

Insulins

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Insulin Product*	Administration	Onset†	Peak†	Duration†
Rapid-acting analogues				
Humalog (insulin lispro)	0-15 minutes before meals (ideally); may be given up to 20 minutes after start of meals	10-15 min	1-1.5 h	4-5 h
NovoRapid (insulin aspart)	5-10 minutes before meals	10-15 min	1-1.5 h	4-5 h
Short-acting				
Humulin R Novolin ge Toronto Hypurin Regular (pork)	30-45 minutes before meals	0.5-1 h	2-4 h	5-8 h
Intermediate-acting				
Humulin N Novolin ge NPH Hypurin NPH (pork)	Usually once or twice daily	1-3 h	5-8 h	Up to 18 h
Long-acting analogues				
Lantus (insulin glargine)	Once daily (usually at bedtime)	1.5 h	None	24 h
Levemir (insulin detemir)	Once or twice daily	1-2 h	6-8 h	Up to 24 h
Premixed				
Humalog Mix25	0-15 minutes before meals	10-15 min	Dual	Up to 18 h
Humulin 30/70 Novolin ge 10/90, 20/80, 30/70, 40/60, 50/50	30-45 minutes before meals	0.5-1 h	Dual	Up to 18 h

* Humulin L, Humulin U, Iletin Regular, Iletin NPH, Iletin Lente, Novolin ge Lente, and Novolin ge Ultralente have been discontinued.

† Onset, peak and duration values are estimates only.

Insulins

- **Long = Basal**

- NPH (Humulin N[®]/Novolin NPH[®])
- Glargine
 - 100u/mL – Lantus[®]
 - 100u/mL - Basaglar[®] (biosimilar)
 - 300u/mL - Toujeo[®]
- Detemir (Levemir[®])
- Degludec (Trusiba[®])

- **Short = Prandial**

- Short
 - Regular (Humulin R)
 - Novolin ge Toronto
- Rapid
 - Lispro (Humalog[®])
 - Aspart (NovoRapid[®])
 - Glulisine (Apidra[®])

- **Premixed**


- 30/70 (and 10/90, 20/80, 40/60, 50/50)
- Humalog Mix-25, NovoMix-30 etc

Which to choose?

Clinical Priorities

Basic Concepts

- Hyperglycemia = Chronic
Hypoglycemia = Acute
 - So, go after **Hypo's** first!
- Fed: 6h/24h = 25%
- Fasting: 18h/24h = 75%
 - So, go after **Fastings** first!
- AM affects PM & HS
 - So, go after **AM** first!

1. ?Any hypo's?- fix 'em!
then,
 2. FBS AM
 3. FBS Noon
 4. FBS PM
 5. FBS HS
then,
 6. 2h PPG AM
 7. 2h PPG Noon
 8. 2h PPG PM
- 

Insulins

• Long – Basal

- NPH / Humulin N
- Glargine (Lantus/Basaglar® & Toujeo®)
 - (Basaglar® = a Lantus® biosimilar)
- Detemir (Levemir®)
- Degludec (Trusiba®)

• Short – Prandial

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• Premixed

- 30/70 (and 10/90, 20/80, 40/60, 50/50) (R + NPH)
- Humalog Mix-25, NovoMix-30 (Rapid + NPH)

Now, which to choose?

Rational Prescribing

- Four priorities of Rational Prescribing:

1. Benefit



2. Harm



3. Cost



4. Convenience

Long – Basal Insulins

- **Benefit:**

- NPH = glargine = detemir = degludec = NPH

- Equivalent

- Morbidity benefits, A1c lowering effect

- Despite the marketing:

- Kinetics don't affect overall efficacy:

- Slowest absorption: Thigh (best for basal insulins)

- Fastest absorption: Abdomen (best for prandial insulins)

- *Lots* of glargine is injected BID

- NPH *can* be used QHS for many (esp. CKD)

