

Insulin Initiation, titration & Insulin switch in the Primary Care-KISS

Rotorua GP CME 9 June 2012

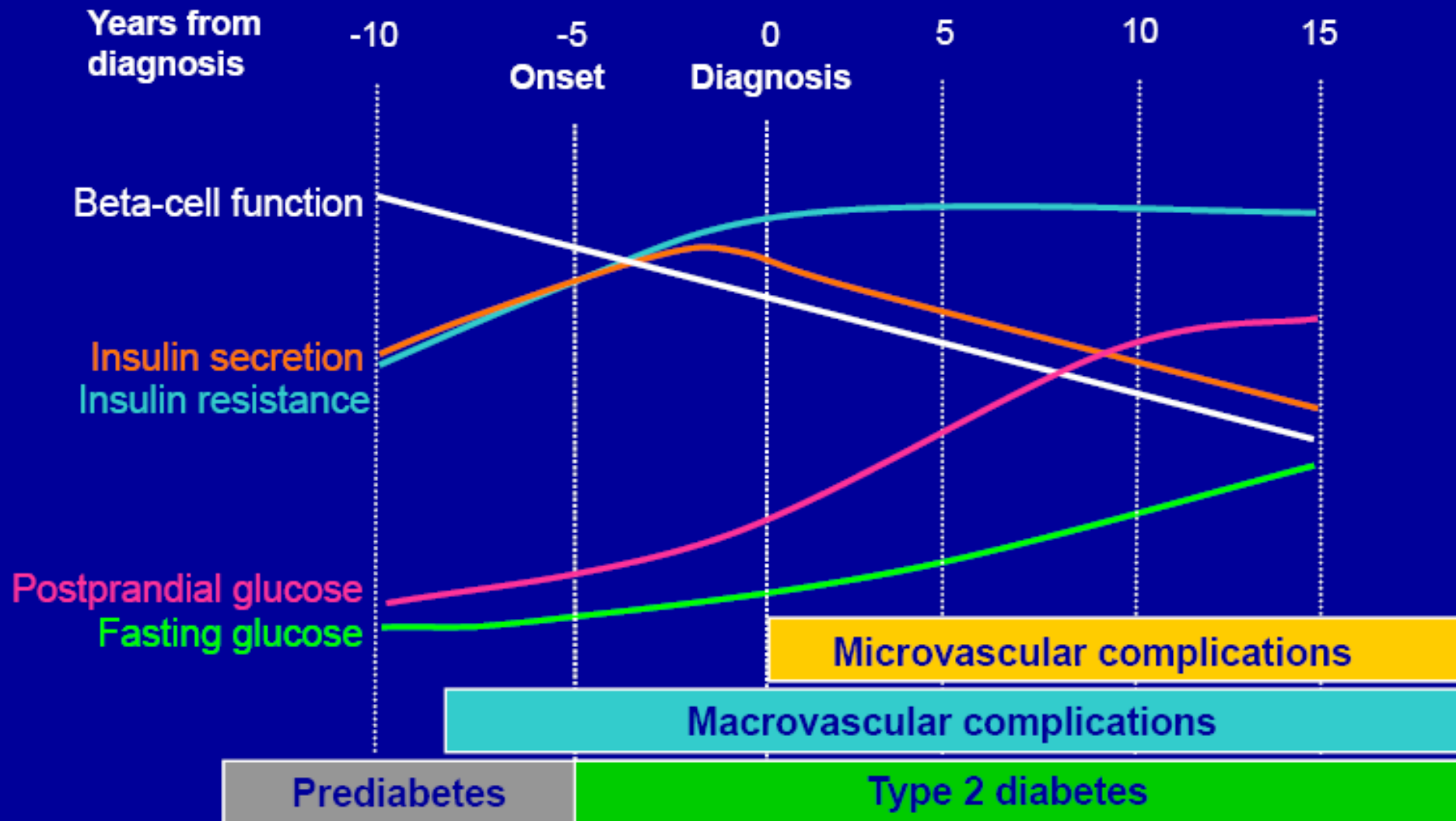
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&

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Natural History of T2DM



Data extrapolated.

Adapted from Holman RR. *Diabetes Res Clin Pract.* 1998;40(Suppl):S21–S25; Ramlo-Halsted BA, et al. *Prim Care.* 1999;26:771–789; Nathan DM. *N Engl J Med.* 2002;347:1342–1349.

Linda



- **51-year-old laboratory technician (works day shifts)**
- **Presents for annual review**
- **Diagnosed with T2D 6 years ago**
- **Married with two sons**

Examination

Height: 1.60 m

Weight: 84 kg

BMI: 33 kg/m²

Waist: 99 cm

BP: 135/90 mmHg

Feet : Sensation adequate,
pulses easily felt

Urinanalysis: No abnormalities noted



Pathology results

HbA_{1c}	10.2%
TC	4.3 mmol/L
TG	2.1 mmol/L
HDL	1.1 mmol/L
LDL	2.7 mmol/L
eGFR	>60 mL/min
ACR	40 mg/mmol
Microalbuminuria	40 µg/24 h

Medications

Metformin	1000 mg bd
Gliclazide	160 mg bd
Aspirin	100 mg daily
Atorvastatin	40 mg daily
Cilazapril	5mg daily

Reviewing A1C target

You previously set an A1c target of $\leq 7\%$ with Linda, but her A1c has been slowly creeping up.

Setting an A1C target

- **1% fall in A1C reduces microvascular complications by 37%,¹ but risk of:²**
 - **Hypoglycaemia ↑**
 - **Weight gain (approx 2kg) ↑**

Initiating insulin therapy

You think you need to start Linda on insulin because of her very elevated A1c, however you decide to check a few other things first.

