NSW GOVERNMENT Health
Central Coast
Local Health District

Insulin Initiation

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Endocrinologist and Credentialled Diabetes Educator
Central Coast Local Health District

GP Club

20 March 2024

phn HUNTER NEW ENGLAND AND CENTRAL COAST
An Australian Government Initiative

Outline

- To discuss the various types of insulins available
- To discuss how to initiate and titrate insulin
- Safety tips on use of insulin
- Effects and sequelae of hypoglycaemia

Case Study 1 - Tracey

- Tracey is 59 years of age
- Married, mother of 2 adult children
- previously casually employed in retail but is now finding it harder to work
- Has had T2D for 20 years
- Very obese – BMI > 50
- Complicated with microalbuminuria, retina microaneurysms
- Developed new foot ulceration in the last few months, including a recent hospital admission

Tracey cont.

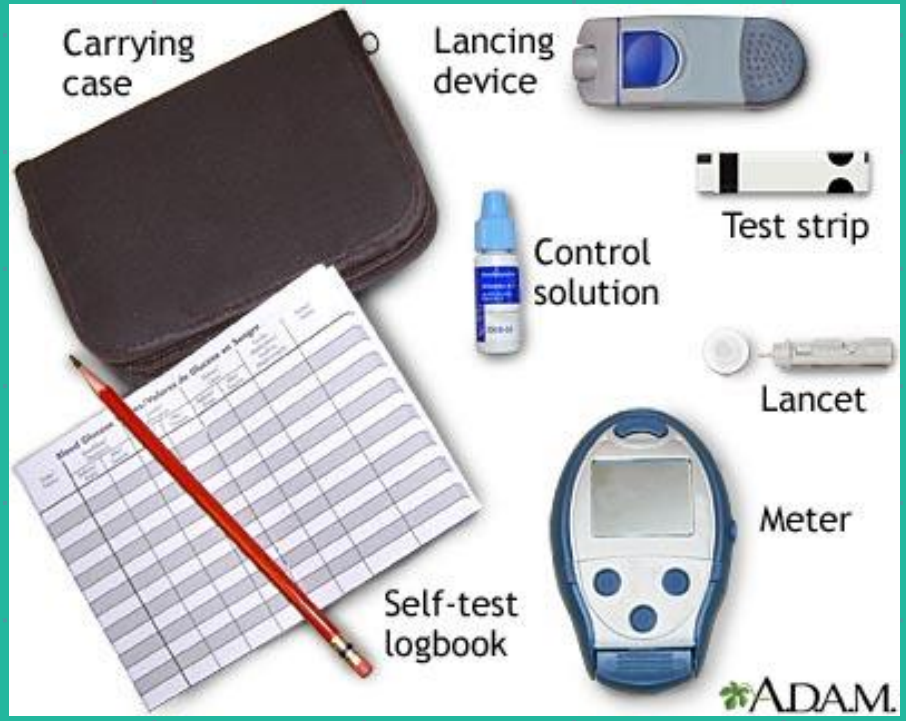
- She now takes metformin 1g bd, gliclazide 120mg mane, semaglutide 1mg weekly
- She didn’t tolerate Jardiance as she experienced severe thrush
- Her HbA1c has been 11% for at least 2 years, last HbA1c was 9%
- Lost 5kg weight

What Would You Do?

A. Retry metformin
B. Perform 1 week of self-monitoring blood glucose (SMBG)
C. Start insulin glargine (Optisulin) 60 units
D. Add in prandial insulin – Apidra/Humalog/Novorapid 10 units with meals
E. Start Ryzodeg 60 units with dinner

Self-Monitoring of Blood Glucose (SMBG)

- Aiding the achievement of HbA1c targets
- Minimizing glucose variability
- Helping to predict severe hypoglycaemia
- SMBG has also been reported to be associated with decreased diabetes-related morbidity and all-cause mortality in type 2 diabetes.
- SMBG can also heighten patients' awareness of the disease and the impact of lifestyle on blood glucose levels



Case 1 Cont.

- Tracey has come back to you with a SMBG diary
- What would you now suggest for Tracey to do?

WEEK BEGINNING: _____ (DATE)

	Insulin Injections					Monitoring Blood Glucose								Remarks Activity, illness, diet changes, time of hypos (noting blood glucose and treatment).
	Type of Insulin	Units given				Breakfast		Lunch		Dinner		Before Supper or Bed	Over night	
		Breakfast	Lunch	Dinner	Before Bed	Before	After	Before	After	Before	After			
Mon						12.1	15.1	15.8	16.9	11.9	20.5			
	Lantus				50									
Tues						10.9	13.4	14.1	18.2	11.0	19.8			
	Lantus				50									
Wed						12.9	15.1	13.2	20.1	14.5	19.1		15.1	
	Lantus				50									
Thu						10.1	15.5		12.1	10.9	18.2			missed lunch
	Lantus				50									
Fri						14.1		12.1	19.1	15.1	18.9			
	Lantus				50									
Sat						13.4	14.2	10.6	13.5	14.9	16.5			
	Lantus				50									
Sun						12.5	13.2	11.9	14.0	15.9	17.0			
	Lantus				50									

What would you do for Tracey?

A. Increase insulin glargine (*Optisulin/Semglee*) to 60 units
B. Add in ultra short acting insulin – glulisine (*Apidra*)/lispro (*Humalog*)/aspart (*Novorapid*) 10 units with meals
C. Try Mixed Insulin – (aspart 30%/protamine 70%) *Novomix 30/70* to 40 units twice a day
D. Try Mixed insulin – degludec 70%/aspart 30% (*Ryzodeg 70/30*) 35 units bd
E. Review again in 2 weeks

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	Lantus				50									
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	Lantus				50									
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C. Try Mixed Insulin – (aspart 30%/protamine 70%) *Novomix 30/70* to 40 units twice a day
D. Try Mixed insulin – degludec 70%/aspart 30% (*Ryzodeg 70/30*) 35 units bd ✓
E. Review again in 2 weeks ✓ ✓

Interpreting SMBG patterns

3 distinct patterns to look for

- Fasting levels: aim 4 – 8 mmol/L
- Pre-prandial levels: aim 4 – 8 mmol/L
- Post-prandial levels: aim 5 – 10 mmol/L
- **Patients must be above 5 mmol/L to drive!!!!**

WEEK BEGINNING: _____ (DATE)

	Insulin Injections					Monitoring Blood Glucose								Remarks
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	Lantus				50									

Starting and adjusting basal insulin[1–3]

STEP 1. SELECT basal insulin and injecting device

STEP 2. START basal insulin: 0.1 units/kg or **10 units** at bedtime or morning

CONTINUE oral glucose-lowering medication

If fasting blood glucose (FBG) is high (pre-breakfast), consider evening or morning insulin dosing of a long-acting (>24 hours) basal insulin

If FBG is on target, but pre-dinner blood glucose level (BGL) is high, consider morning insulin dosing of intermediate-acting insulin e.g. steroids

The Royal Australian College of General Practitioners. Management of type 2 diabetes: A handbook for general practice. East Melbourne, Vic: RACGP, 2020.

