How to use insulin glargine U300 in everyday clinical practice?

Case studies with expert comment

Introduction

Outcomes seen in randomised clinical trials may not always reflect the outcomes seen in everyday clinical practice. This review focuses on real-world practice – providing data and two case studies that illustrate the practical clinical use of insulin glargine U300 (Gla-300), an ultra-long acting insulin. Use of Gla-300 in real-world clinical settings was evaluated in the retrospective observational KANTAR study using data from physician surveys and medical charts, with the objective of evaluating changes in dosing and clinical outcomes pre- and post-initiation of Gla-300 in insulin-naïve type 2 diabetes mellitus (T2DM) patients or those switching to Gla-300 from another basal insulin (Gla-100 or insulin detemir). Another retrospective observational study, DELIVER-2, used data from electronic medical records to evaluate clinical outcomes of patients with T2DM using basal insulin who switched to Gla-300 or other basal insulins (Gla-100, insulin detemir or insulin degludec).

KEY MESSAGES

- The use of insulin glargine U300 (Gla-300) is characterised by low within-day fluctuation of blood sugar levels and high between-day reproducibility
- In type 2 diabetes mellitus, use of Gla-300 achieved consistent reductions in confirmed and/or severe nocturnal hypoglycaemia incidents at six months compared with Gla-100
- In type 1 diabetes mellitus, use of Gla-300 achieved similar or lower confirmed and/or severe nocturnal hypoglycaemia at six months compared with Gla-100
- Real-world evidence indicates that switching from Gla-100 to Gla-300 is significantly associated with a lower daily dose of basal insulin, lower HbA1c, and fewer hypoglycaemic events
- Real-world evidence indicates that switching from a prior basal insulin to Gla-300 results in significantly fewer hypoglycaemic incidents than switching to other basal insulins
- Gla-300 and Gla-100 are not bioequivalent and therefore not interchangeable.

Properties of Gla-300: clinical trial data

Gla-300 has more stable and prolonged pharmacokinetic and pharmacodynamic profiles that last beyond 24 hours,1,2 compared to Gla-100. Gla-300 is characterised by low within-day fluctuation of blood sugar levels and high between-day reproducibility.3 The EDITION studies compared the therapeutic efficacy of Gla-300 to that of Gla-100 in type 1 diabetes mellitus (T1DM) and T2DM (Table 1). Gla-300 and Gla-100 have a similar safety and tolerability profile.4-10
Table 1. Patient-level meta-analysis of the EDITION studies – therapeutic efficacy of Gla-300 vs Gla-100

<table>
<thead>
<tr>
<th></th>
<th>T1DM[^8]</th>
<th>T2DM[^7,9,10]</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c reduction</td>
<td>Similar HbA₁c reduction from baseline across six-month study period</td>
<td>No significant difference in mean HbA₁c change from baseline across six-month study period</td>
</tr>
<tr>
<td>Confirmed (&lt;3.9mmol/l) or severe nocturnal hypoglycaemic events</td>
<td>Titration phase – Gla-300 demonstrated lower rates (31%) from baseline to week eight Maintenance phase – Similar rates during week nine to month six</td>
<td>Gla-300 demonstrated lower rates (2.10 vs 3.06 events per participant-year) across six-month study period</td>
</tr>
</tbody>
</table>

Real-world evidence – clinical outcomes when switching to Gla-300 from other basal insulins

Switching to Gla-300 from another basal insulin – the KANTAR study

Real-world evidence from the KANTAR study shows that compared with pre-switch baseline, switching from Gla-100 or insulin detemir to Gla-300 was significantly associated with a lower daily dose of basal insulin (0.73 vs 0.58 units/kg; p=0.02), lower HbA₁c (8.50 vs 7.55; p<0.0001) and fewer reported hypoglycaemic events (0.77 vs 0.13; p<0.0001). Insulin treatment-usage patterns analysed included date of initiation, prior dosage, dosage initiated, titrated dosage and frequency of dosing. The number of hypoglycaemic events experienced six months prior to switch was compared to the number experienced six months since switch (Figure 1).[^11]

![Figure 1. Switching basal insulin to Gla-300](image-url)

[^7]: EDITION studies 1, 2, 3, 4, 5, 6, 7, 8
[^8]: EDITION studies 1, 2, 3, 4, 5
[^9]: EDITION studies 1, 2, 3, 4
[^10]: EDITION studies 1, 2, 3
[^11]: KANTAR study
How to use insulin glargine U300 in everyday clinical practice?