NOVO NORDISK - BALANCING INSULIN AND DELIVERY.

Brand	Presentation	Schematic Time-Action Profile*	Insulin Profile*
NovoRapid® Rapid-acting insulin aspart (rys)	3mL Penfill® 10mL Vial		Onset: 10-20 minutes Peak: 1-3 hours Duration: 3-5 hours
Levemir® Long-acting insulin detemir (rys)	FlexPen®		Peak: 3-14 hours Duration: Up to 24 hours
Actrapid® Short-acting human insulin (rys)	3mL Penfill® 10mL Vial		Onset: 30 minutes Peak: 1-3 hours Duration: 8 hours
Protaphane® Intermediate-acting human insulin (rys)	3mL Penfill® 10mL Vial		Onset: 1.5 hours Peak: 4-12 hours Duration: 24 hours
PenMix® 30 & Mixtard® 30 (10mL) 30% Short-acting & 70% Intermediate-acting human insulin (rys)	3mL Penfill® 10mL Vial		Onset: 30 minutes Peak: 2-8 hours Duration: 24 hours
PenMix® 10 10% Short-acting & 90% Intermediate-acting human insulin (rys)	3mL Penfill®		Onset: 30 minutes Peak: 2-8 hours Duration: 24 hours
PenMix® 20 20% Short-acting & 80% Intermediate-acting human insulin (rys)	3mL Penfill®		Onset: 30 minutes Peak: 2-8 hours Duration: 24 hours
PenMix® 40 40% Short-acting & 60% Intermediate-acting human insulin (rys)	3mL Penfill®		Onset: 30 minutes Peak: 2-8 hours Duration: 24 hours
PenMix® 50 & Mixtard® 50 (10mL) 50% Short-acting & 50% Intermediate-acting human insulin (rys)	3mL Penfill® 10mL Vial		Onset: 30 minutes Peak: 2-8 hours Duration: 24 hours

Please review Data Sheet before prescribing. Full Data Sheet is available from the Novo Nordisk Customer Care Centre 0800 733 737. *In clinical practice, the duration of insulin action may be shorter or longer than the durations specified. Variations between and within patients may occur depending upon injection site and technique, insulin dosage, as well as diet and exercise. © Registered trademark of Novo Nordisk A/S. Novo Nordisk Pharmaceuticals Ltd, PO Box 51268 Pakuranga, Auckland. www.novonordisk.co.nz

Novo Nordisk Customer Care Centre
0800 733 737
www.novonordisk.co.nz



Lilly Insulin Range*



FULL RANGE NOW FUNDED*

Brand Name ^{1,2}	Type of Insulin (generic name) / Product Description	Presentation	Schematic Action Profile*
Humalog®	insulin lispro Rbe RAPID-ACTING	10mL vials and 3mL cartridges	Onset: 0-15 mins Peak: 1 hour Duration: 3.5-4.5 hours
Humulin® R	insulin neutral (Soluble) SHORT-ACTING	10mL vials and 3mL cartridges	Onset: 30 mins Peak: 2-4 hours Duration: 6-8 hours
Humulin® NPH	isophane (NPH) INTERMEDIATE ACTING	10mL vials and 3mL cartridges	Onset: 1 hour Peak: 4-10 hours Duration: 16-18 hours
Humalog® Mix25®	25% insulin lispro, 75% insulin lispro protamine suspension Rbe PREMIXED INSULIN LISPRO	3mL cartridges	Onset: 0-15 mins Peak: 1 hour Duration: 16-18 hours
Humalog® Mix50®	50% insulin lispro, 50% insulin lispro protamine suspension Rbe PREMIXED INSULIN LISPRO	3mL cartridges	Onset: 0-15 mins Peak: 2 hours Duration: 16-18 hours
Humulin® 30/70	30% insulin neutral, 70% isophane (NPH) PREMIXED INSULIN	10mL vials and 3mL cartridges	Onset: More rapid than NPH alone Peak: 2-12 hours Duration: 16-18 hours

HUMAPEN LUXURA CAN ONLY BE USED WITH LILLY 3mL INSULIN CARTRIDGES, BEFORE PRESCRIBING PLEASE REVIEW THE PRODUCT DATA SHEET.