STEP 3. TITRATION

If using long-acting basal insulin doses (morning or evening doses), adjust doses to achieve FBG targets

If using intermediate-acting basal insulin, use pre-dinner glucose targets to adjust the morning doses and FBG targets to adjust any additional evening doses

Practitioner-led titration (below left) can achieve target in a shorter time period than patient-led titration (below right)

Practitioner-led titration OR Patient-led titration

Adjust insulin dose twice weekly as shown, until FBG target is achieved

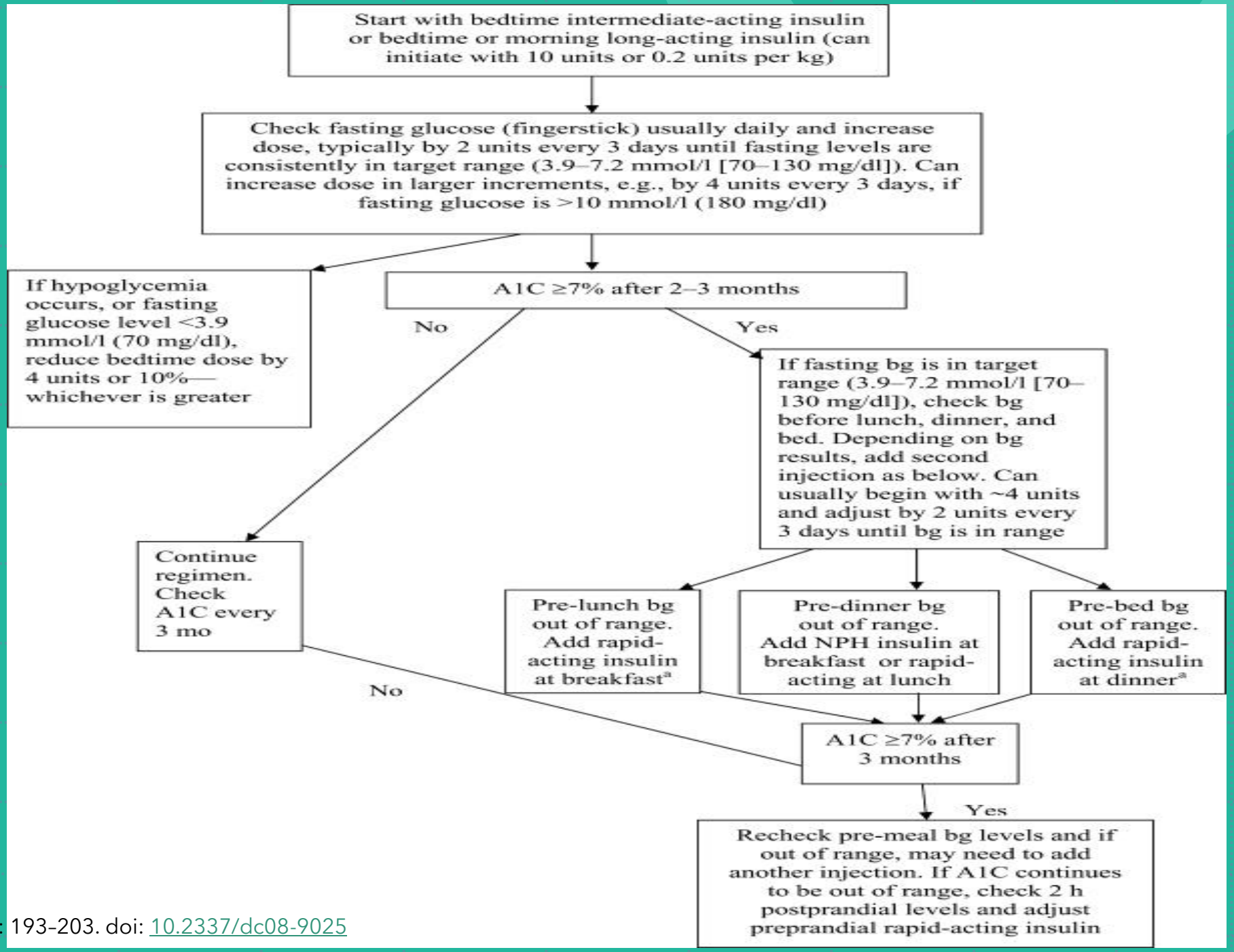
Mean FBG over previous two days (mmol/L)*	Insulin dose adjustment
≥10.0	↑ by 4 units
8.0–9.9	↑ by 2–4 units
7.0–7.9	No change or ↑ by 2 units
6.0–6.9	No change
4.0–5.9	No change or ↓ by 2 units
<4.0	↓ by 2–4 units

Adjust insulin dose every three days. Increase by 2 units until FBG target is achieved

Mean FBG over previous three days (mmol/L)*	Insulin dose adjustment
≥6.0 mmol/L but ≤8.0 mmol/L	No change
4.0–6.0 mmol/L	↓ insulin dose by 2 units
<4.0 mmol/L	↓ insulin dose by 4 units

*Do not increase insulin dose if FBG <4.0 mmol/L at any time in the preceding week.

Starting Insulin



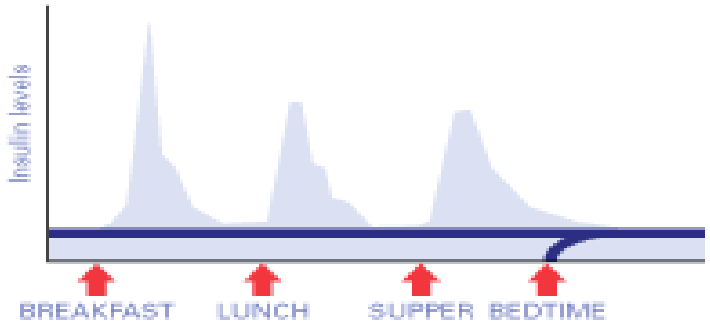
Nathan et al. Diabetes Care 2009 Jan; 32(1): 193–203. doi: 10.2337/dc08-9025

Mixed long acting with ultra short acting	 NovoMix 30® Flexpen (Insulin aspart/insulin aspart protamine) Other less commonly used formulations include Humalog Mix 50® (Insulin lispro/insulin lispro protamine)  Humalog Mix 25® KwikPen (Insulin lispro/insulin lispro protamine)	ONCE or TWICE daily IMMEDIATELY before meals
Mixed ultra long acting with ultra short acting	 Ryzodeg 70/30® FlexTouch (Insulin degludec/Insulin aspart)	ONCE or TWICE daily IMMEDIATELY before meals
Long acting	 Levemir® Flexpen (Insulin detemir)	ONCE or TWICE daily
	 Optisulin® Solostar (Insulin glargine)  Semglee® (Insulin glargine)	ONCE daily
Long acting high concentration	Different strengths of insulin glargine are not interchangeable It is recommended patients continue their same preparation whilst in hospital.  Toujeo® Solostar (Insulin glargine) 300units/1mL	ONCE daily

Acting time	**100 units/1mL** unless otherwise stated	When to administer
Ultra short acting	 Fiasp® FlexTouch (Insulin aspart)  NovoRapid® Flexpen (Insulin aspart)  Humalog® KwikPen (Insulin lispro)  Apidra® Solostar (Insulin glulisine)  Humalog® U-200 KwikPen (Insulin lispro) 200 units/1mL	IMMEDIATELY before meals
Short acting	 Actrapid® (Neutral)  Humulin R® (Neutral) Insulin Infusat® (Neutral) is available via SAS	Within 30 minutes before meals
Intermediate acting	 Humulin NPH® (Isophane)  Protaphane® (Isophane)  Protaphane® Innolet (Isophane)	ONCE or TWICE daily