Long – Basal Insulins

- **Harm:**
 - All: Hypoglycemia
 - NPH:
 - Peak effect at ~ 8hrs (4-10hrs)
 - Greater risk of hypoglycemia vs glargine
 - Small difference
 - Insulin analogues:
 - Glargine / Detemir:
 - Increased breast cancer risk?
 - » Glargine: 1.4 fold higher risk vs NPH
 - » Detemir – more research needed
 - Degludec: too new - unknown

1. Lipska KJ, et al. Association of Initiation of Basal Insulin Analogs vs Neutral Protamine Hagedorn Insulin With Hypoglycemia-Related Emergency Department Visits or Hospital Admissions and With Glycemic Control in Patients With Type 2 Diabetes. *JAMA*. 2018;320(1):53–62. doi:10.1001/jama.2018.7993. <https://jamanetwork.com/journals/jama/fullarticle/2685850> Accessed Mar 12/19
2. Rosenstock J, et al. Reduced risk of hypoglycemia with once-daily glargine versus twice-daily NPH and number needed to harm with NPH to demonstrate the risk of one additional hypoglycemic event in type 2 diabetes: Evidence from a long-term controlled trial. *J Diabetes Complications*. 2014;28(5):742-9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4802045/> Accessed Mar 12/19
3. Wu, JW et al. Long-Term Use of Long-Acting Insulin Analogs and Breast Cancer Incidence in Women With Type 2 Diabetes. DOI: 10.1200/JCO.2017.73.4491 *Journal of Clinical Oncology* 35, no. 32 (November 10 2017) 3647-3653. <https://ascopubs.org/doi/full/10.1200/JCO.2017.73.4491>

Long – Basal Insulins

- **Cost:**

- **All:** covered under ODB

- **N.B.** No Rx *required* for any insulins – all Schedule II (behind the counter)

- NPH: ~ **\$59**

- Glargine (Lantus[®]: ~ \$114) (Basaglar[®]: ~ \$87)

- Detemir (Levemir[®]): ~ \$114

- Degludec ~ \$155

- **Convenience:**

- All sc injections, via penfills

- All QD – BID

Bottom Line – **Basal Insulins**

- All equivalent
- Choose therapy based on cost (NPH)
 - For the very small proportion suffering from hypoglycemia due to the peak effect of NPH or lamenting BID dosing, consider glargine or detemir.

Starting Basal Insulin

- Fancy Way:
 - calculate unit/kg dose = 0.1 - 0.2u/kg/day sc
 - Risk hypoglycemia on first dose – lose your patient's buy-in forever.
- Primary Care Method:
 - Initiate 5u or 10u qhs sc
 - Titrate by **1-2u q3-4d until AM FBS = 4 - 7 mmol/L**
 - 10% titrations
 - If dose = 30's – increase by 3 units
 - If dose = 40's – increase by 4 units etc.
 - Alternative: 1 unit every day till AM FBS = 4-7 mmol/L

Rx

1. NPH

- Sig: 10u qhs sc or ud
- M: 1 box penfills
- Repeat x 12

2. Needle tips – 28G - 6mm

- Sig: ud
- M: 1 box
- r x 12
- N.B. (Please teach pt pen technique)