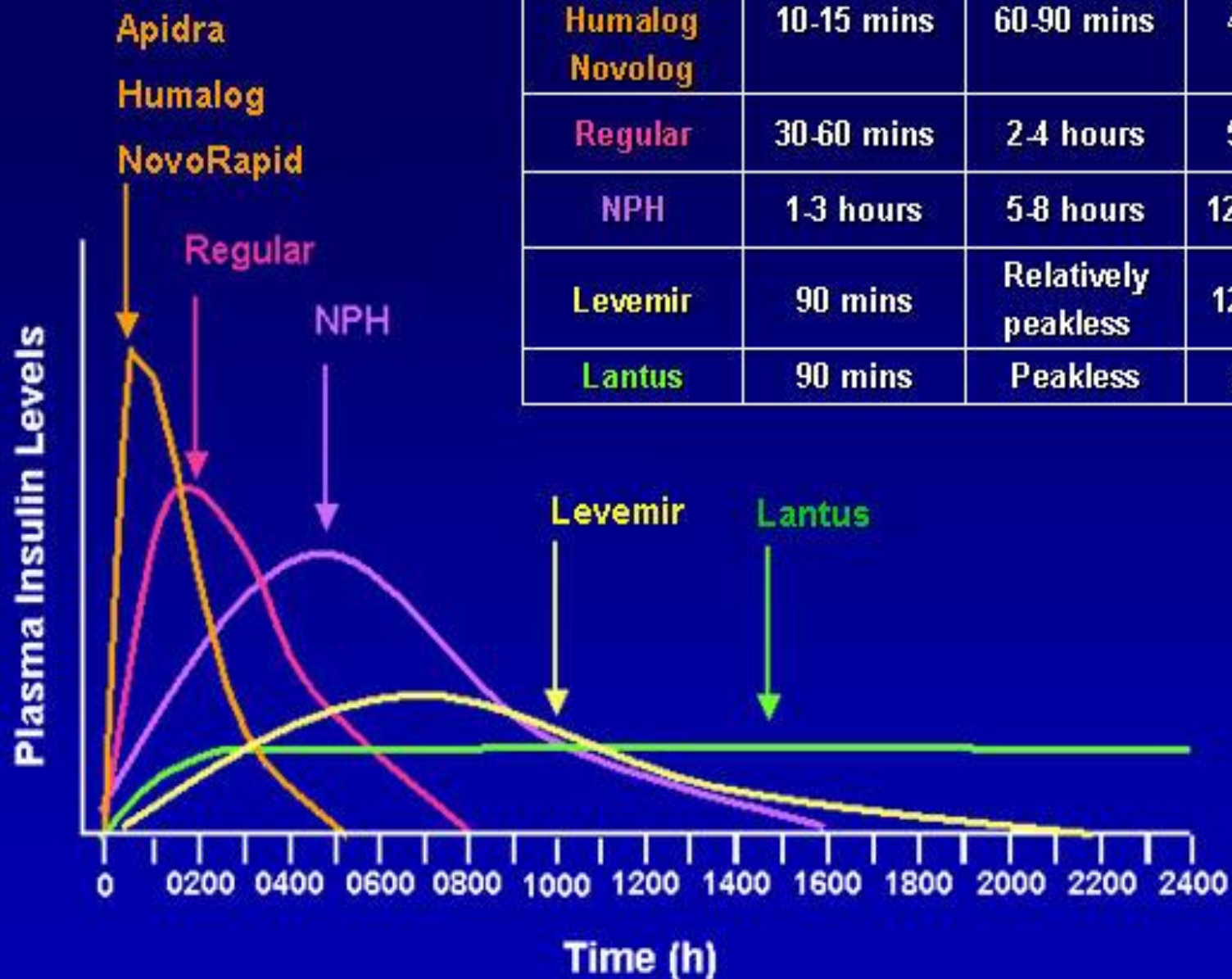
Humapen®
LUXURA



Lilly



Insulin	Onset	Peak	Duration
Apidra Humalog Novolog	10-15 mins	60-90 mins	4-5 hours
Regular	30-60 mins	2-4 hours	5-8 hours
NPH	1-3 hours	5-8 hours	12-18 hours
Levemir	90 mins	Relatively peakless	12-24 hours
Lantus	90 mins	Peakless	24 hours



