

# Welcome to UVM ECHO: Treatment of Diabetes Mellitus Type II

Facilitators: Mark Pasanen MD, Liz Cote

October 22, 2020



# “Introduction” to ZOOM

- Please mute microphone when not speaking
- Please use camera as much as possible
- Test both audio & video before joining
- Communicate clearly during clinic:
  - Can use “raise hand” feature to comment
  - Speak clearly
  - Use chat function for technical issues
- We are recording the didactic section



# CME disclosures

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## **Interest Disclosures:**

- As an organization accredited by the ACCME to sponsor continuing medical education activities, UVMCMIE is required to disclose any real or apparent conflicts of interest (COI) that any speakers may have related to the content of their presentations.



# Disclosures: None or have been resolved

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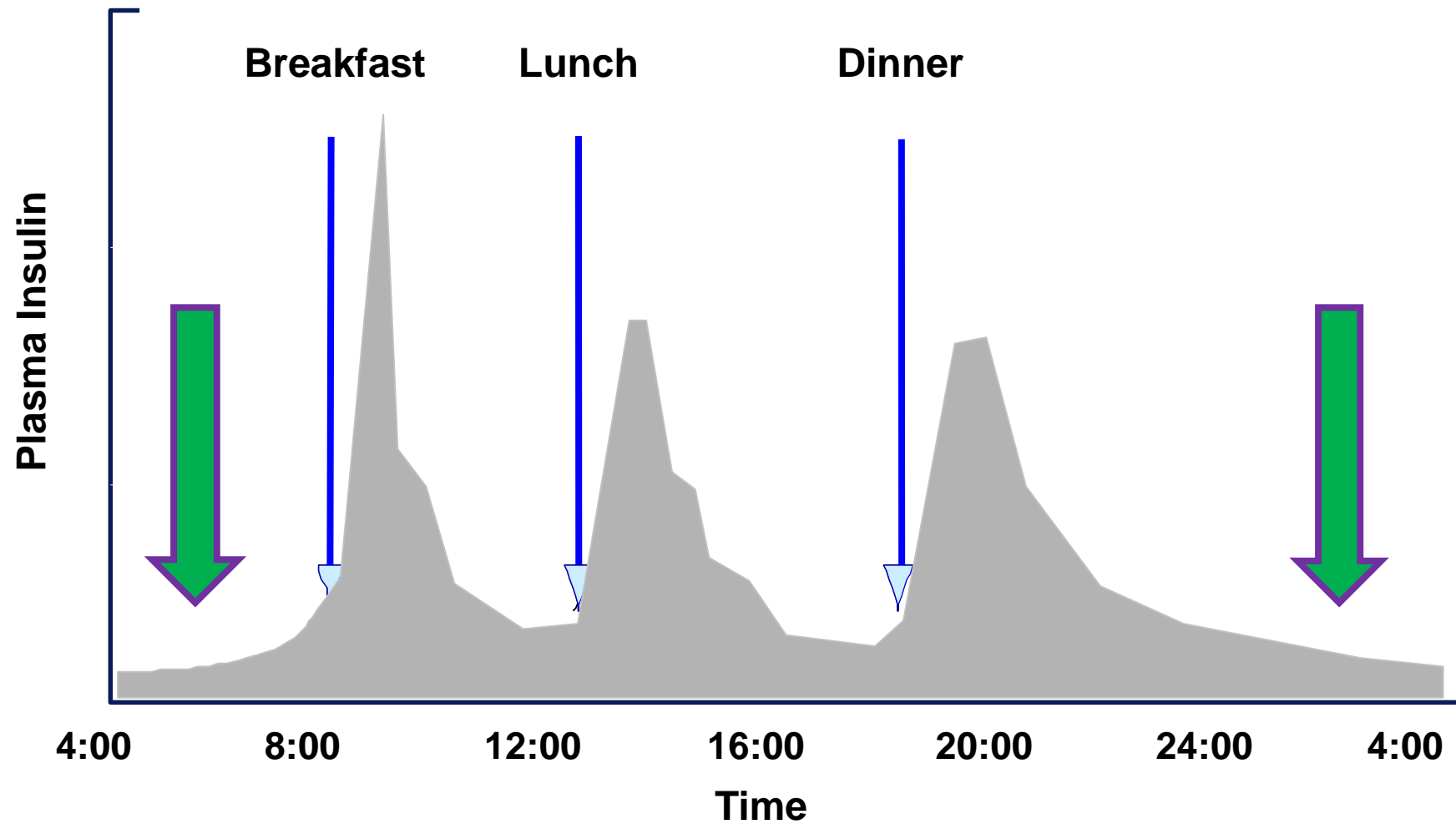
**Diabetes Echo**  
**Basal Insulins and Basal Insulin Therapy**

Jack L. Leahy, M.D.  
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# Key Principles of Basal Insulin Therapy.

1. Starting basal insulin therapy in uncontrolled type 2 DM is a common practice in primary care.
2. Mechanism: Use insulin to return overnight hepatic glucose production towards normal so that next day's FBG is at target range (<100-<130 mg/dL).
3. Implies that one knows the characteristics of an "ideal" basal insulin.