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- **Premixed**

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Short – Prandial Insulins

- **Efficacy**

- Equivalent reduction in morbidity, HgbA1c

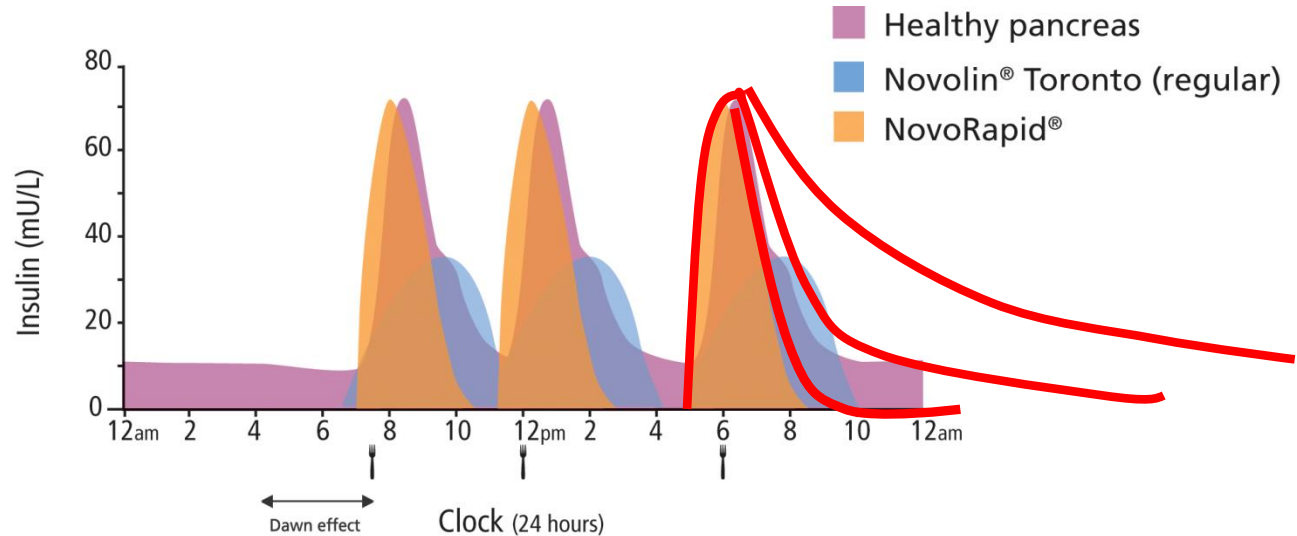
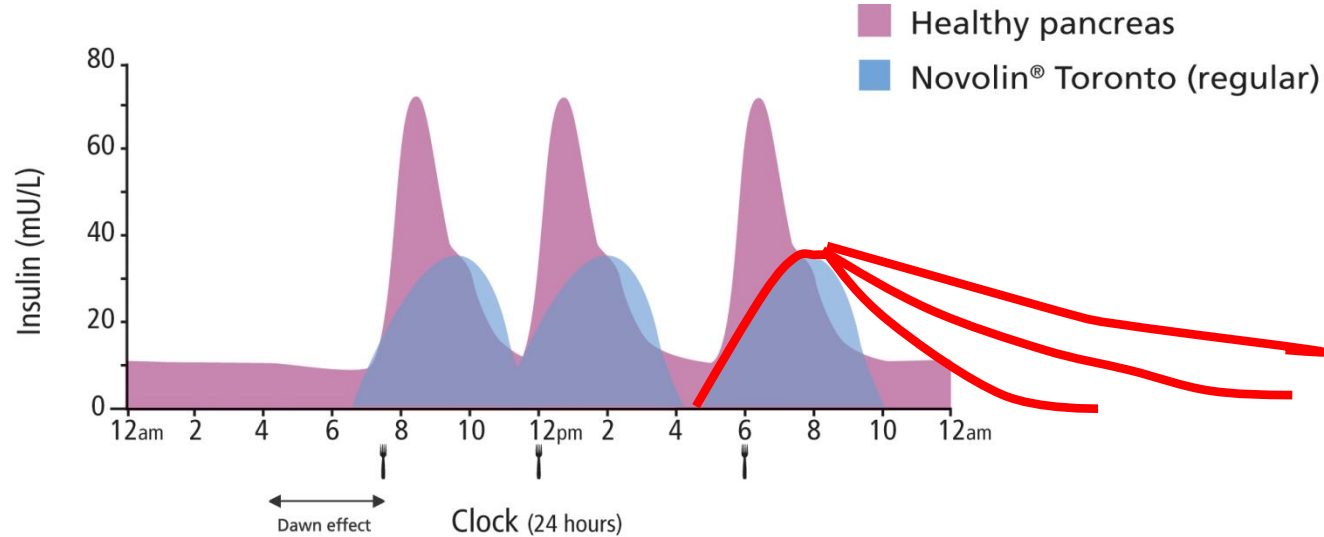
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Short – Prandial Insulins