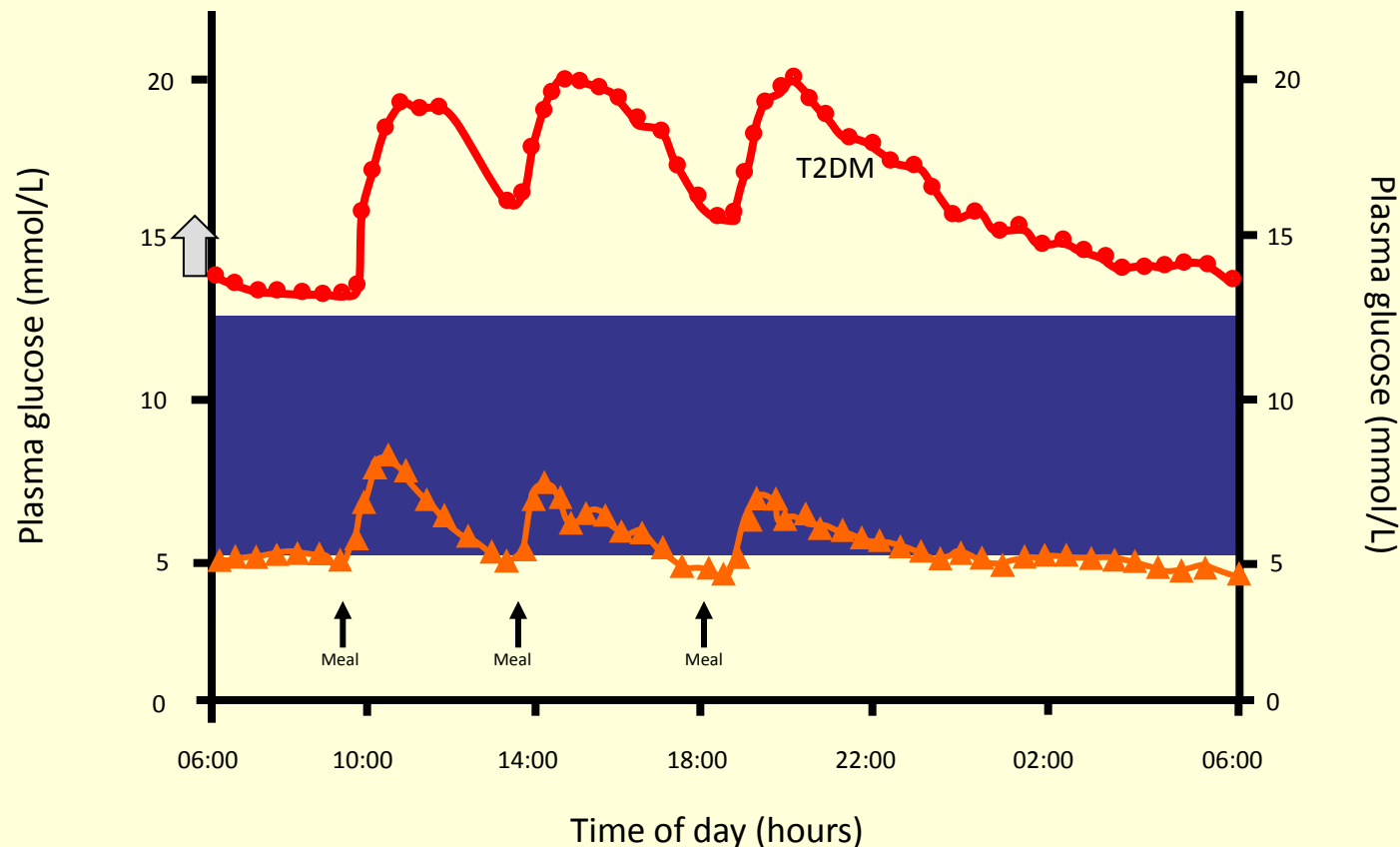
Selecting an insulin

RACGP & ADA/EASD guidelines state...

- ☆ Start with **single daily dose (10 units) of bedtime intermediate-acting insulin or morning or bedtime long-acting insulin^{1,2}**
- ☆ **Rapid-acting insulin is not necessarily needed at initiation¹**
- ☆ **Premixed insulin is not recommended during dosage adjustment period²**
- ☆ **Insulin regimens should be designed taking **lifestyle and meal schedule** into account²**

Why start with basal insulin?

Comparison of 24-hour glucose levels in untreated vs treated patients with diabetes



Adapted from Hirsch I et al. *Clin Diabetes* 2005; 23: 78–86.

Which basal insulin?

	Onset	Peak	Duration	Funded
Intermediate-acting				
Isophane (OD/BD)	1 – 2 h	4 –12 h	16 – 24 h	Yes
Long-acting				
Glargine (OD)	2 – 4 h	None	24 h	Yes
Detemir (OD/BD)	1 – 2 h	6 – 12 h	20 – 24 h	No

12 May

		Breakfast	Lunch	Dinner	Bed		Before Breakfast	After Breakfast	Before Lunch	After Lunch	Before Dinner	After Dinner	Before Bed	Over Night
FRI	Primary Insulin Units					BGL mmol/L	11.0				17.2			
	Other Insulin Units					Carb serves/gram								
SAT	Primary Insulin Units					BGL mmol/L	15.2							
	Other Insulin Units					Carb serves/gram								
SUN	Primary Insulin Units					BGL mmol/L								
	Other Insulin Units					Carb serves/gram								

Notes:

Timing of single insulin dose

Morning or evening is acceptable

Timing depends on blood glucose profile:

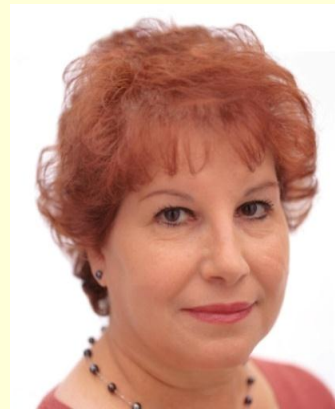
- If fasting BGL is high → give at bedtime
- If fasting BGL on target but evening BGL high → give in morning
- If both are high → give bd NPH or once daily glargine



* Usually the fasting BG target is ≤ 6.0 mmol/L; however, targets may vary from one person to the next.

Linda's summary to this point

- **Elevated A1C on optimal doses of two (2) OHAs**
- **Lifestyle measures reviewed, no secondary causes of hyperglycaemia**
- **Insulin therapy is appropriate**
- **Basal insulin is most appropriate at this time**
- **Bedtime injection of 10 U insulin NPH/ Glargine to reduce Linda's fasting BGL**
- ☆ **Up-titration to be self-managed in consultation with Practice Nurse**
- **Linda to return for review in 3 months with lab tests completed prior to visit**



Dose adjustment – first fix fasting

Two dose adjustment schedules possible:

1. SLOW SCHEDULE (CAN BE PATIENT-LED)

Increase by 2 units of insulin every 3 days

continue until fasting BGL is ≤ 6.0 mmol/L

Adapted from RACGP 2009/10 and Davies et al 2005.

Increase dose only if FBG >4 mmol/L and accordingly decrease dose if FBG is <4 mmol/L.

Titration reviewed by HCPs at each contact.

Dose adjustment – first fix fasting

2. FAST SCHEDULE (PHYSICIAN-MANAGED)

Increase by 2–8 units of insulin depending on fasting BGL over previous 2–3 days

Mean fasting blood glucose (mmol/L)	Increase in insulin dose
<4	* See below
4–5.9	No change
6–6.9	2 units
7–7.9	4 units
8–10	6 units
>10	8 units

Starting dose 10 units, adjust dose twice weekly to reach the target FBG of <6mmol/L

Insulin dose may be decreased (small decreases of 2 to 4 units) if there is severe hypoglycaemia (requiring assistance) or if BGL <3.0 mmol/L in preceding week.

Do not increase insulin dose if fasting BGL <4 mmol/L at any time in preceding week.