BASAL (Lantus®)

LONG-ACTING INSULIN

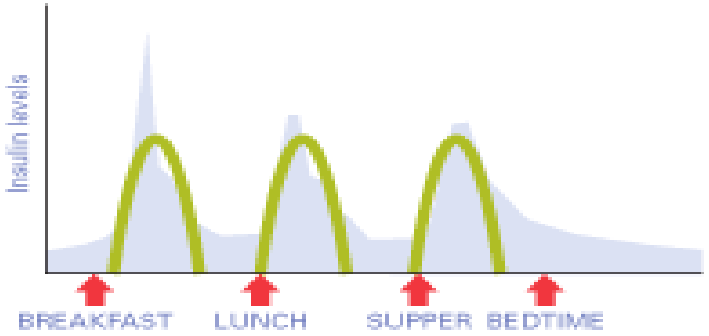


Onset
2-4 hours

Duration
24 hours

PRANDIAL

RAPID-ACTING INSULIN

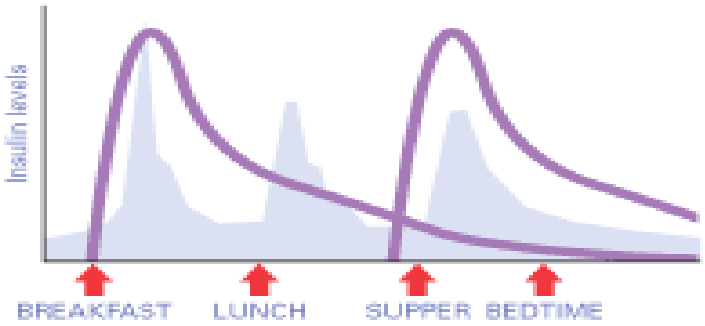


Onset
~5 minutes

Duration
4-5 hours

PREMIX

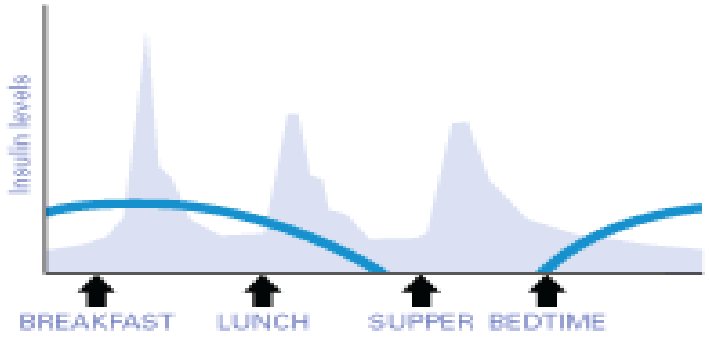
PREMIXED INSULIN (ANALOG)



Onset
5-15 minutes

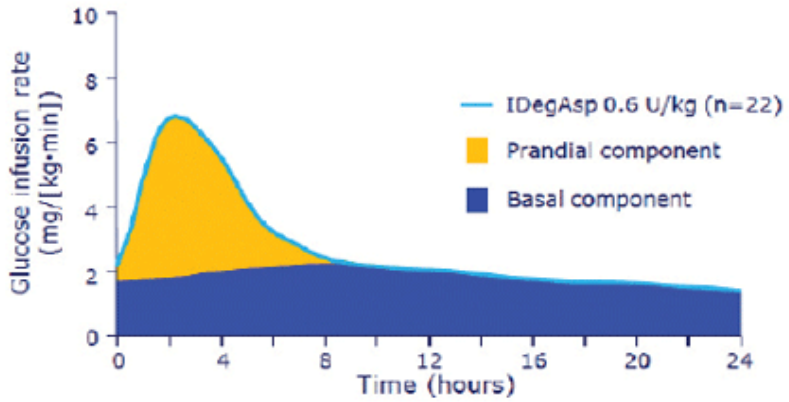
Duration
10-16 hours

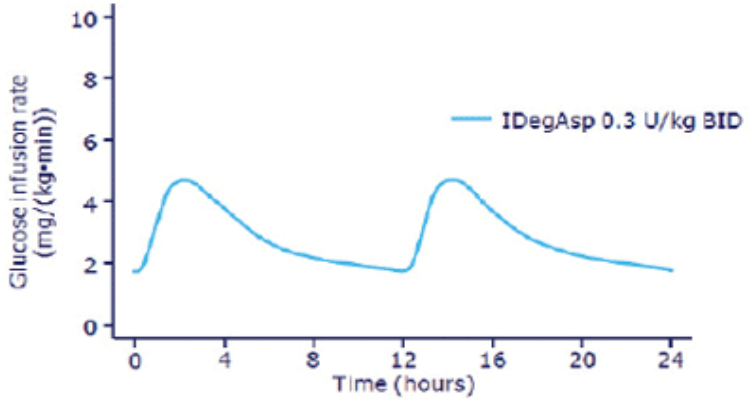
INTERMEDIATE-ACTING INSULIN (NPH)



Onset
0.5-1 hours

Duration
10-16 hours





(a) (b)

Fig. 3: Pharmacodynamic profile of insulin degludec/insulin aspart. Mean glucose infusion rate profile of (a) once-daily and (b) simulated twice daily at steady state of insulin degludec/insulin aspart administered in subjects with type 1 diabetes mellitus. IDegAsp, Insulin degludec/insulin aspart; BID, twice daily. Source: Adapted from Ma et al. 2012, Heise et al. 2014

Unnikrishnan, J Association of Physicians in India, 2

Guide to basal plus insulin intensification schedules

Basal Plus Insulin

STEP 1. SELECT rapid-acting (prandial) insulin and injecting device to be added in addition to basal insulin

STEP 2. START rapid-acting insulin (4 units) to be given before the meal with the largest carbohydrate content

CONTINUE basal insulin at the current dose

CONTINUE metformin, consider tapering sulfonylureas as glycaemic control improves

MONITOR two-hour postprandial BGL. Continue to assess FBG and preprandial glucose levels – goal is 4.0–7.0 mmol/L

The Royal Australian College of General Practitioners. Management of type 2 diabetes: A handbook for general practice. East Melbourne, Vic: RACGP, 2020.

STEP 3. TITRATION

Increase rapid-acting (prandial) insulin dose by 2 units every three days to achieve target

Two-hour postprandial BGL (mmol/L)	Rapid-acting (prandial) insulin dosage adjustment
≥8 (for three consecutive days)	No change or ↑ by 2 units
6.0–7.9	No change
4.0–5.9	No change or ↓ by 2 units
<4.0 on any day	↓ by 2–4 units

STEP 4. Basal plus titration to basal bolus – intensification

When?

If HbA1c is not at target after three months, add a further prandial insulin dose to another meal (eg basal plus 2 to basal bolus)

How?