Switching to Gla-300 or another basal insulin from a prior basal insulin – the DELIVER-2 study

The DELIVER-2 study evaluated real-world clinical outcomes of T2DM patients not only in those using basal insulin and switching to Gla-300, but also those switching to a different basal insulin (Gla-100, insulin detemir or insulin degludec). Patients were matched 1:1 based on baseline demographics and clinical characteristics, with 947 patients switched to Gla-300 compared to 947 patients switched to other basal insulins. Data available for 12 months prior to switching (baseline) were compared with data from six months after switching (follow-up). Compared with other basal insulins, switching from a prior basal insulin to Gla-300 was associated with similar significant reductions in HbA1c from baseline and comparable achievement of HbA1c treatment targets (Figure 2). At six-month follow up, the group switched to Gla-300 reported significantly fewer hypoglycaemic incidents compared to those switched to other basal insulins (15.1 vs 19.9; p=0.03), with significantly fewer patients with hypoglycaemia, based on inpatient or emergency department encounters (4.3 vs 9.7; p<0.01) (Figure 3).12

Figure 2. Glycaemic control when switching from prior basal insulin to Gla-300 or other basal insulins12

Figure 3. Glycaemic control (HbA1c) target attainment at six-month follow up

<table>
<thead>
<tr>
<th>HbA1c %</th>
<th>Patients reaching HbA1c goal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7%</td>
<td>16.9</td>
</tr>
<tr>
<td>&lt;8%</td>
<td>18.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HbA1c %</th>
<th>Patients reaching HbA1c goal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7%</td>
<td>45.0</td>
</tr>
<tr>
<td>&lt;8%</td>
<td>42.2</td>
</tr>
</tbody>
</table>

Gla-300

Other basal insulin: Gla-100 or insulin detemir
How to use insulin glargine U300 in everyday clinical practice?

Hypoglycaemia incidence at six-month follow up
aOR 0.75 (95% CI 0.58-0.97)

Hypoglycaemia associated with inpatient or emergency department encounter at six-month follow-up
aOR 0.52 (95% CI 0.34-0.77)

Figure 3. Hypoglycaemia when switching from prior basal insulin to Gla-300 or other basal insulins\(^2\)
### Questions and answers

1. Meta-analysis of the T2DM arms of the EDITION studies comparing therapeutic efficacy of Gla-300 to Gla-100 show:

   A. Similar mean HbA1c change from baseline across the six-month study period
   B. Lower rates of confirmed or severe nocturnal hypoglycaemic events with Gla-300
   C. Both of the above

2. Gla-300 and Gla-100 have a similar safety and tolerability profile.

   A. True
   B. False

3. Which statement is false?

   A. Gla-300 achieves lower within-day fluctuation of blood sugar levels than Gla-100
   B. Gla-100 achieves lower within-day fluctuation of blood sugar levels than Gla-300

4. From the KANTAR study, compared with pre-switch (Gla-100 or insulin detemir) baseline in T2DM, Gla-300 showed:

   A. Similar daily doses of basal insulin required with fewer reported hypoglycaemic events
   B. Significantly lower daily doses of basal insulin required with fewer reported hypoglycaemic events

5. From the KANTAR study, compared with pre-switch (Gla-100 or insulin detemir) baseline in T2DM, Gla-300 showed lower HbA1c.

   A. True
   B. False

6. From the DELIVER-2 study - switching to Gla-300/other basal insulin from a prior basal insulin in T2DM, Gla-300:

   A. Was associated with similar significant reductions in HbA1c from baseline
   B. Showed comparable achievement of HbA1c treatment targets
   C. Both of the above

7. At six-month follow-up, which arm of the DELIVER-2 study reported significantly fewer hypoglycaemic incidents, with significantly fewer hypoglycaemia-related inpatient or emergency department encounters?

   A. Gla-300
   B. Other basal insulins
Case studies

Case study 1 – Switching from Gla-100 to Gla-300 in T2DM

A 46-year-old woman who is morbidly obese was diagnosed with T2DM eight months previously. She has obstructive sleep apnoea. Despite already using Gla-100 twice daily, with liraglutide and metformin, she has poor glycaemic control that is worsening. She has been attempting to counteract nocturnal hypoglycaemia (once weekly) by eating excessive amounts of sugar, contributing to weight gain.

**Expert comment:** Professor Barber describes a very common scenario - the compensatory behaviour of increased sugar intake as a strategy to avoid nocturnal hypoglycaemia. The implication is that as weight increases, the patient becomes more insulin resistant and more insulin is needed for glycaemic control.