# Physiology of Insulin Secretion



# Key Principles of Basal Insulin Therapy.

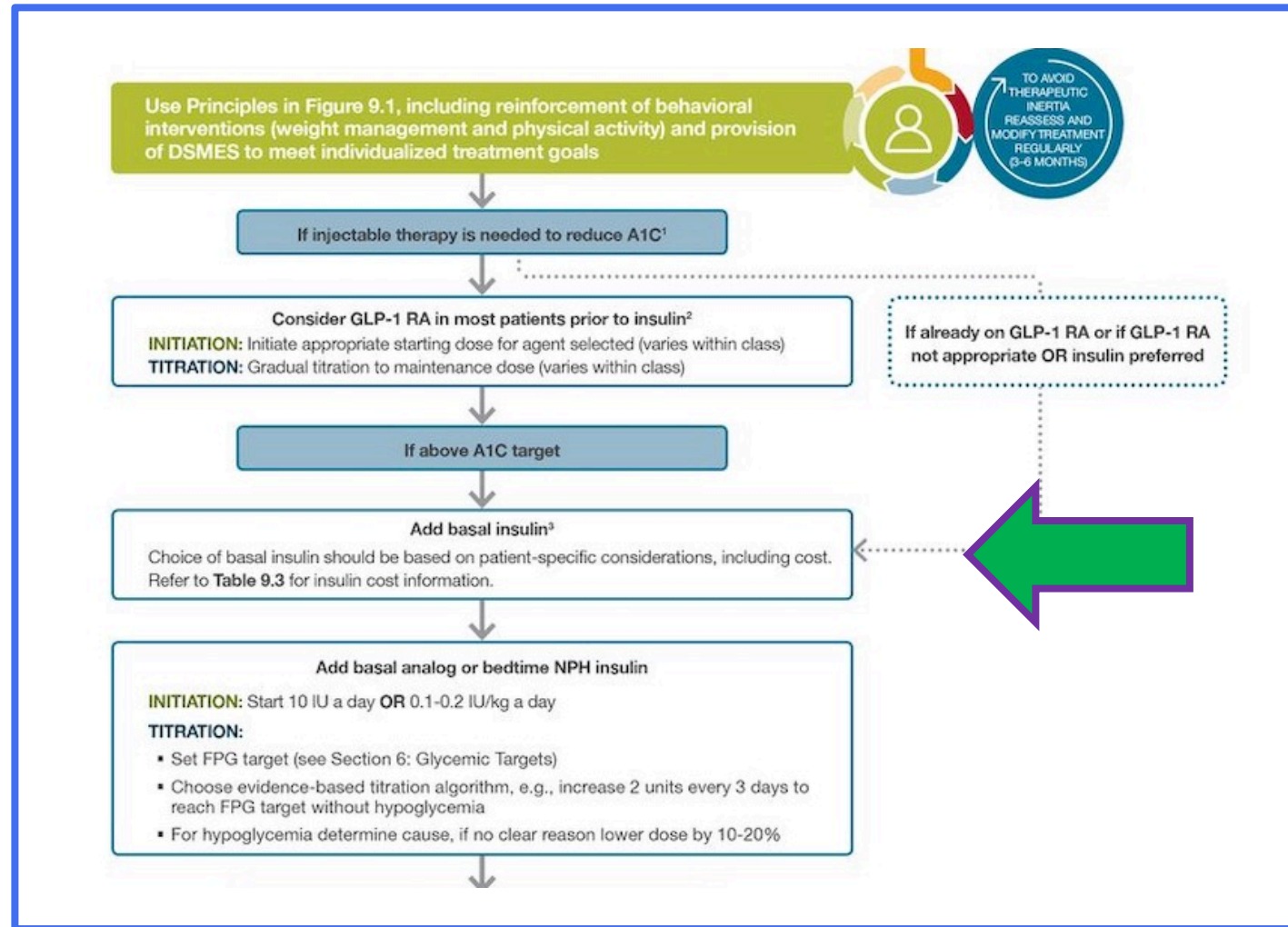
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4. Discuss with patient reason why adding insulin, general details, why not non-insulin therapy, address fears and concerns.



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3. Implies that one knows the characteristics of an "ideal" basal insulin.
4. Discuss with patient reason why adding insulin, general details, why not non-insulin therapy, address fears and concerns.
5. Follow ADA guidelines – practical instructions.