1. **Keep the current prandial and basal insulin doses unchanged**
2. **Add a new rapid-acting (prandial) insulin to the next largest meal of the day (starting at 10% of the basal insulin dose or 4 units)**
3. **↑ new prandial insulin dose by 2 units every three days until postprandial target is achieved as per Step 3 above**

Starting Mixed insulin

Starting and adjusting pre-mixed (biphasic) and co-formulated insulin

STEP 1. SELECT premixed or co-formulated insulin and injecting device

INSULIN-NAÏVE patients

STEP 2. START premixed or co-formulated insulin **10 units** immediately before or soon after the largest meal (usually evening meal)

CONTINUE metformin if indicated; consider tapering sulfonylureas as glycaemic control improves

STEP 3. TITRATION

Adjust the evening pre-mixed insulin dose once or twice a week according to the schedule below to FBG[2,3]

Co-formulated insulin should be titrated once a week

Lowest BGL reading (mmol/L) of the previous three days – fasting or preprandial	Insulin dosage adjustment
≥10	↑ by 6 units
8.0–9.9	↑ by 4 units
6.0–7.9	↑ by 2 units
4.0–5.9	No change
<4.0	↓ by 2 units

If a morning insulin dose is given, adjust the insulin dose according to evening preprandial BGL according to the same titration recommendations

Hypoglycaemia should prompt a review of other oral therapy. Which insulin is adjusted depends on regimen and target glucose

STEP 4. INTENSIFICATION: Once-daily insulin to twice-daily premixed insulin

When?

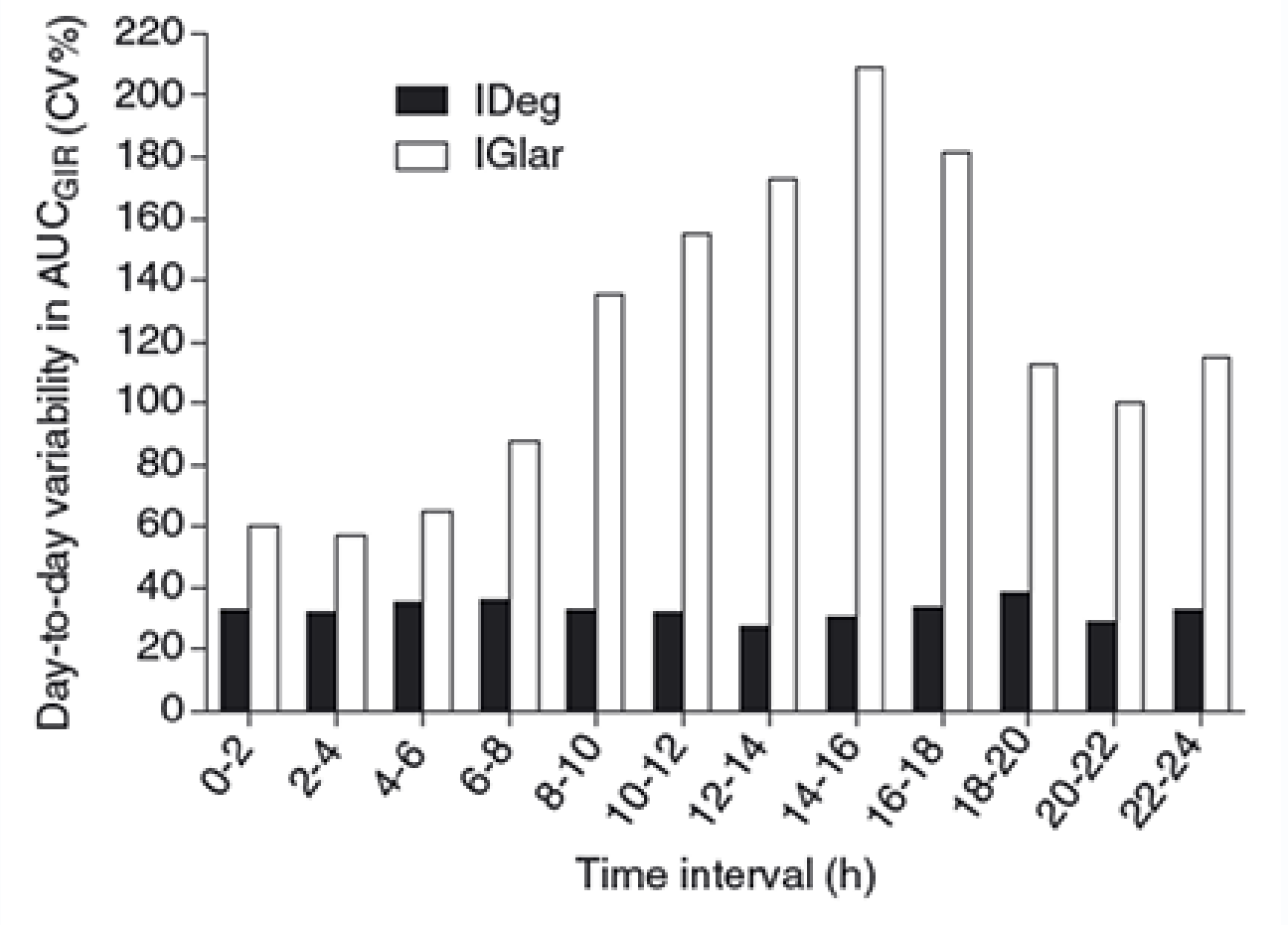
- With FBG at target, if evening preprandial BGL > FBG, or if evening preprandial BGL is high, or
- After three months if glycated haemoglobin (HbA1c) > target, despite FBG and evening preprandial BGL at target

How?

- Calculate any increased total daily insulin dose and divide this into two doses, considering the continued need to maintain FBG and postprandial targets
- Give the increased dose adjustment as twice-daily injections (pre-breakfast and pre-dinner). This may not be a 50/50 split, as prandial targets may require a higher proportion to be given at the largest meal of the day (eg 60/40)
- Monitor pre-dinner BGL and FBG against targets
- Once a week, adjust both insulin doses independently (according to protocol above in step 3); pre-breakfast insulin is adjusted according to pre-dinner BGL, and pre-dinner insulin is adjusted according to FBG

The Royal Australian College of General Practitioners. Management of type 2 diabetes: A handbook for general practice. East Melbourne, Vic: RACGP, 2020.

diabetes queensland



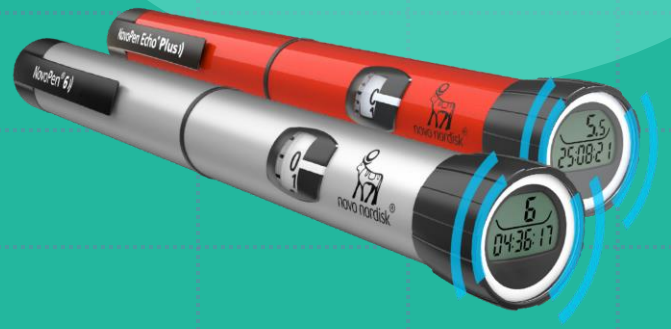
Adjusting from basal bolus to degludec + aspart (*Ryzodeg*)