<table>
<thead>
<tr>
<th>Visit 1 (initial presentation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
</tr>
<tr>
<td><strong>T2DM diagnosis</strong></td>
</tr>
<tr>
<td><strong>HbA₁c (mmol/mol)</strong></td>
</tr>
<tr>
<td><strong>Medication</strong></td>
</tr>
<tr>
<td>• Metformin: 1g bd</td>
</tr>
<tr>
<td>• Insulin detemir: 48U morning and 34U evening</td>
</tr>
<tr>
<td>• Liraglutide: 1.8mg od</td>
</tr>
<tr>
<td>• Aspirin, atorvastatin 40mg od, omeprazole</td>
</tr>
<tr>
<td><strong>Past medical history</strong></td>
</tr>
<tr>
<td><strong>Other details</strong></td>
</tr>
<tr>
<td>• Nocturnal hypos about once weekly</td>
</tr>
<tr>
<td>• Compensating for hypos with increased carbohydrate intake</td>
</tr>
<tr>
<td>• Worsened glycaemic control over the last year</td>
</tr>
<tr>
<td>• Erratic day-to-day capillary blood glucose measurements (BMs) between 3 and 14</td>
</tr>
<tr>
<td>• BP: 139/63mmHg</td>
</tr>
<tr>
<td>• U&amp;E, LFT and TGT N; eGFR: 56ml/min/1.72m²; total chol: 5.0mmol/l, HDL-C: 1.2mmol/l</td>
</tr>
</tbody>
</table>

**Why is this patient experiencing regular nocturnal hypoglycaemia?**

She is taking an evening dose of Gla-100. With most of the insulin being absorbed within the first five hours, she is being exposed to too much insulin during the night.

**8. What are the three main aspects to focus on in managing this patient’s diabetes?**

| A. Improve glycaemic stability and thereby reduce the frequency of her hypos and her need to take in excess glucose |
| B. Improve her overall glycaemic control |
| C. Lower her BMI |
| D. All of the above |

**How can this patient’s glycaemic stability and overall glycaemic control be improved?**

Switching her Gla-100 bd to Gla-300 od (at 80% of total daily insulin dose) is likely to stabilise her glycaemia based on the flatter pharmacokinetic and pharmacodynamic profile of Gla-300. In turn, this should reduce the swings in glycaemia she has experienced and also enable a subsequent up-titration of her Gla-300 to achieve better overall glycaemic control.
How to use insulin glargine U300 in everyday clinical practice?

9. What support can be provided to assist the patient to improve her weight?

| A. A consultation with a dietician to enable focused dietary advice and support |
| B. A reduction in hypoglycaemic events with a different insulin strategy |
| C. A and B |

Initial management as recommended and introduced by the attending physician

<table>
<thead>
<tr>
<th>Dietician</th>
<th>Regular follow-up with dietary support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commenced Gla-300</td>
<td>Initial dose 64U od (80% of total daily insulin dose); Gla-100 discontinued at time of Gla-300 commencement</td>
</tr>
</tbody>
</table>

Visit 2 – first follow-up (four months)

| Weight | 135kg (weight loss 2kg) |
| Glycaemic control | • No further hypos  
• Glycaemic stability improved: BMs typically 5-9 |
| HbA1c (mmol/mol) | 77 (9.2%), reduced from 91 (10.5%) |
| Current glycaemic medications | • Metformin: 1g bd  
• Gla-300: titrated up to 74U od  
• Liraglutide: 1.8mg od |
| Other progress | • Low CHO diet, dietary support, feels better  
• Reduced insulin requirements  
• Option of bariatric surgery to consider  
• Engagement in respect of lifestyle much improved as she now has better control of her glycaemia |

After switching to Gla-300 od, what improvements are evident at four-month follow up?

Her HbA1c has improved as a result of switching to Gla-300, going from 10.5% to 9.2%. The inter-day variability of her BMs shows improved glycaemic stability. She has experienced no hypoglycaemic episodes, with less need for sugar intake. This combined with dietary input has contributed towards her weight loss.

Expert comment: As a result of her improved glycaemic control, she reported feeling more engaged in respect of lifestyle, allowing her to focus better on diabetes self-management.

10. What are the preferred further management options for this patient?

| A. Up-titration of the Gla-300 dose |
| B. Bariatric surgery |

Case study 2 – Long-standing poor glycaemic control with multiple complications in T2DM

A 49-year-old male patient, diagnosed with T2DM 15 years earlier, has a long-standing history of very poor glycaemic control. He was a truck driver earlier in his diabetes management, and very resistant to any intensification in insulin therapy due to fear of hypos that would have implications for his livelihood.
How to use insulin glargine U300 in everyday clinical practice?