Linda: 3 month review after starting insulin

- **Medication:**

Insulin NPH 30 U at bedtime

Metformin 1000 mg bd

Gliclazide 120 mg morning

Aspirin 100 mg daily

Atorvastatin 40 mg daily

cilazapril 10 mg daily



Review: 3 months

Linda's A1c is 8.9% (down from 10.2%) – been on 'slow' titration schedule

18 August

[illegible]

Next steps

You organise for the Practice Nurse to work with Linda to more rapidly uptitrate the dose of insulin NPH to achieve a FBG of ≤ 6.0 mmol/L.

You also ask the Practice Nurse to discuss hypoglycaemia and sick day management with Linda. Linda is requested to return to you in 3 months time.

Review: 6 months

- **Linda's FBG readings ≤ 6 mmol/L**
- **OHAs unchanged**
- **Insulin NPH 45 U**
- **Her BP, urinalysis – all okay**
- **Pathology results:**
 - **A1c 7.7%**
 - **No evidence of microalbuminuria, and a satisfactory lipid profile**



Review: 6 months

Linda's A1c is 7.7% (down from 8.9%) – been on 'fast' titration schedule

20 November

[illegible]

Reviewing OHA use

Linda is doing well on basal insulin and had no problems with the rapid up-titration process. Linda is now stable at 45 units of basal insulin daily. Linda asks if she still needs her OHAs.

Linda's OHAs

- Don't stop OHAs immediately
 - Stopping OHAs may require more insulin
 - Get A1c under control and consider stopping OHAs later
- Understand what each drug does
 - Metformin [& glitazones] = insulin sensitisers
 - should be continued
 - Sulphonylureas = insulin secretagogues
 - will need to be removed when β -cells stop secreting insulin
- Discontinue if side effects are an issue
 - Metformin:
 - SU:
- Glitazone: fluid retention, weight gain, cardiovascular risks

1. Phillips PJ. Medicine Today 2007; 8(3): 23-34; 2. Phillips PJ. Aust Fam Physician, 2006; 35: 975-78; 3. Phillips PJ. Medicine Today 2007; 8(6): 43-52; 4. Nathan D et al. Diabetologia 2008; 52: 8-11; 5. Nathan D et al. Diabetologia 2006; 49: 1711-21.

Find hidden hypers

- ✓ Fasting preprandial BGL on target (4 – 6 mmol/L)
- ✓ 2 hour postmeal BGL on target (4 – 8 mmol/L)

Is A1C 6-12 weeks later at target?

Yes → Continue with current schedule

No → Find and fix the hidden hyperglycaemia

a) check 2 hours after breakfast & before bed
to check for morning and evening postprandial
hyperglycaemia

b) check during the night (only if really necessary!)