- Add up the total daily insulin to be replaced by the Ryzodeg dose(s)
- E.g Lets replace **insulin glargine 20 units** and **8 units breakfast** and **10 units for dinner** = 38 units total
- Reduce by 20%
- 38 – (20% x 38 = ~8 units) = 30 units
- Divide by total number of doses (usually 2 or 1 or 3)
- 30 / 2 = 15 units
- Check doses are appropriate as 70% basal and 30% bolus
- E.g. basal = ~10 + 10 units and bolus = ~5 + 5 units

Tips on Ryzodeg adjustment of doses

- If boluses doses appear relatively low – e.g. patient needs higher bolus amounts, consider using the Ryzodeg as a single dose for one meal and insulin aspart for the other meals
  - E.g. 30 units Ryzodeg for dinner = ~10 units of aspart and ~20 units of degludec
  - Give 8 units for breakfast
- If using 2 doses of Ryzodeg, the third mealtime dose may need to be continued
- *Generally* use Ryzodeg with biggest carbohydrate meal
- Cautious use in patients who are unstable medically (e.g. inpatients) or who have renal dysfunction

Shortage of Ryzodeg 70/30 FlexTouch pens



- The Therapeutic Goods Administration (TGA) has advised of a current shortage of Ryzodeg 70/30 FlexTouch insulin prefilled pens. The shortage is expected to continue until mid-next year.
- To help manage the shortage, pharmacists can give people living with diabetes Ryzodeg 70/30 Penfill cartridges instead of Ryzodeg 70/30 FlexTouch prefilled pens under certain conditions.
- Both products contain the same medicine, at the same strength, have the same storage requirements, and are administered by injection under the skin (subcutaneous injection). However, the device used to administer the medicine is different.

https://www.diabetesaustralia.com.au/news/shortage-of-ryzodeg-70-30-flextouch-insulin-prefilled-pens/

Acting time	**100 units/1mL** unless otherwise stated	When to administer
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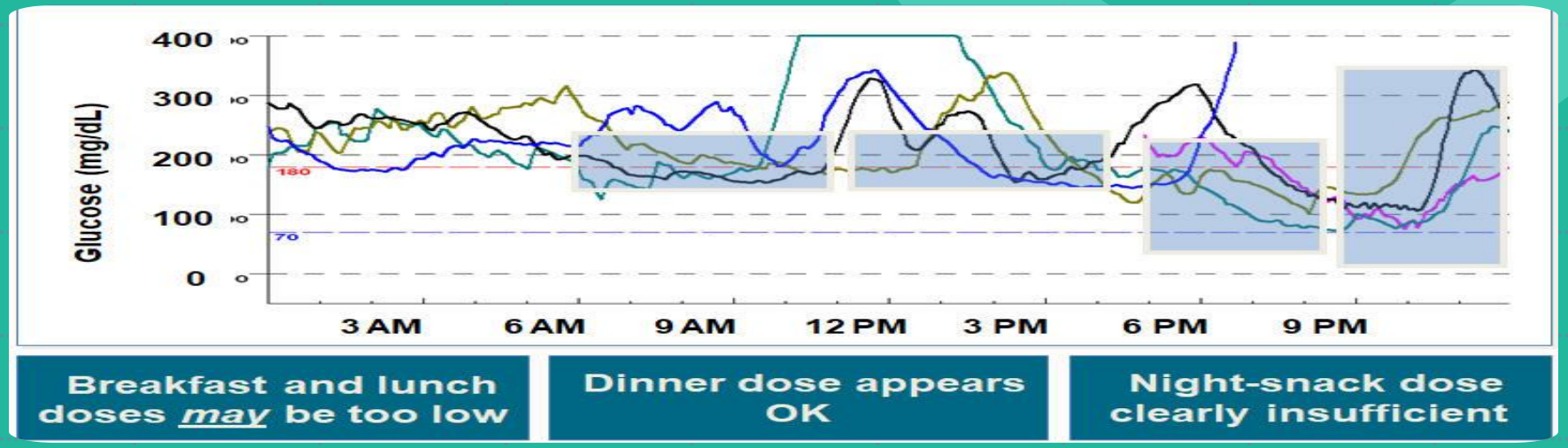
Bolus Dose Titration



- Use pre- and post- meal SMBG or CGM to determine whether the dose needs to be adjusted
- Gradually increment the bolus dose by approximately 10-20% per meal until range is 5-10 mmol/L post meal
- Up titration is limited by any hypoglycaemia experienced
- Encourage patient to vary dose according to carbohydrate serves (1 serve = 15g CHO)
- E.g. 1 serve = 2 units extra
- Alternatively limit their carbohydrate variation if dose adjustment isn't possible
- e.g. 3 serves of CHO each meal

STEP 3. TITRATION

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Practitioner-led titration (below left) can achieve target in a shorter time period than patient-led titration (below right)

Practitioner-led titration OR Patient-led titration

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Adjust insulin dose every three days. Increase by 2 units until FBG target is achieved

Mean FBG over previous three days (mmol/L)*	Insulin dose adjustment
≥6.0 mmol/L but ≤8.0 mmol/L	No change
4.0–6.0 mmol/L	↓ insulin dose by 2 units
<4.0 mmol/L	↓ insulin dose by 4 units

*Do not increase insulin dose if FBG <4.0 mmol/L at any time in the preceding week.

Case 2 - Robert

- Robert is a 59 year old gentleman, has been diagnosed with Type 2 diabetes 5 years prior, just moved to the Coast
- Works for himself, repairs boats
- Muscular build, nil central adiposity, weight 71kg
- Initially started on Metformin, has been up titrated to sitagliptin and empagliflozin by previous GP over the last 1 year
- Fasting levels are always elevated: 10-18 mmol/L
- Doesn't have time to check again until pre-dinner where they are 10-20 mmol/L
- Last HbA1c 10.4% (90 mmol/mol)
- You commenced him on insulin glargine (*Optisulin*) 10 units a few months back
- Reports readings are not much improved, brings only scant self-monitoring of blood glucose (SMBG) records

What Would You Recommend for Robert?

A. Encourage diet and lifestyle changes
B. Increase SMBG
C. Add GLP-1 RA i.e. semaglutide
D. Add in a sulfonylurea
E. Uptitrate insulin glargine to 15 units
F. Add in basal insulin e.g. aspart (*Novorapid*), glulisine (*Apidra)* or lispro (*Humalog*)
G. Change to a mixed insulin e.g. Ryzodeg 70/30, NovoMix 30/70 or Humalog Mix 25
H. A + see him again in 3 months with repeat HbA1c