# ADA/EASD Guidelines for Basal Insulin Therapy in Type 2 DM



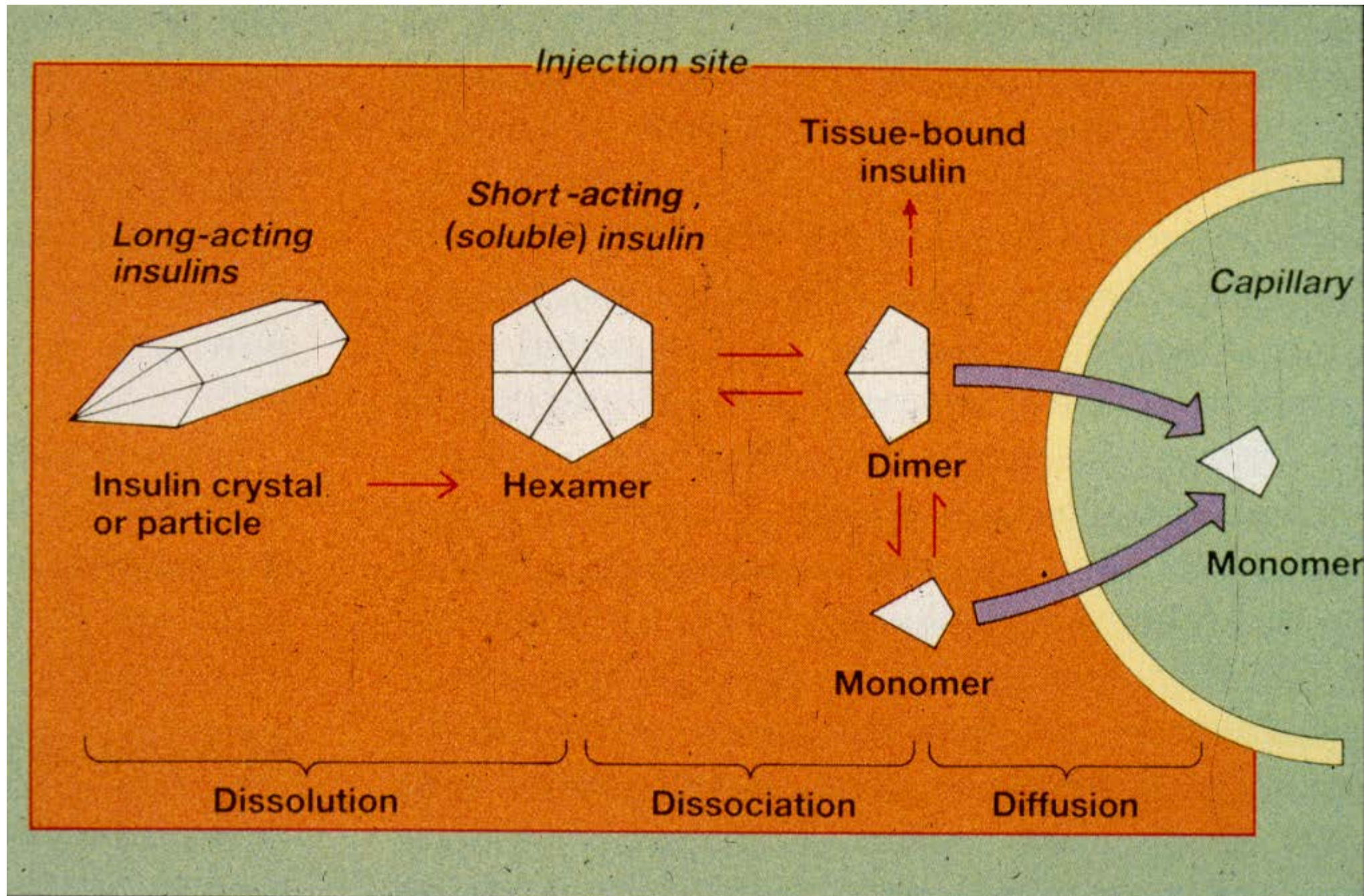
# **Basal Insulins in the US**

# Basal Insulins

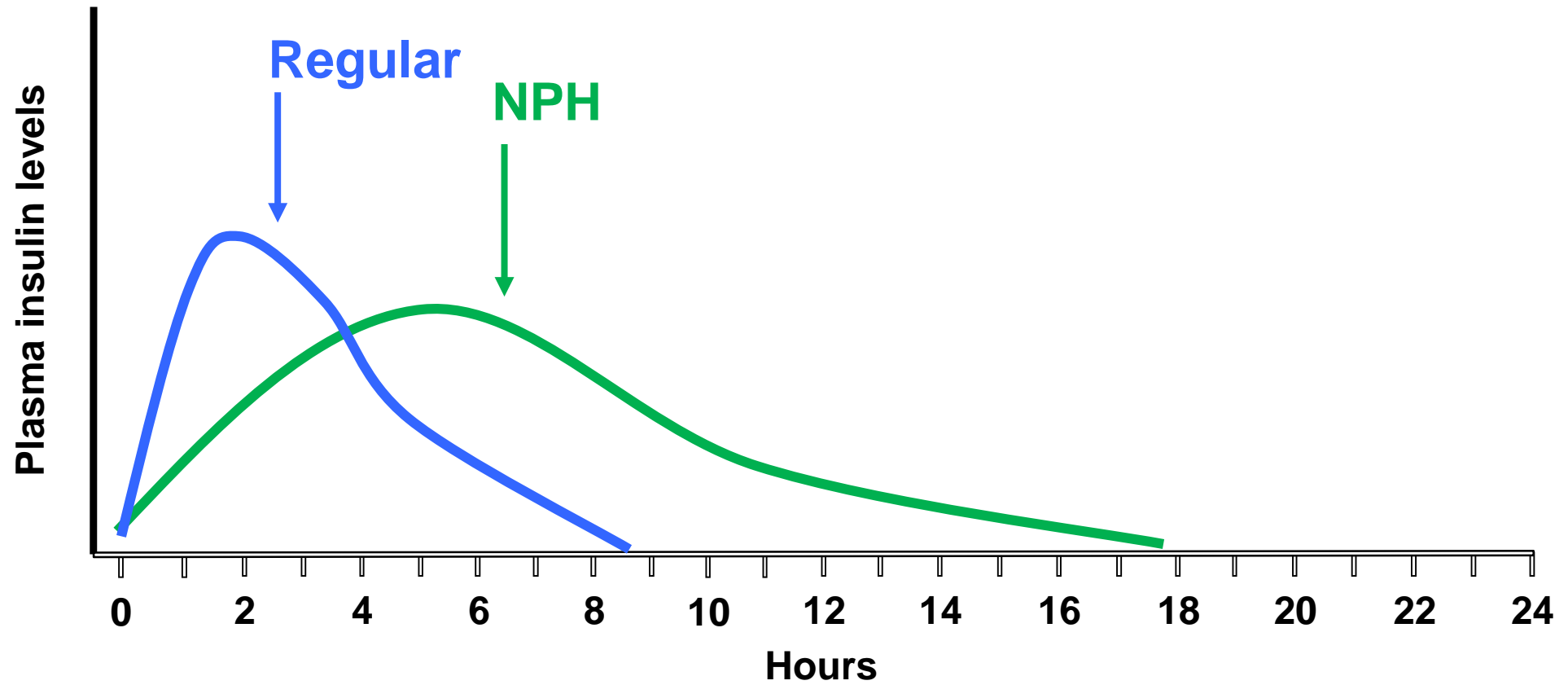
Human  
Insulins

1946

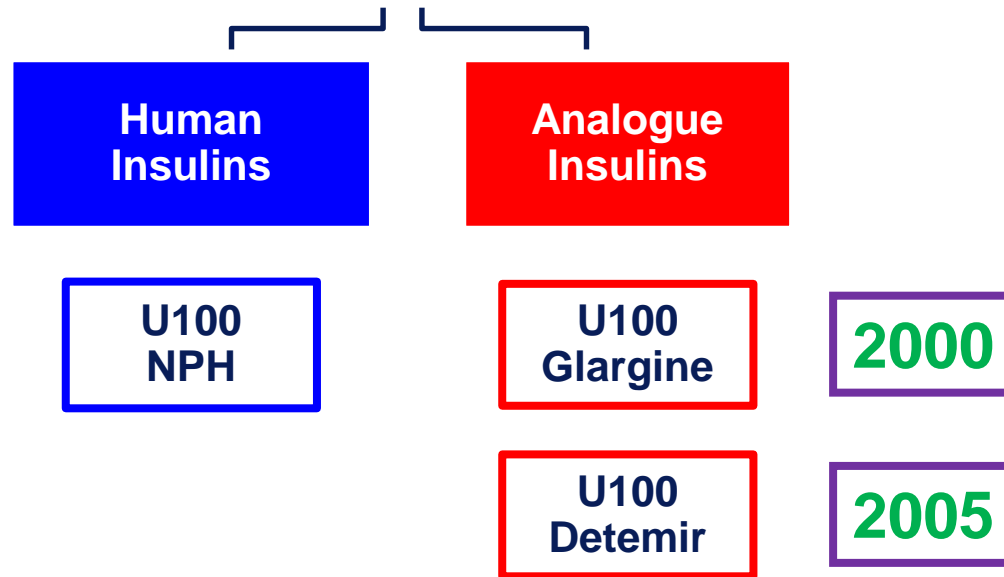
U100  