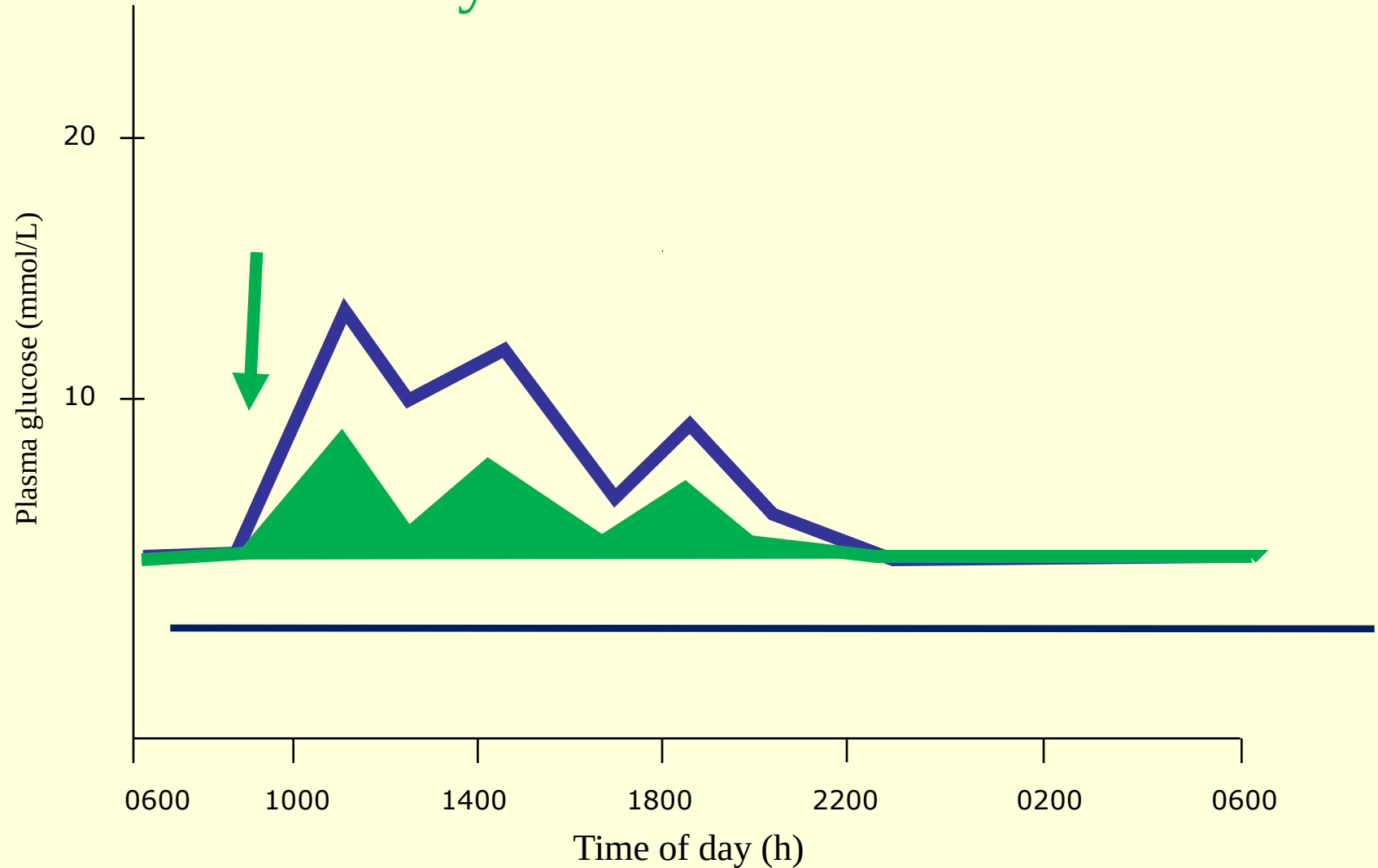
Improving glycaemic control

You inform Linda that her BGLs 2 hours after breakfast are consistently high indicating hyperglycaemia after breakfast.

Adjusting insulin therapy

You discuss options with Linda and agree that modifying the insulin schedule is the best option for her.

Then Tackle The Meal Responsible for the Greatest Glycaemic Excursion

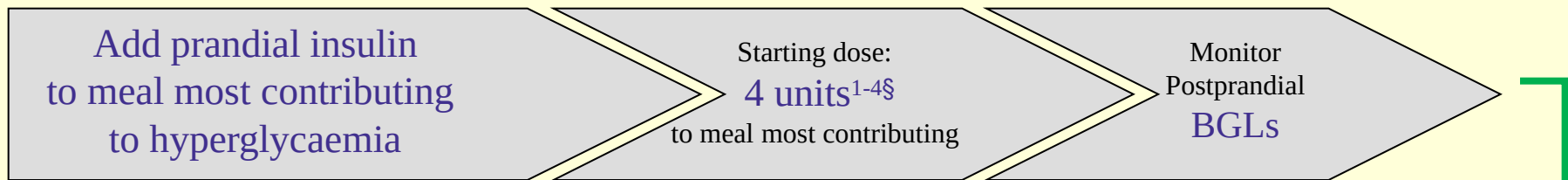


Starting prandial insulin

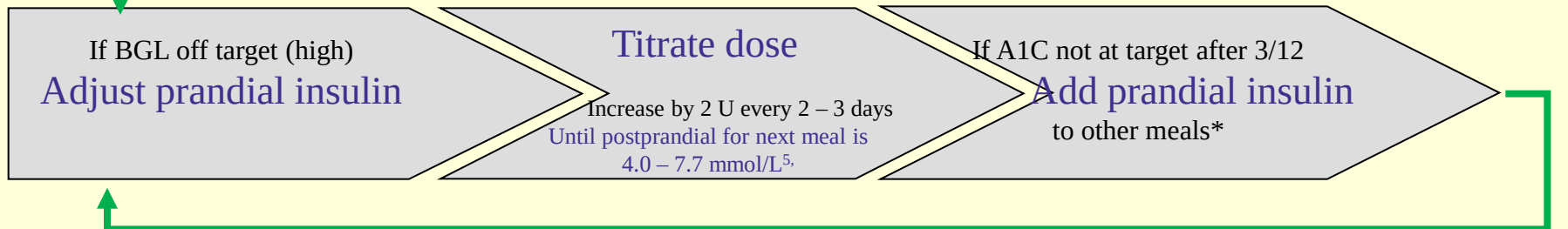
You discuss treatment options and you both agree that adding a single dose of prandial insulin prior to the meal contributing most to hyperglycaemia would be appropriate as she finds it difficult to change her morning eating habits and exercise schedule.

Start prandial insulin at 4 Units

Step 1:



Step 2:



§ These dosing guidelines are based on recommendations from a number of authors. They are provided for guidance only. All insulin dosing and titration / adjustments require professional judgment and should be individualised to patient circumstances .

Once prandial insulin is added, insulin secretagogues may be discontinued

1. Garg S, et al. J Fam Pract April 2006. Suppl_S1-S12.
2. Raccach D, et al. Diabetes Metab Research and Reviews. 2007; 23: 257-264.
3. Tibaldi J, American Journal of Medicine. 2008; 121 (6A) S20-S29
4. Nathan D, et al. Diabetologia 2006; 51:8-11.
5. RACGP/Diabetes Australia. Diabetes Management in General Practice, 2009/10.

Reviewing BGLs: 4 weeks later

Linda shows you her BGL readings after 4 weeks of prandial insulin (15U) at breakfast

10 Feb

Units of rapid-acting insulin

Units of basal insulin

Before Breakfast

After Breakfast

After Lunch

Before Bed

Before Breakfast

After Breakfast

Before Bed

Date	11/6	Breakfast	Lunch	Dinner	Bed	Before Breakfast	After Breakfast	Before Lunch	After Lunch	Before Dinner	After Dinner	Before Bed	Over Night
MON	Primary Insulin Units	18			45	BGL mmol/L	5.9	7.2					
	Other Insulin Units	15				Carb serves/gram							
TUE	Primary Insulin Units				45	BGL mmol/L			6.2			4.8	
	Other Insulin Units	15				Carb serves/gram							
WED	Primary Insulin Units				45	BGL mmol/L	6.8	6.3				5.4	
	Other Insulin Units	15				Carb serves/gram							
THU	Primary Insulin Units				45	BGL mmol/L	5.2	6.9				5.2	
	Other Insulin Units	15				Carb serves/gram							

	Breakfast	Lunch	Dinner	Bed	Before Breakfast	After Breakfast	Before Lunch	After Lunch	Before Dinner	After Dinner	Before Bed	Over Night
FRI	Primary Insulin Units			45	BGL mmol/L							
	Other Insulin Units	15			Carb serves/gram							
SAT	Primary Insulin Units			45	BGL mmol/L	5.0	7.1				5.8	
	Other Insulin Units	15			Carb serves/gram							
SUN	Primary Insulin Units			45	BGL mmol/L	4.8	5.0					5.9
	Other Insulin Units	15			Carb serves/gram							

Notes:

Much better!