Visit 1 (initial presentation)

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>36 (105kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM diagnosis</td>
<td>15 years prior</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>99 (11.2%); BMs typically 6-16</td>
</tr>
</tbody>
</table>

Medication
- Gla-100: 30U od pm (commenced one month prior)
- Liraglutide: 1.2mg od
- Metformin: 1g tds
- Fenofibrate: 267mg od
- Atorvastatin: 40mg od
- Losartan: 100mg od
- Omeprazole, naproxen

Past medical history
- Hypertension
- Background retinopathy with maculopathy (previous laser)

Other details
- BP: 140/79mmHg
- BMs improved with insulin
- No hypoglycaemic episodes
- Ex-smoker
- U&E N; ALT 60U/l, but LFT N otherwise; TFT N; eGFR: 50ml/min/1.72m²; total chol: 5.1mmol/l, LDL-C: 3.3mmol/l; urea: 9.6; creat: 130; ALT: 77

Expert comment: Professor Barber noted that at this time, there were no second-generation insulins available, with basal-bolus as the best available option in cases such as this.

11. What should be the primary focus in managing this patient’s diabetes?

A. To improve his overall glycaemic control
B. To avoid hypoglycaemic episodes on insulin therapy, which would compromise his truck driver’s permit

Expert comment: The clinician decided to increase the dose of Gla-100.

Visit 2 – one year later

Management
Increase dose of Gla-100

Cardiovascular update
Had a recent STEMI with PCI

Driver’s permit update
Recently received permit again (as had remained hypo-free with insulin), currently not driving due to recent MI

Glycaemic control and HbA1c
- No hypos, but HbA1c remains poor at 97mmol/mol (11%)
- BMs 9-16 typically

Weight
Stable

Current glycaemic medications
- Gla-100: dose increased to 64U od
- Metformin MR: 1.5mg bd
- Liraglutide: 1.2mg od

Other therapy changes
- Commenced on bisoprolol, aspirin, clopidogrel and glyceryl trinitrate spray
- Losartan changed to perindopril

Other progress
eGFR remains 50ml/min/1.72m²
How to use insulin glargine U300 in everyday clinical practice?

**Visit 3 – six months later**

<table>
<thead>
<tr>
<th>Management</th>
<th>Still continues to increase Gla-100 dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular update</td>
<td>Had further myocardial event three months after first one, requiring further stenting and cardiac rehab</td>
</tr>
<tr>
<td>Driver's permit update</td>
<td>Still awaiting licence to be reinstated</td>
</tr>
</tbody>
</table>
| Glycaemic control and HbA1c | • No hypos, but HbA1c remains poor at 101mmol/mol (11.4%)  
• BM 9-16 typically, and can rise after a meal |
| Weight | Stable |
| Current glycaemic medications | • Gla-100: dose increased to 70U od  
• Metformin MR: 1.5mg bd  
• Liraglutide: 1.2mg od |
| Other therapy changes | • Perindopril switched back to losartan due to cough  
• Atorvastatin dose increased to 80mg od |
| Other progress | • Recent diagnosis of irritable bowel syndrome (IBS)  
• eGFR remains at 50ml/min/1.72m²  
• BP: 148/88mmHg |

**Expert comment:** Despite gradual increments in Gla-100 dose, the patient still has very poor glycaemic control. At this time, there are still no second-generation insulins available.

12. **How can this patient's glycaemic stability and overall glycaemic control be improved?**

   A. Continue to increase the dose of Gla-100  
   B. Add another insulin (e.g. insulin aspart), to be taken with each meal  
   C. A and B

**Visit 4 – 18 months later**

| Management | • Gradual increments in Gla-100 dose  
• Addition of IAsp with each meal |
| Cardiovascular update | No further cardiovascular events, has remained pain free |
| Driver's permit update | Has retired from truck driving because of visual impairment and multiple medical problems |
| Glycaemic control and HbA1c | • No hypos  
• Some improvement in HbA1c, but remains poor at 88mmol/mol (9.9%) |
| Weight | Stable |
| Current glycaemic medications | • Gla-100: 134U od (evening)  
• IAsp: 20-30U with each meal  
• Metformin: 1g bd  
• Liraglutide: 1.2mg od |
| Other progress | • Deteriorating renal function; renal team involvement  
• Creat: 165; eGFR: 38ml/min/1.72m²  
• New vessel disease affecting sight – ophthalmologist involvement and further laser therapy  
• Investigation by claudication clinic  
• BP: 145/84mmHg |

**Expert comment:** Possibly as a result of his chronic poor glycaemic control, this patient has developed multiple micro- and macrovascular complications and has retired from truck driving because of visual impairment and multiple medical problems.
**Why is this patient’s declining renal function important?**

His declining renal function has implications for his insulin dosing, given that insulin is renally excreted.