NPH



# Profiles of Human Insulins



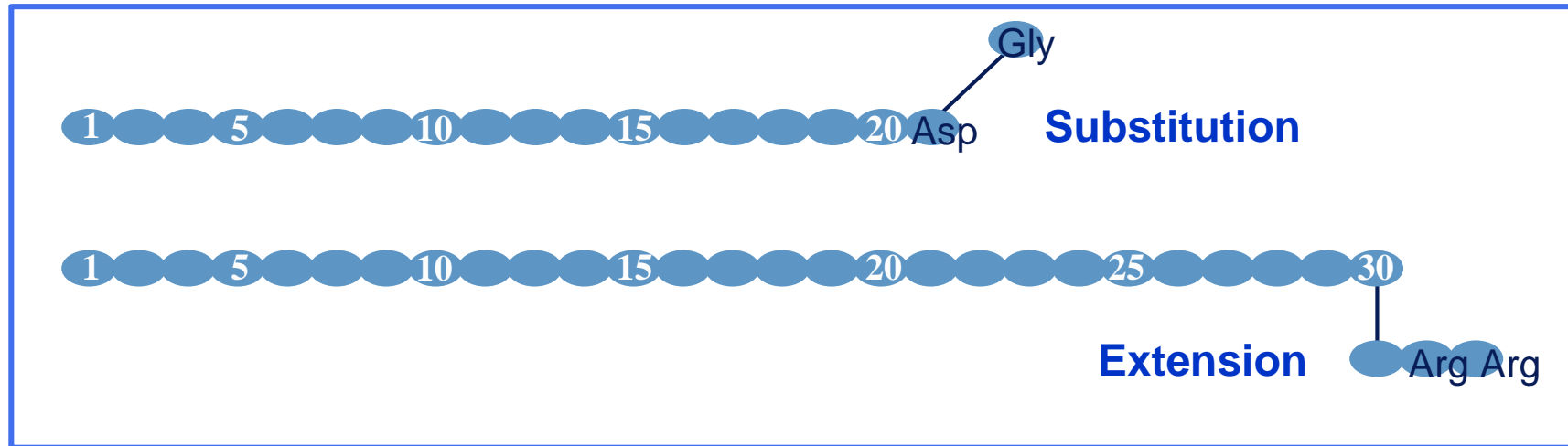
# Basal Insulins



First analogue insulins used amino acid changes in the insulin sequence to create more physiologic profiles of insulin transfer from subcutaneous to intravascular space.