Linda: summary

- Linda self-titrated insulin dose from 10 U to 45 U (slow titration schedule initially and changed to rapid titration)
- 6 months after starting basal insulin Linda's fasting BGLs were on target
- Hidden hyperglycaemia suspected with A1C slightly elevated
- Post-breakfast hyperglycaemia identified with more regular BGL testing
- Prandial insulin considered appropriate treatment
- 15 U at breakfast improved glycaemic control
- ☆ Regular review with Practice Nurse
- Linda to return for review in 3 months



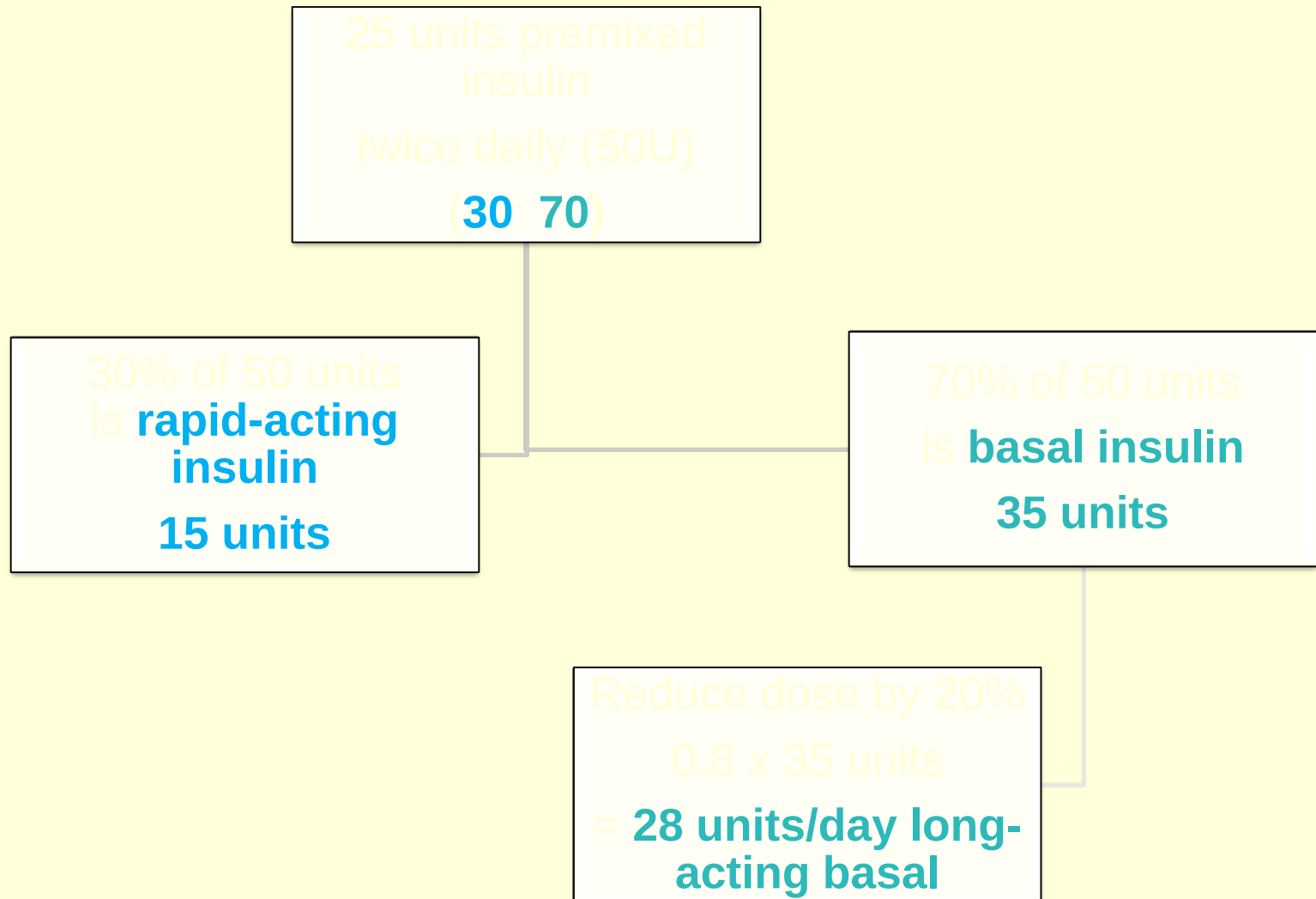
Practice points

- Don't delay insulin initiation
- Keep it simple for you and patient – 10 units basal insulin
- Ensure patient has expectation that basal dose will increase and what the dose may end up at
- Titrate! Fix the fasting first! Then look for hidden hypers

