; TIR, time in range

1. Fox, B. Q., et al., *Clinical Diabetes* 2021;**39**:160-166

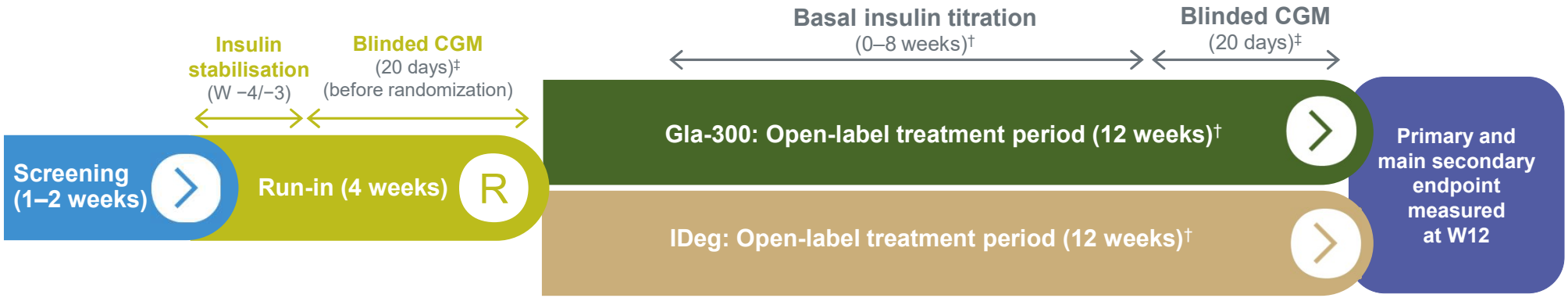
Study design

12-week, multicentre, randomized, active-controlled, parallel-group, open-label study

Study population (N=343)

- Adults aged 18–70 years with T1D
- HbA_{1c} ≥7 % to ≤10 %
- MDI regimen with any
  - Basal insulin analogue
  - Rapid-acting insulin analogue
- No Gla-300 or IDeg-100 in last 30 days

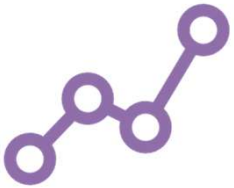
- During the titration period, doses of Gla-300 or IDeg-100 were titrated to achieve the target fasting self-measured plasma glucose (SMPG) of ≥70 to <100 mg/dL
- Mealtime insulin analogue was titrated to achieve 2-hour post-prandial SMPG target of ≥130 to ≤180 mg/dL while avoiding hypoglycaemia
- CGM data was blinded to both investigators and participants
- Post-treatment safety information was collected 2–4 days after the last insulin dose



Randomisation stratified by screening HbA1c values of <8.0 % vs ≥8.0 %; †Telephone calls by investigators to monitor insulin titration weekly between site visits for all participants, unless participants attended the study site for sensor replacement (participant had option to visit the site on day –10 and 74 for sensor replacement). BI dose adjustments were based on a median of fasting SMPG values from last 3 days. Mealtime insulin dose adjustments were based on a pattern of post-meal SMPG data from last 3 days OR the carbohydrate content of the meal. ‡Baseline CGM data collection was started in W –3 and stopped at randomization visit. Endpoint CGM data was collected over 20 consecutive days during W10–W12

CGM, continuous glucose monitoring; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; MDI, multiple daily injections; R, randomisation; SMPG, self-measured plasma glucose; T1D, type 1 diabetes

The InRange study is the first RCT comparing second-generation BI analogues, Gla-300 and IDeg-100, in T1D using TIR as the primary endpoint

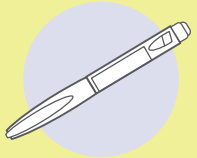
Primary endpoint met	Main secondary endpoint met	Hypoglycaemia and safety profile
		
Non-inferiority for glycaemic control (% TIR)	**Non-inferiority for glycaemic variability** (total glucose CV)	**Similar occurrences of hypoglycaemia, with no unexpected safety findings**

Gla-300 is non-inferior to IDeg-100 in people with T1D in terms of glycaemic control (TIR), and in terms of glycaemic variability, with no difference in occurrences of hypoglycaemia or safety profiles

BI, basal insulin; CV, coefficient of variation; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; MDI, multiple daily injections; RCT, randomised controlled trial; T1D, type 1 diabetes; TIR, time in range

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

BI, basal insulin; Gla-300, insulin glargine 300 U/mL; HCP, healthcare practitioner; IDeg, insulin degludec; T2D, type 2 diabetes

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