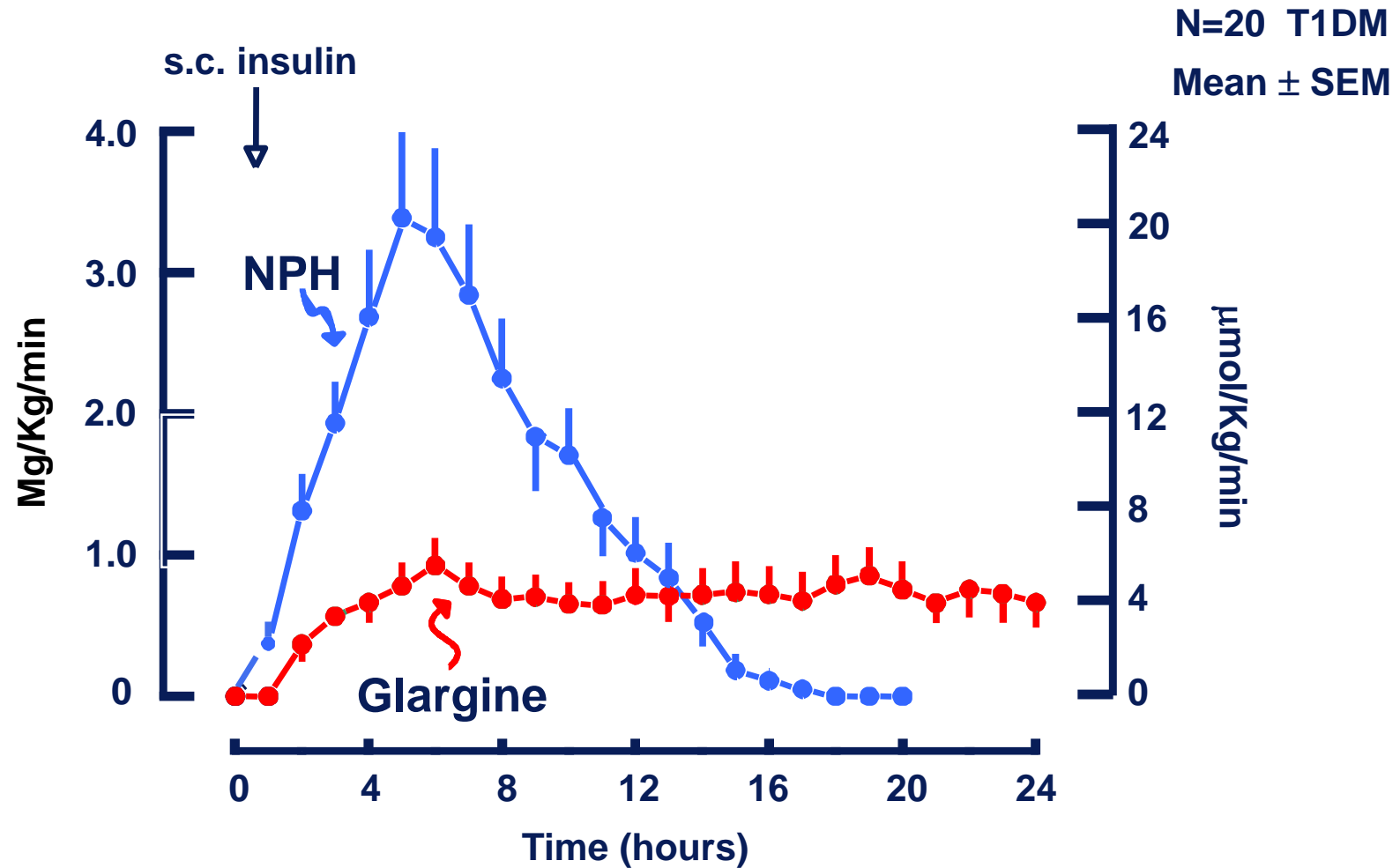
# Insulin Glargine



- Stable crystal at physiologic pH.
- Gradual release pattern from injection site.
  - Relatively peakless, long-lasting insulin profile.
- Clinical trials versus NPH:
  - Same A1c with less nocturnal and/or overall hypoglycemia.
  - Soluble (not suspension) – better maintenance of U-100 concentration.