**13. What are the implications of impaired kidney function on insulin dose requirements?**

| A. The insulin dose should be increased due to poorer control |
| B. The insulin dose should be decreased |
| C. A different strategy – using an ultralong-acting insulin |

**Expert comment:** This patient’s conversion to a basal-bolus regimen had a disappointing effect on his glycaemia. One of the problems has been his glycaemic variability on Gla-100 therapy. At this time, Gla-300 becomes available for use as therapy.

**How can this patient’s overall glycaemic control be improved?**

As with case study 1, the rationale for switching from Gla-100 to Gla-300 is to improve his glycaemic variability and enable up-titration of his Gla-300 dose with minimal risk of hypoglycaemia.

<table>
<thead>
<tr>
<th>Visit 5 – six months later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management</td>
</tr>
<tr>
<td>Cardiovascular update</td>
</tr>
<tr>
<td>Glycaemic control and HbA1c</td>
</tr>
<tr>
<td>Weight</td>
</tr>
<tr>
<td>Current glycaemic medications</td>
</tr>
<tr>
<td>Other progress</td>
</tr>
</tbody>
</table>

**14. After switching to Gla-300 od, what improvements would you expect at six-month follow-up?**

| A. Improvement in HbA1c |
| B. No hypoglycaemic episodes |
| C. Better 24-hour glucose control |
| D. All of the above |

**Expert comment:** As can be seen from his graph of HbA1c values (Figure 4), following his conversion to Gla-300 his HbA1c improved and he has experienced no hypoglycaemic episodes. His BMs have improved, and now range from 7-10.
How to use insulin glargine U300 in everyday clinical practice?

15. How can this patient’s glycaemic stability and overall glycaemic control be improved further?

A. Increase the dose of Gla-300
B. Add a post-prandial insulin
C. Both of the above

Visit 6 – six months later

<table>
<thead>
<tr>
<th>Management</th>
<th>Increased Gla-300 dose to 100U od</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycaemic control</td>
<td>No hypos, BMs remain much improved (8-12)</td>
</tr>
<tr>
<td>and HbA₁c</td>
<td>Continued improvement in HbA₁c at 69mmol/mol (8.5%); this is now the best glycaemic control he has ever had</td>
</tr>
<tr>
<td>Weight</td>
<td>Stable</td>
</tr>
<tr>
<td>Current glycaemic</td>
<td>Gla-300: 100U od</td>
</tr>
<tr>
<td>medications</td>
<td>IAsp: 20-30U with each meal</td>
</tr>
<tr>
<td></td>
<td>Metformin: 1g bd</td>
</tr>
<tr>
<td></td>
<td>Liraglutide: 1.2mg od</td>
</tr>
<tr>
<td>Other progress</td>
<td>Renal function stable – ongoing renal team involvement</td>
</tr>
<tr>
<td></td>
<td>Ongoing ophthalmologist involvement</td>
</tr>
<tr>
<td></td>
<td>BP: 154/82mmHg</td>
</tr>
<tr>
<td></td>
<td>Developed some memory problems – referral to memory clinic</td>
</tr>
</tbody>
</table>

After switching to Gla-300 od, what improvements are evident at one-year follow up?

After many years of struggling with his glycaemic control despite basal-bolus and multiple other therapies, this patient’s glycaemic control has continued to improve and is now the best it has ever been.
Important safety information

Gla-300 and Gla-100 are not bioequivalent and are therefore not interchangeable. Hypoglycaemia, in general, is the most frequent adverse reaction to insulin therapy and may occur if the insulin dose is too high in relation to the insulin requirement. Patient adherence to dose and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. To prevent medication errors, patients should check that they have the correct insulin before injecting and never withdraw insulin from the pen with a needle and syringe. Be cautious when using pioglitazone with insulin. There is no clinical experience of Gla-300 use in pregnant women.

Conclusions

Use of Gla-300 in T2DM patients offers a more stable and prolonged pharmacokinetic and pharmacodynamic profile compared to Gla-100, allowing for prolonged 24-hour glycaemic control with less fluctuation in glucose levels and a significant reduction in confirmed nocturnal hypoglycaemia. Real-world data support the benefits of switching to Gla-300 from a prior basal insulin, with significantly fewer hypoglycaemic experiences compared with switching to other basal insulins.

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