- **Toxicity**

- Hypoglycemia
- Rapid insulins better reflect physiological effect of pancreatic insulin (vs Regular insulin)

- **More important in CKD (=longer insulin $t_{1/2}$)**



Short – Prandial Insulins

- **Cost**

- All covered under ODB

- Regular (R) / Toronto ~ \$40
- NovoRapid (aspart) ~ \$56
- Humalog (lispro) ~ \$55
- Apidra (glulisine) ~ \$48

- **Convenience**

- All injected with meals

- Regular insulin injected 30-45 min before meal

- Rapid insulin can be with meal

- Reduced risk of hypo if taken if pt injects, then forgets to eat
- Easier / more intuitive Carb Counting

Bottom Line – Prandial Insulins

- All equivalent
- Choose therapy based on cost / familiarity
 - Rapid insulins reflect pancreatic insulin release better than [R]/Toronto.
 - The worse the CrCL, the more important this fact becomes.

Starting Prandial Insulin

- Fancy Way:
 - Total dose: 0.5u/kg
 - 40% of total dose - basal insulin qHS
 - 20% of total dose TID with meals (60%) – prandial insulin 15-30 min before meals
 - Eg. 80kg pt – 0.5u/kg = 16u basal (40%); 8u TID (20% x 3 = 60%)
- Primary Care Method:
 - Start 5u sc with meals
 - Titrate AM to HS to target
 - Monitor 2h PPG
 - Start injection TID or only single meal as required
 - If poor control: inj TID sc; If mediocre control: inj qAM sc
 - Still aim for ~ 2/3^{rds} split (40% basal / 60% prandial)

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Pre-mixed Insulins

Premixed				
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Humulin 30/70 Novolin ge 10/90, 20/80, 30/70, 40/60, 50/50	30-45 minutes before meals	0.5-1 h	Dual	Up to 18 h

- NovoMix-30 = Humalog Mix25 (equivalent)
- Efficacy
 - All ~ 30% short / 70% long
- Toxicity
 - Hypoglycemia (less with Rapid vs Regular insulin as CrCL drops)
- Cost: ~\$53 (Rapids) ~\$40 (Regular 30/70)
- Convenience ~ Rapids can be injected with/after meal

Starting Pre-mixed Insulins

- Fancy Way:
 - Estimate total starting daily dose
 - (0.3-0.6 units/kg)
 - Divide daily dose:
 - 2/3 before breakfast; 1/3 before supper
- Primary Care Method:
 - From scratch: Start 5-10u QD-BID and titrate
 - From other insulins: Calculate approximate amount of basal and prandial units and divide 2/3rd - 1/3rd AM and PM