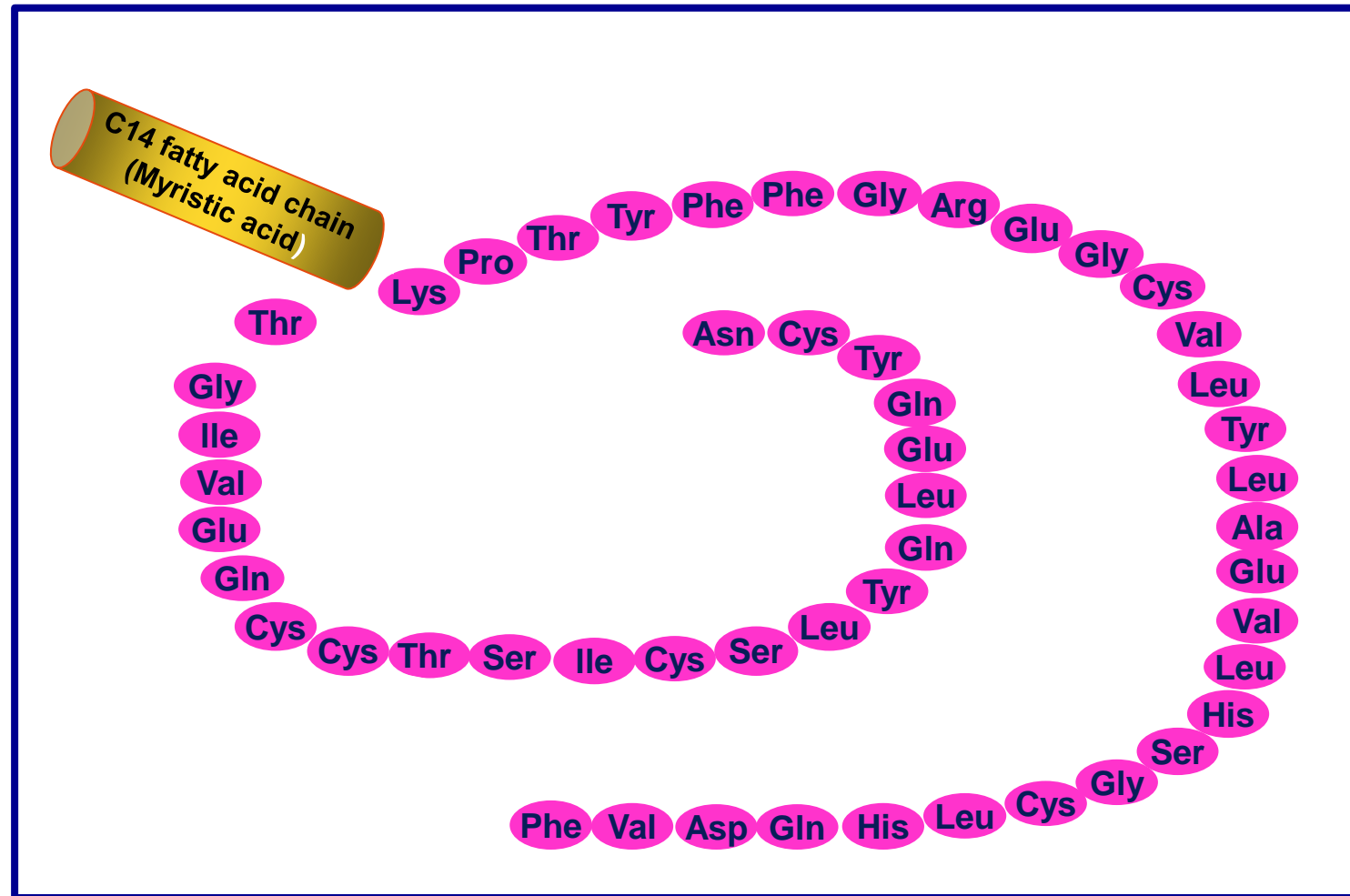
# Basal Insulin Profiles

## Glucose Infusion Rates

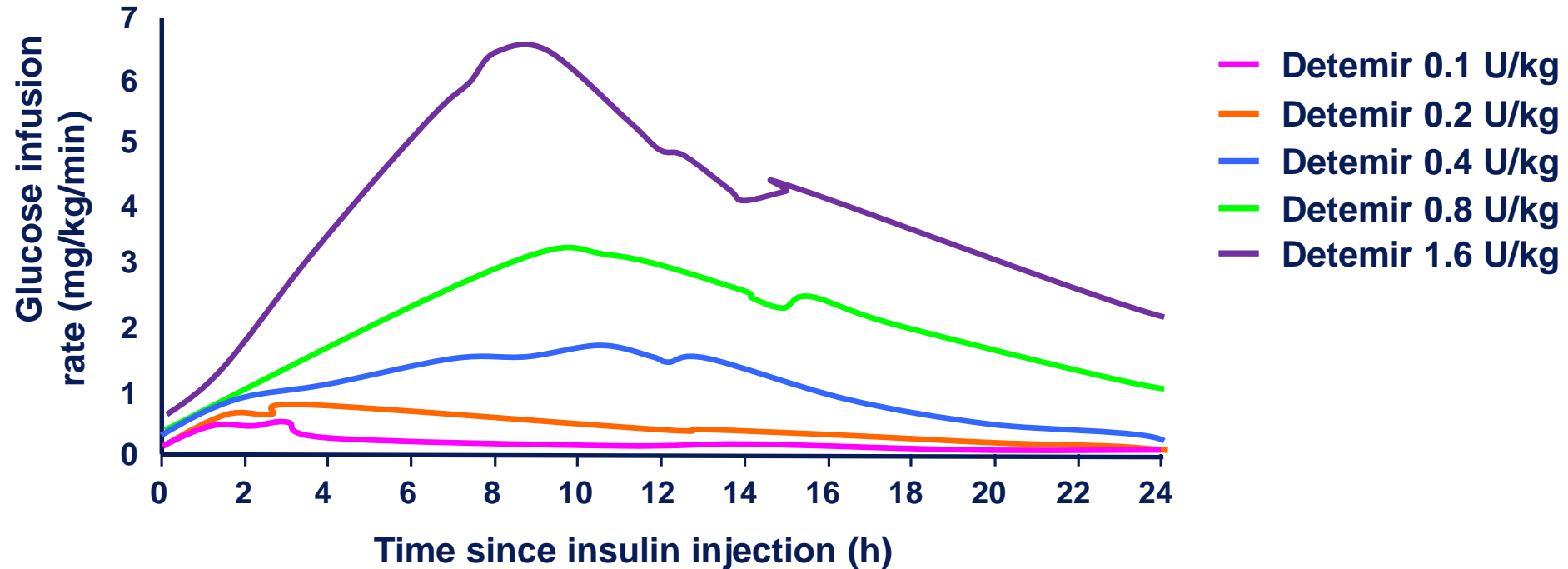


A second analogue technology was insulin post-translational modifications that modestly altered its absorption profile, but mostly retarded its binding to cellular insulin receptors through enhanced protein/albumin binding.