What I Recommended for Robert

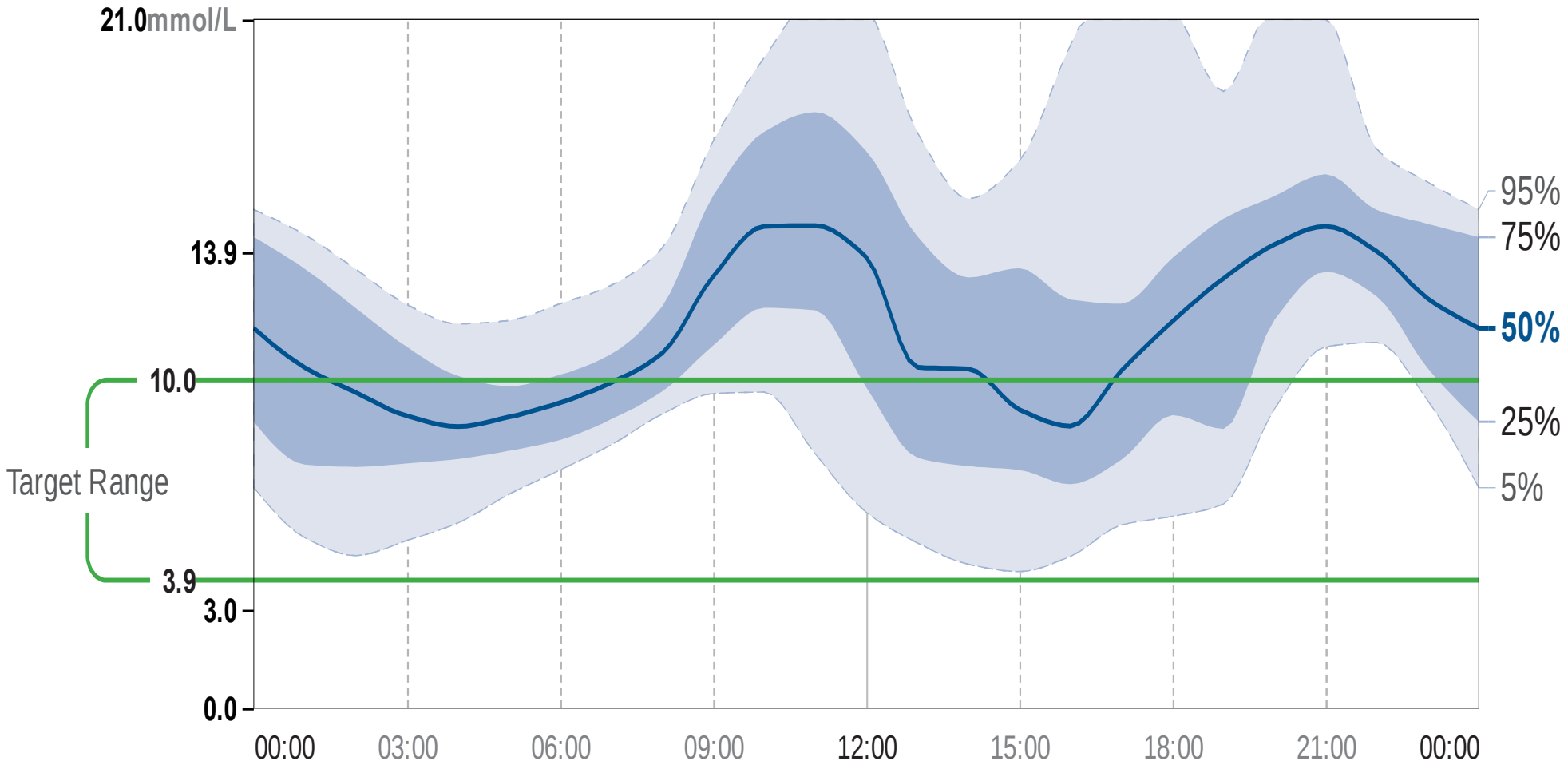
A. Encourage diet and lifestyle changes ✓ ✓
B. Increase SMBG ✓ ✓
C. Add GLP-1 RA i.e. semaglutide ✓
D. Add in a sulfonylurea
E. Uptitrate insulin glargine to 15 units ✓
F. Add in basal insulin e.g. aspart (*Novorapid*), glulisine (*Apidra)* or lispro (*Humalog*) ✓
G. Change to a mixed insulin e.g. Ryzodeg 70/30 ✓, NovoMix 30/70 or Humalog Mix 25
H. A + see him again in 3 months with repeat HbA1c ✓ ✓

Case 3 - Kirk

- Kirk has Type 3c diabetes diagnosed around 5 years ago
- On insulin glargine (Toujeo) 16 units nocte and insulin aspart ~6 units with meals
- His Hba1c has always been out of range > 8 %
- He tries to maintain his BGLs by eating one meal a day, but often snacks late at night
- Weighs 75kg, but trying to lose weight by fasting to improve his diabetes

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



What would you suggest for Kirk?