Pearls

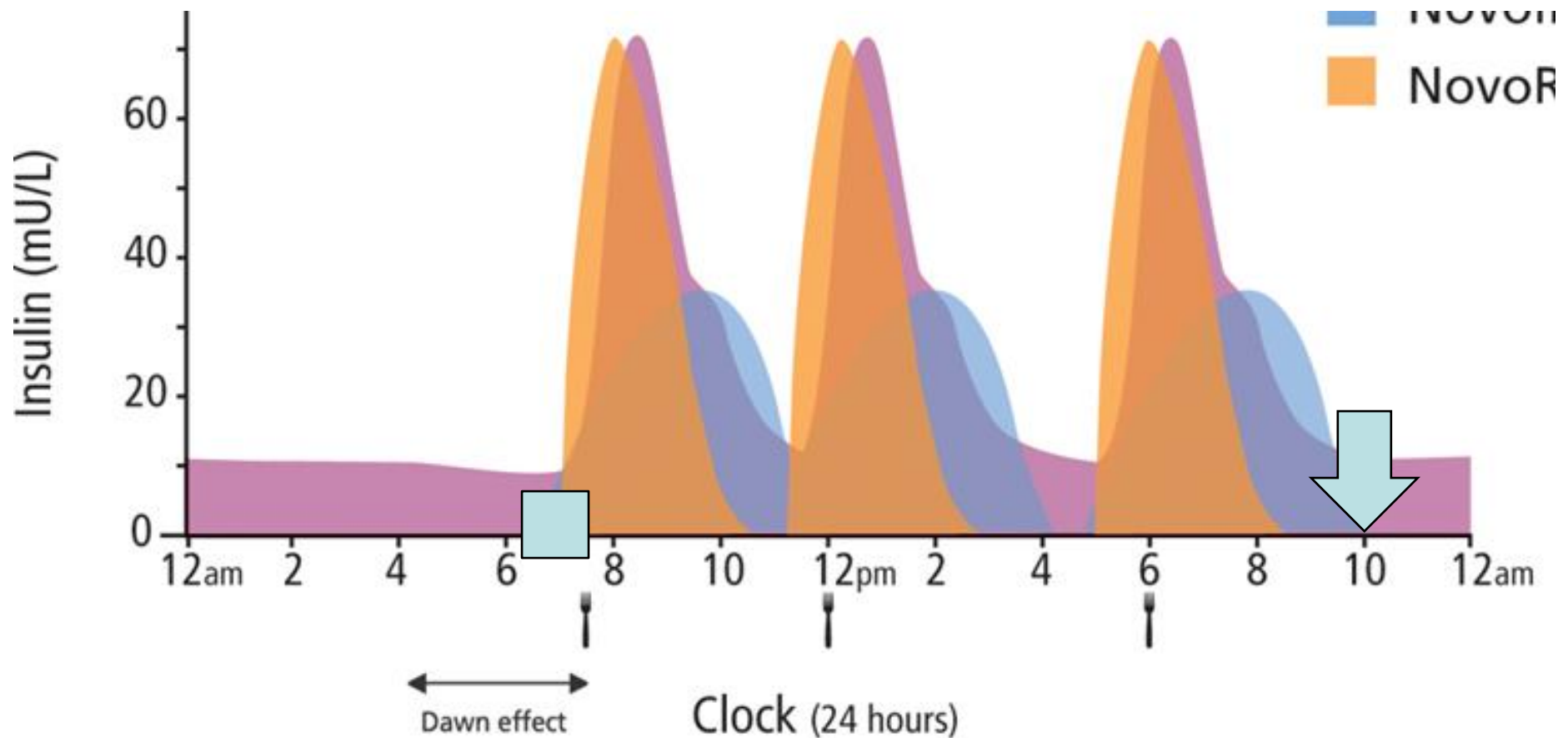
- Insulin is 2nd line after metformin when a1c is far from target (No need to save it for last!)
- Better than adding a 3rd PO drug
 - Better efficacy, lower toxicity, better studied
- Improve buy-in from patient:
 - “Natural” supplement
 - Only BID glucochecking at alternating times required:
 1. Pre-Breakfast + Post-Breakfast,
 2. Pre-Breakfast + Pre-Lunch,
 3. Pre-Breakfast + Post-Lunch,
 4. Pre-Breakfast + Pre-Supper,
 5. Pre-Breakfast + Post-Supper,
 6. Pre-Breakfast + Pre-Bedtime
 7. *Repeat*

Pearls (cont'd)

- D/C secretagogues after starting insulin to reduce risk of hypo's.
 - Eg. Sulfonylureas, meglitinides
 - Black box warning against combo with glitizones!
(Actos, Avandia)