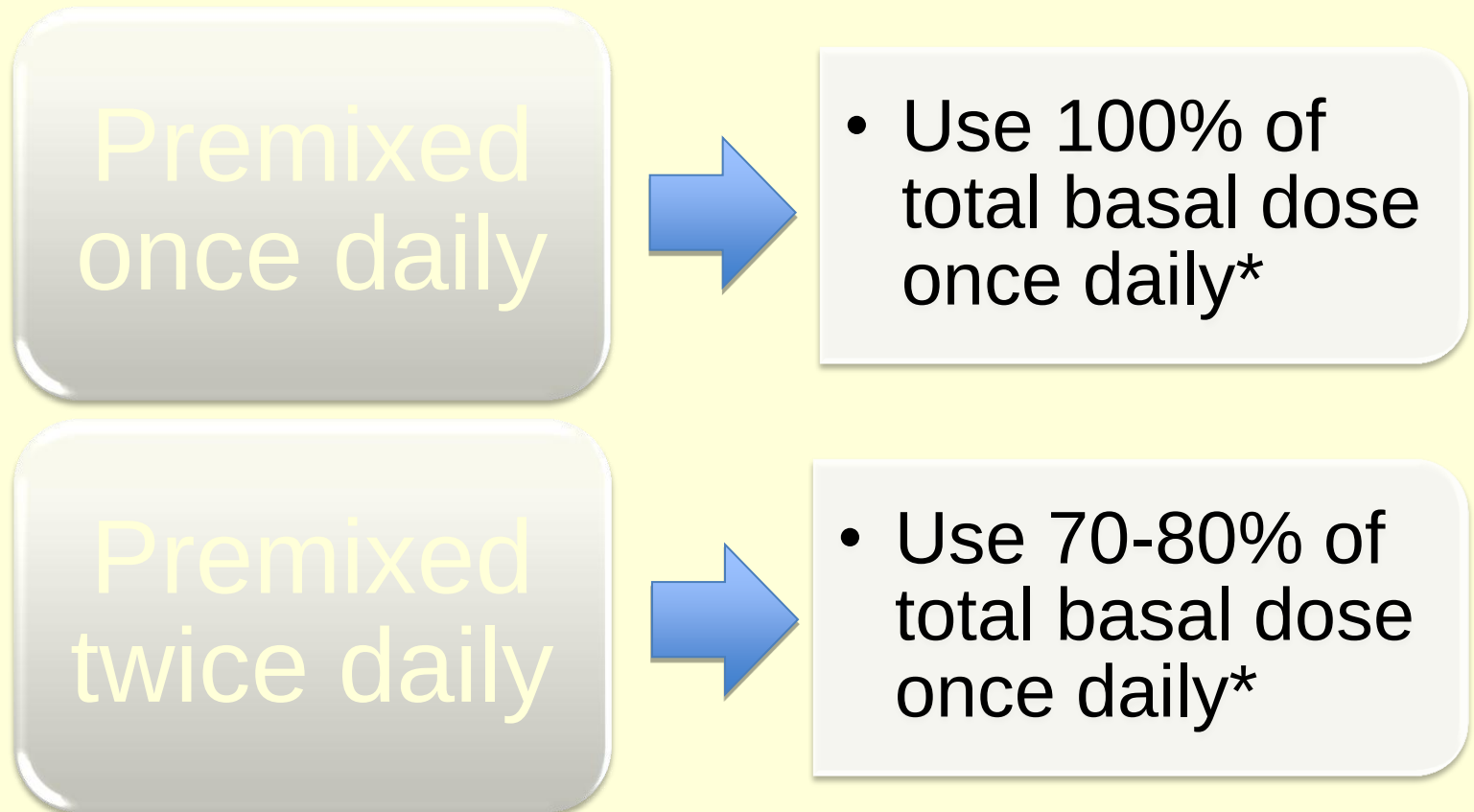
Insulin Switch- NPH to Long acting analogues (Glargine or Detemir)

- From once daily NPH
1 unit of NPH= 1 unit of Long acting analogue
- From twice daily NPH
80 % of total daily (NPH) dose= Units of Long acting analogue

Premixed BD to long-acting basal Insulin



Converting from premixed to long-acting basal insulin



*Fix the fasting BG then review the need for prandial insulin

Insulin Switch- NPH to Twice daily preMix insulins

eg; Penmix 30/70, HumalogMix 25/75

- If already on twice daily NPH dose, initiate same dose of Premix insulin dose twice daily
- If on once a day NPH insulin, you may consider splitting the dose twice daily.
- Either $2/3^{\text{rd}}$ in the morning and $1/3^{\text{rd}}$ in the evening with meals

eg; Patient is on 60 units of NPH insulin, therefore you can split the dose as 40 units of premix insulin mane and 20 units of premix insulin in the evening.

Insulin Switch- Twice daily PreMix insulins to Basal –bolus regimen

- Calculate Basal Insulin dose (eg; Glargine/Detemir)

1. Determine Total daily dose of NPH

eg: Patient on Penmix 30 insulin 50 units twice daily
(NPH 35 units and Regular insulin 15 units twice daily)

Lantus/Levemir dose would be =80% of 70 Units of
NPH=56 units

- Calculate bolus insulin dose (eg; Apidra, Novorapid or Humalog)

Above patient will need = total daily dose of regular insulin
÷ 3, $30/3 = 10$ units

Insulin Switch-

Basal insulin to Twice daily PreMix insulins

eg; Penmix 30 or HumalogMix 25

- Calculate the total daily basal insulin dose
2 options;
 - ▶ give $\frac{2}{3}$ rd in the morning with breakfast and $\frac{1}{3}$ rd with dinner meal
or
 - ▶ give $\frac{1}{2}$ with breakfast and $\frac{1}{2}$ with dinner meal

eg: Patient takes 46 units of NPH at night and 34units of NPH at breakfast

Therefore, either 40 units twice daily or 54 units mane and 26units evening of Premix insulin

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“The healthiest part of a donut is the hole. Unfortunately, you have to eat through the rest of the donut to get there!”

Thank you.

Acknowledgement

- A/Prof Tim Kenealy
- Dr Brandon Orr- Walker