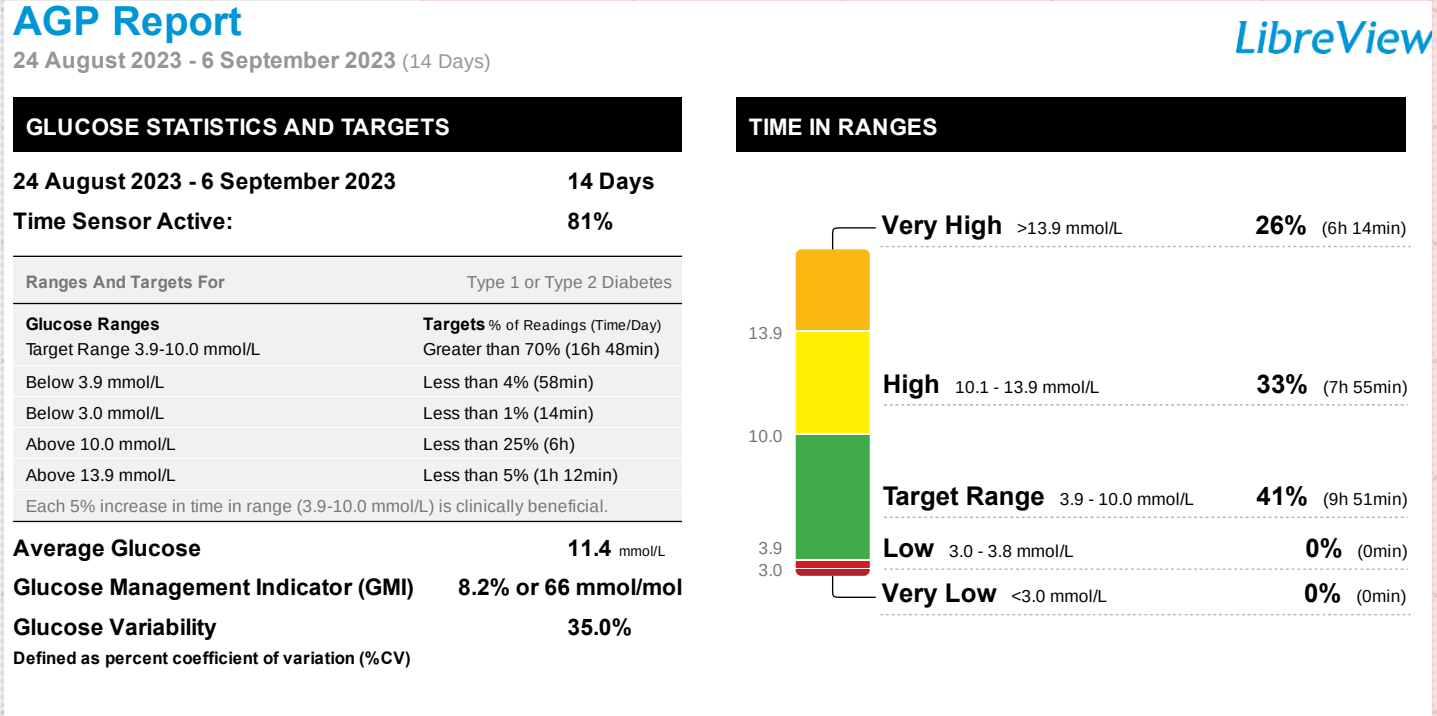
A. Increase all insulin by 20%

B. Increase mid-morning and evening insulin aspart by 2 units to 8 units

C. Counselling around use of insulin with meals

D. Refer to dietitian

E. Refer to educator



AGP Report

24 August 2023 - 6 September 2023 (14 Days)

LibreView

GLUCOSE STATISTICS AND TARGETS

24 August 2023 - 6 September 2023	**14 Days**
Time Sensor Active:	**81%**

Ranges And Targets For	Type 1 or Type 2 Diabetes
Glucose Ranges	**Targets** % of Readings (Time/Day)
Target Range 3.9-10.0 mmol/L	Greater than 70% (16h 48min)
Below 3.9 mmol/L	Less than 4% (58min)
Below 3.0 mmol/L	Less than 1% (14min)
Above 10.0 mmol/L	Less than 25% (6h)
Above 13.9 mmol/L	Less than 5% (1h 12min)

Each 5% increase in time in range (3.9-10.0 mmol/L) is clinically beneficial.

Average Glucose	**11.4** mmol/L
Glucose Management Indicator (GMI)	**8.2% or 66 mmol/mol**
Glucose Variability	**35.0%**

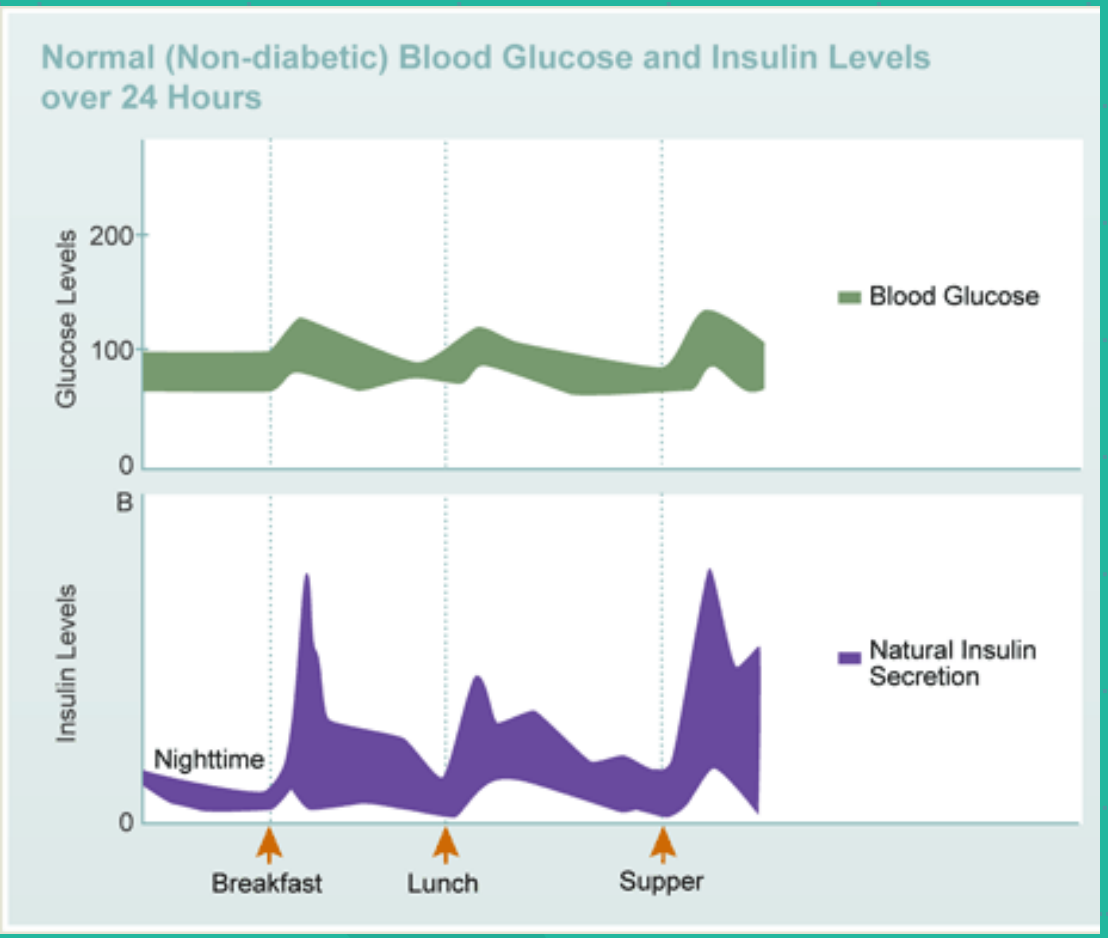
Defined as percent coefficient of variation (%CV)

TIME IN RANGES

13.9
10.0
3.9
3.0

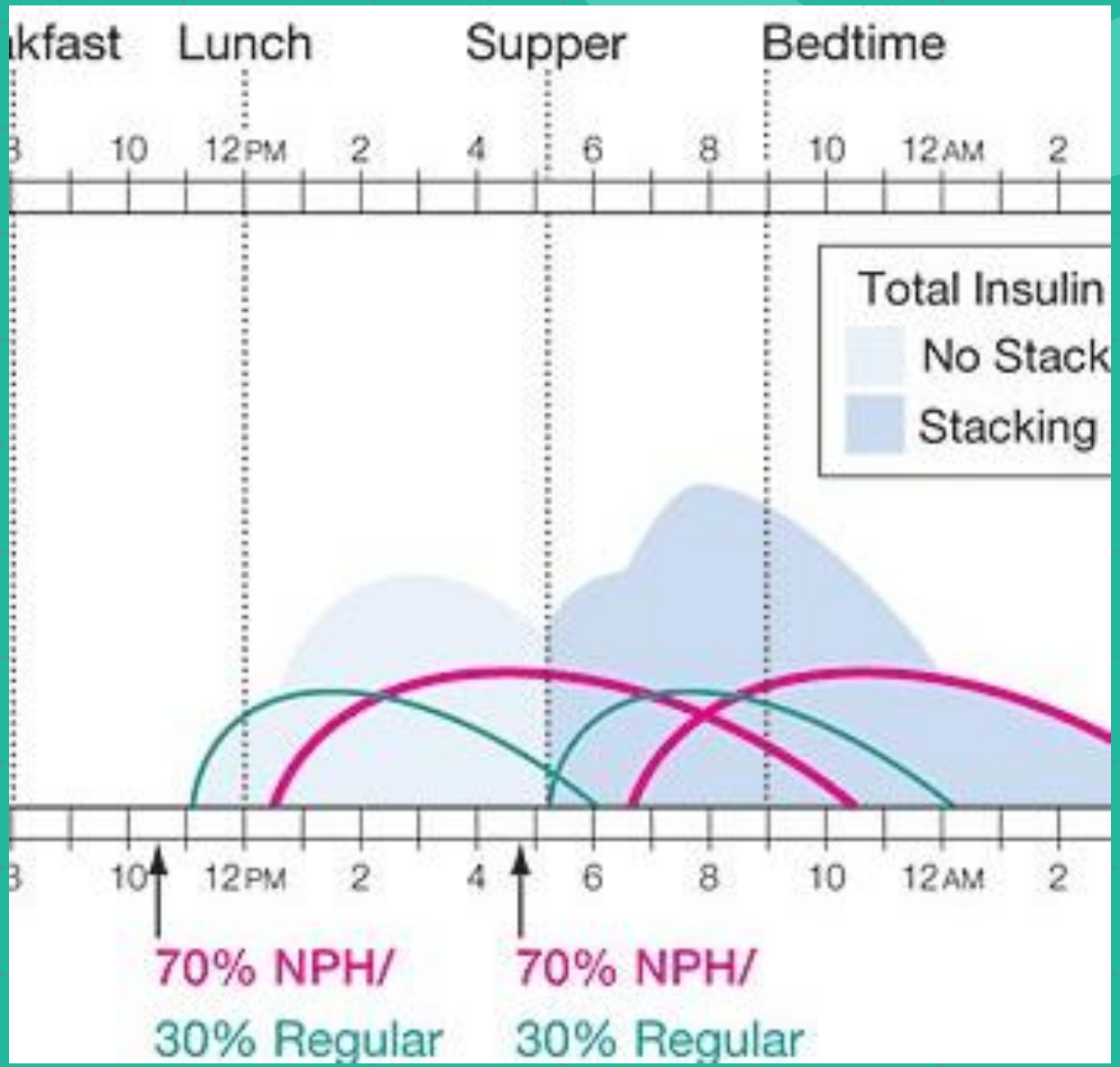
Very High	>13.9 mmol/L	**26%**	(6h 14min)
High	10.1 - 13.9 mmol/L	**33%**	(7h 55min)
Target Range	3.9 - 10.0 mmol/L	**41%**	(9h 51min)
Low	3.0 - 3.8 mmol/L	**0%**	(0min)
Very Low	<3.0 mmol/L	**0%**	(0min)