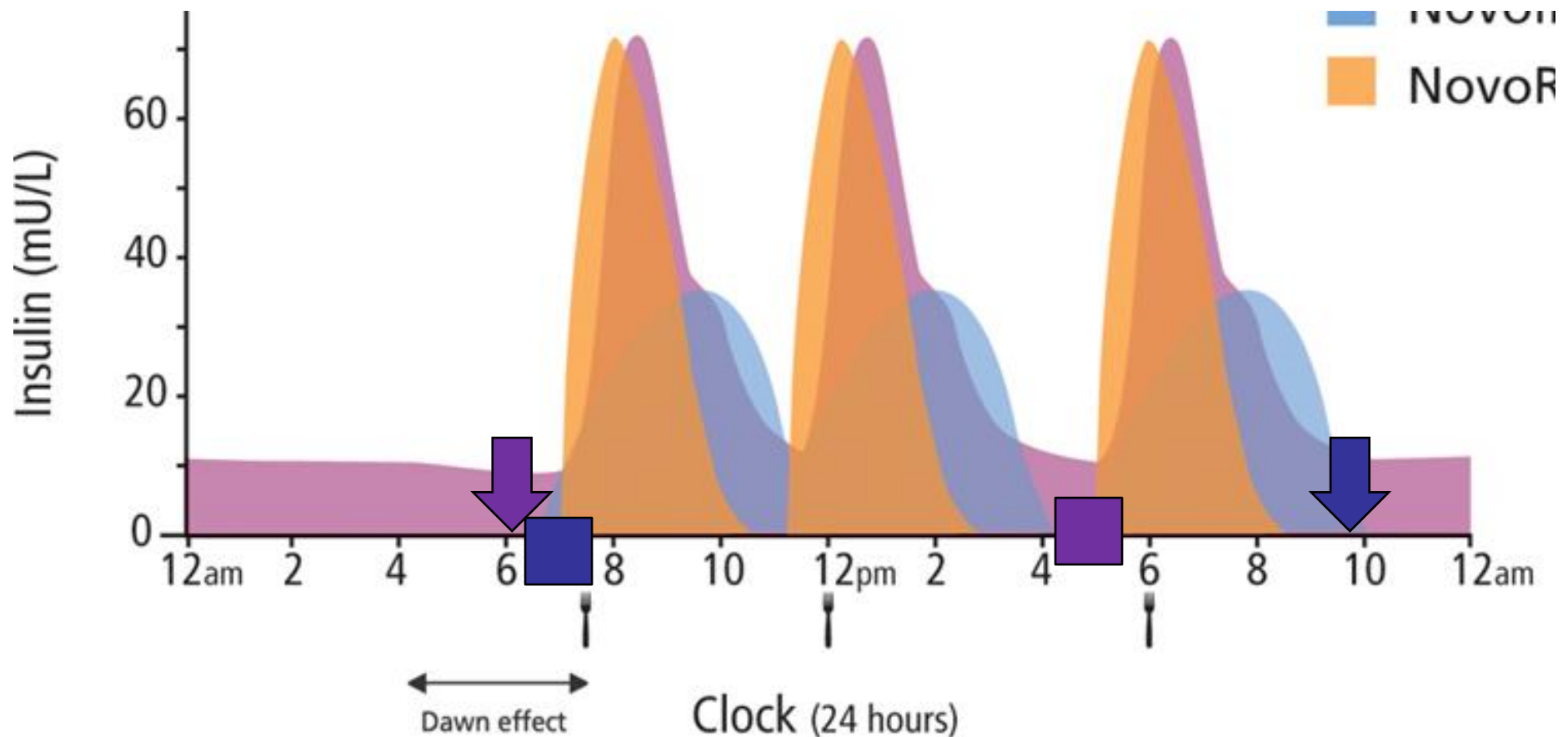
Glucose monitoring

NPH 45u QHS



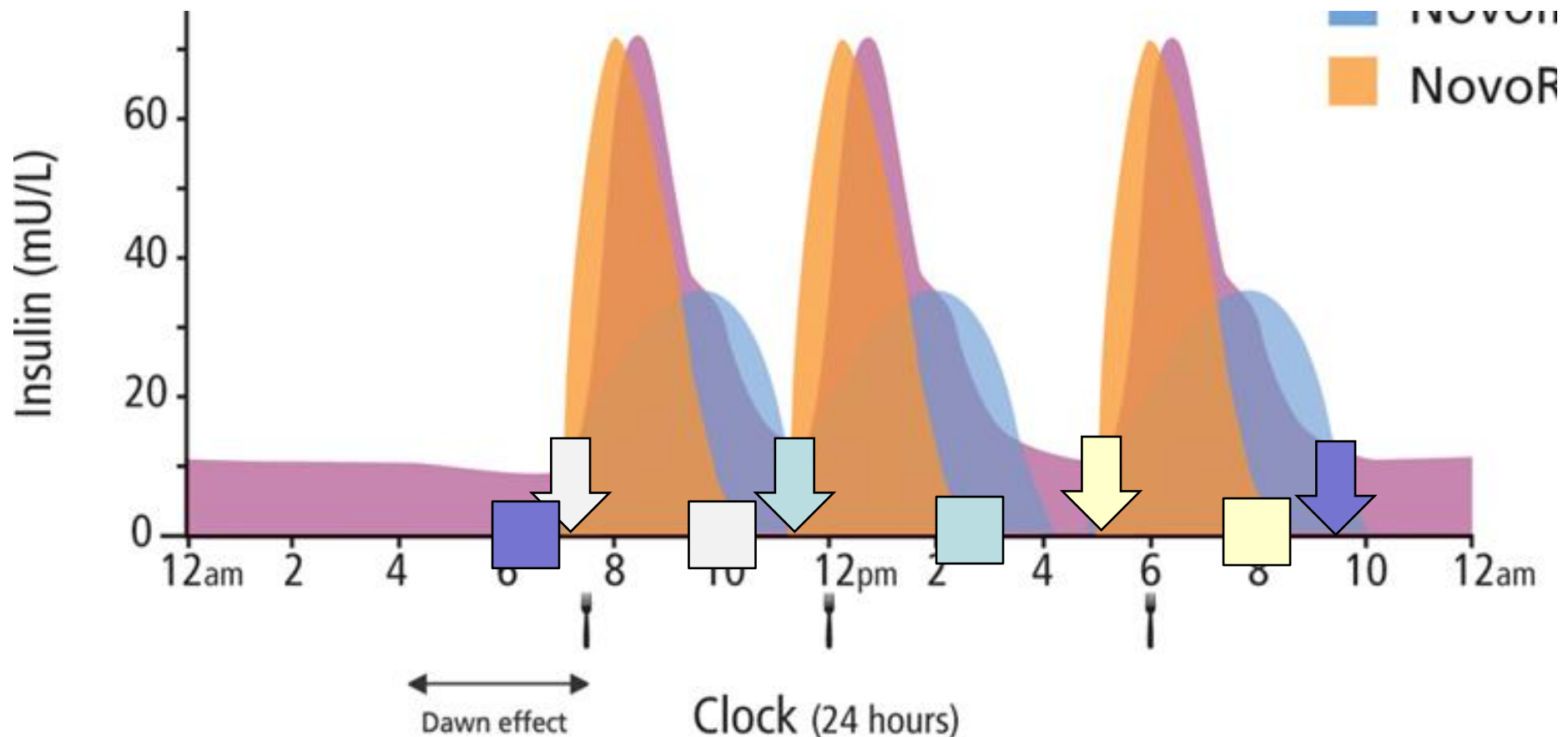