# Insulin Detemir: Structure

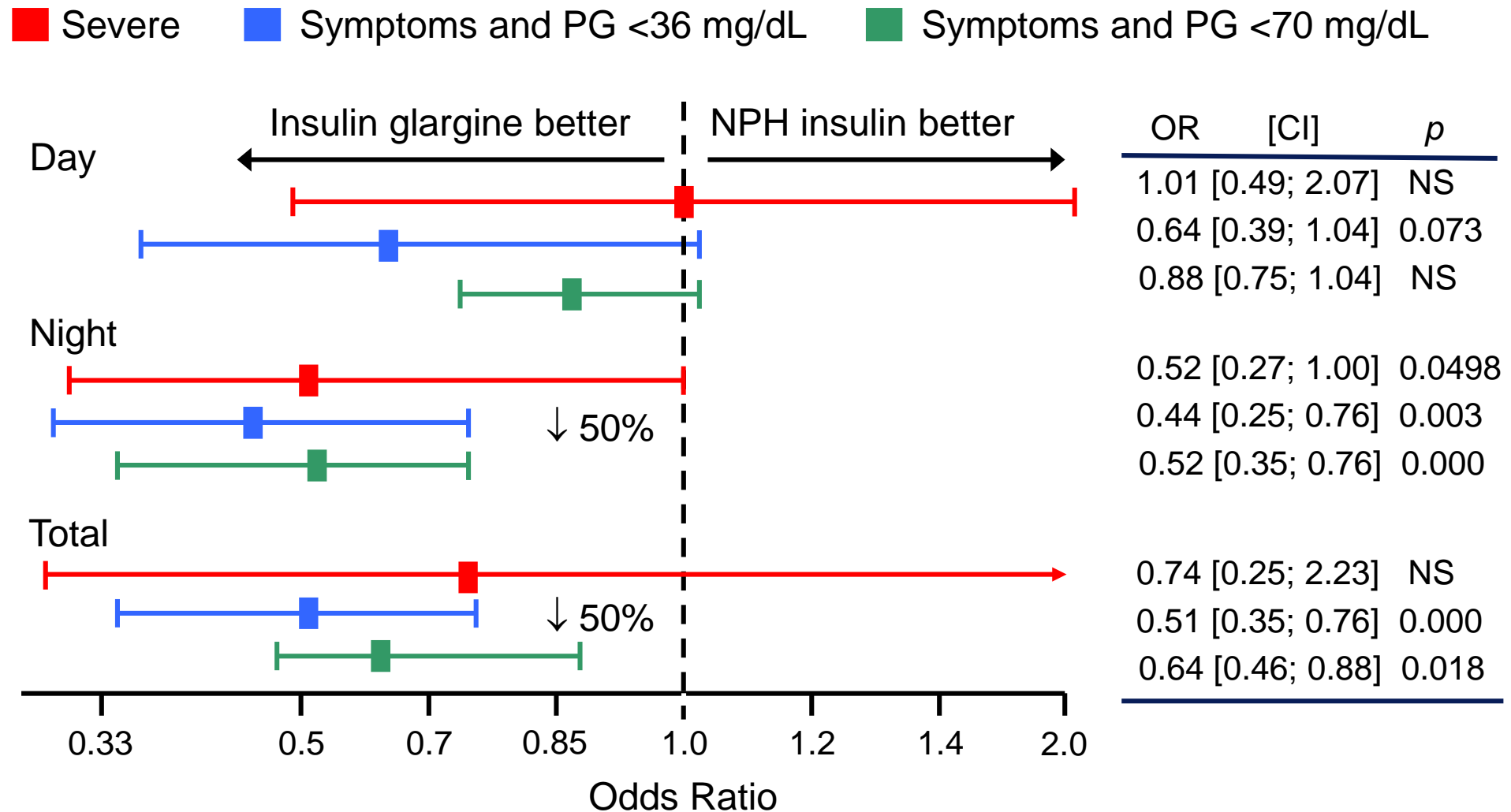


# Dose Dependency of Action Profiles of Insulin Detemir



DETEMIR DOSE (U/kg)	0.1	0.2	0.4	0.8	1.6
DURATION OF ACTION (h)	5.7	12.1	19.9	22.7	23.2

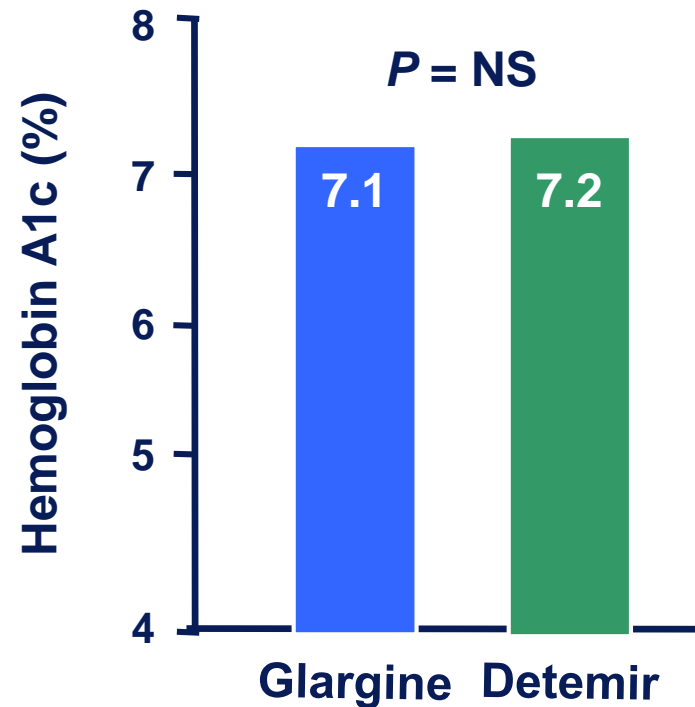
# Less Hypoglycemia With Insulin Glargine Versus NPH: Meta-analysis in T2DM



**Are there important clinical differences  
between insulin Glargine (Lantus)  
and Detemir?**

# Head to Head Comparison of Glargine Versus Detemir in Type 2 Diabetes

52-weeks. Once daily Glargine or Detemir - could be titrated to BID Detemir (55%). Baseline A1c 8.6%  $n = 582$