My Tips For Success on Insulin



- Encourage daily self-monitoring of blood glucose (SMBG)
- Ideally initially 6-8 times a day – this may be limited by strip access/costs
- Can drop to 4 times a day when stable
- Pre- and post-meal SMBG are best to assess bolus pattern
- Work out the patient's BGL pattern:
- Fasting hyperglycaemia = increase basal insulin
- Pre-prandial hyperglycaemia = increase basal insulin
- Post-prandial hyperglycaemia = increase bolus insulin

Insulin Stacking

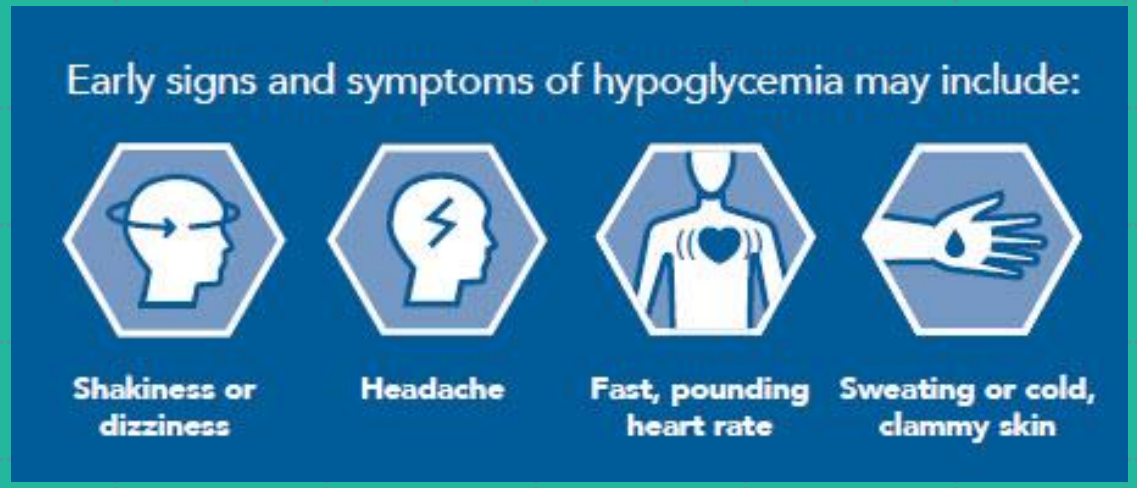


If patient experiences hypoglycaemia

- Check the circumstances surrounding: e.g. extenuating circumstances, over usage, timing, inadequate carbohydrate intake
- Presence of fasting or pre-meal hypoglycaemia = reduce dose of basal insulin
- Hypoglycaemia after meals = over bolusing → reduce bolus doses
- Overnight hypoglycaemia = change to morning basal insulin and reduce dose

Hypoglycaemia

- Although basal insulin is associated with less hypoglycaemia than prandial insulin, hypoglycaemia can occur when the dose of basal insulin is titrated to cover meals.
- If the patient subsequently eats less than usual, hypoglycaemia may occur.
- Alternatively, some patients develop daytime hypoglycaemia on a dose of basal insulin that controls fasting blood glucose (FBG).
- Both of these scenarios lead to obligate snacking, which may fuel insulin-associated weight gain.
- This problem may be identified by asking about symptoms of hypoglycaemia when meals are skipped or snacking to prevent hypoglycaemia.
- Other potential triggers (e.g., changes in diet or activity) should be identified.
- Patients who make significant dietary changes (e.g., starting a ketogenic diet) or commencement of a GLP-1 agonist may require substantial reductions in insulin dosing (e.g., ≥50% reduction).



Impacts of Hypoglycaemia

Cognitive Impairment:

Acute Effects: Recurrent hypoglycemic episodes can lead to temporary cognitive impairment, affecting concentration, memory, and overall cognitive function.

Long-Term Impact: Prolonged exposure to hypoglycemia may contribute to cognitive decline over time.

Hypoglycemia Unawareness:

Reduced Awareness: Some individuals with diabetes may develop hypoglycemia unawareness, a condition where they have diminished ability to sense or recognize the symptoms of low blood sugar. This increases the risk of severe hypoglycemic episodes.

Fear of Hypoglycemia:

Psychological Impact: Individuals who have experienced recurrent hypoglycemia may develop a fear of low blood sugar events. This fear can lead to anxiety and impact their quality of life.

Long Term Sequelae of Hypoglycaemia

Cardiovascular Effects:

Increased Risk: Recurrent hypoglycemia may be associated with an increased risk of cardiovascular events. It can lead to arrhythmias, increased heart rate, and changes in blood pressure.

Neurological Consequences:

Brain Damage: Severe or prolonged hypoglycemia can potentially cause brain damage, particularly if the brain is deprived of glucose for an extended period.

Quality of Life:

Impaired Daily Functioning: The fear of hypoglycemia and its potential impact on cognitive function can affect an individual's ability to carry out daily activities and may lead to a reduced quality of life.

Management Challenges:

Treatment Adjustments: Recurrent hypoglycemia may necessitate adjustments to diabetes management, including changes in medication dosages, meal planning, and lifestyle factors.

Increased Mortality Risk:

Severe Consequences: Severe hypoglycemia can have life-threatening consequences, and in some cases, it has been associated with an increased risk of mortality.