Glucose monitoring

NPH 33u BID



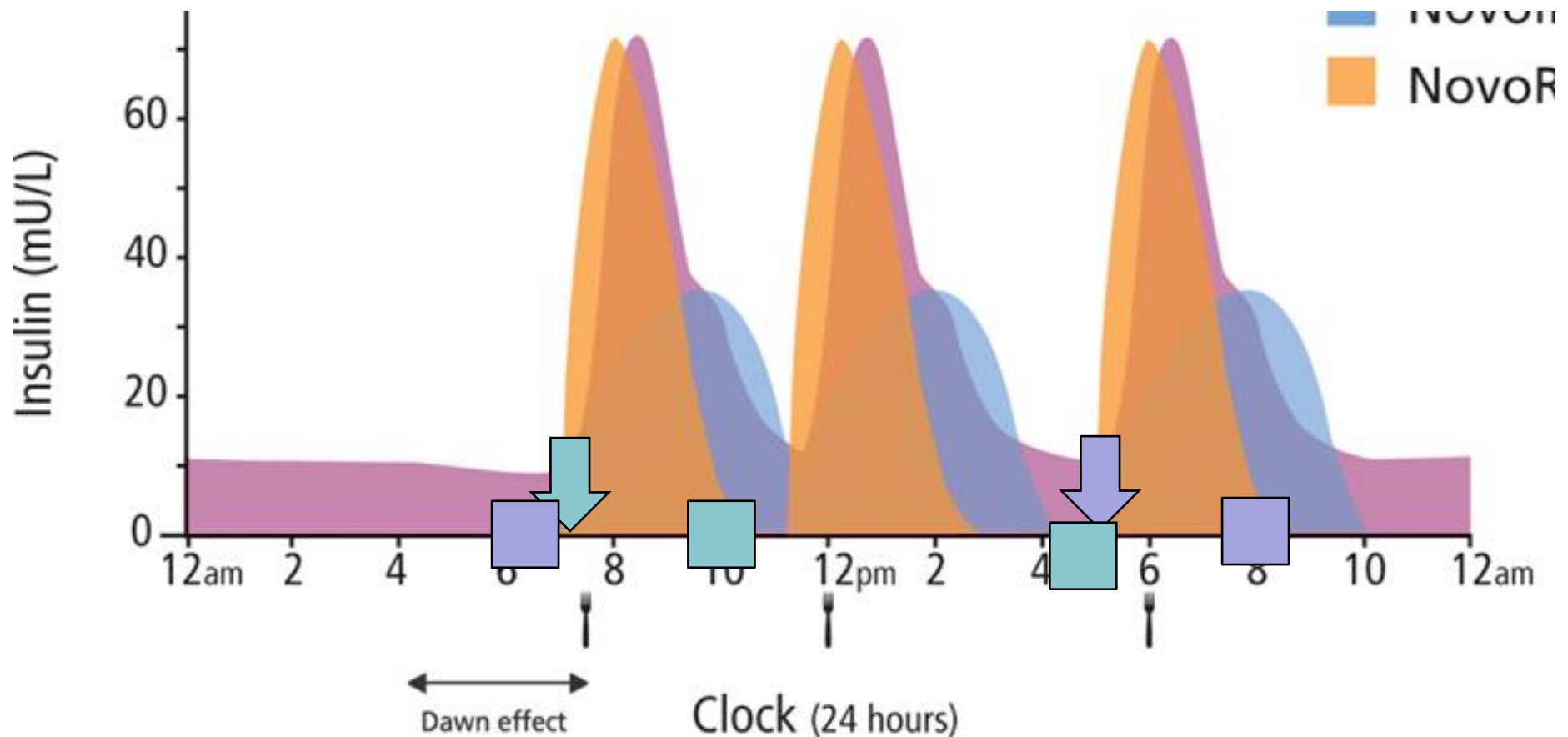
Glucose monitoring

NPH 40u QHS + Glulisine 12u TID cf



Glucose monitoring

Novomix30 – 20u BID



Questions?

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