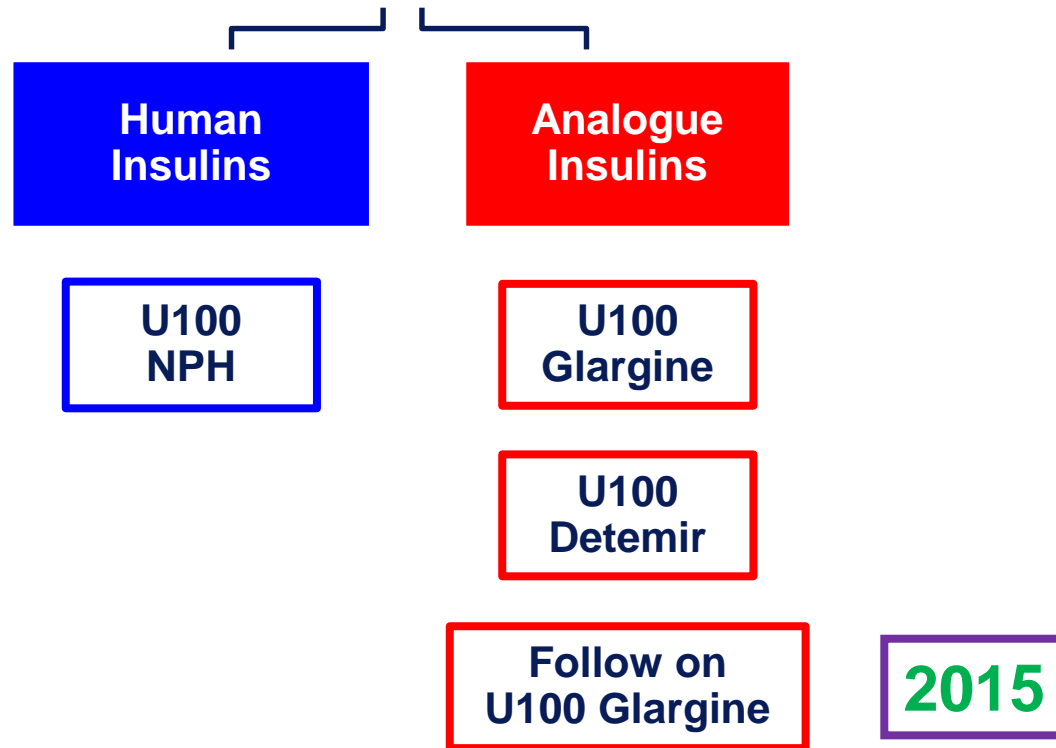




# Summary of Results

- 55% of patients on insulin Detemir were titrated to twice daily injections
- All patients on insulin Glargine received only 1 injection per day
- Average daily doses:
  - Detemir once daily 0.52 U/kg.
  - Detemir twice daily 1.00 U/kg.
  - Glargine once daily 0.44 U/kg
- 3.9 kg weight gain with Glargine versus 3.0 kg with Detemir - no difference between Glargine and twice daily Detemir.
- No difference in rates of hypoglycemia.

# Basal Insulins



**What is a follow-on insulin?**

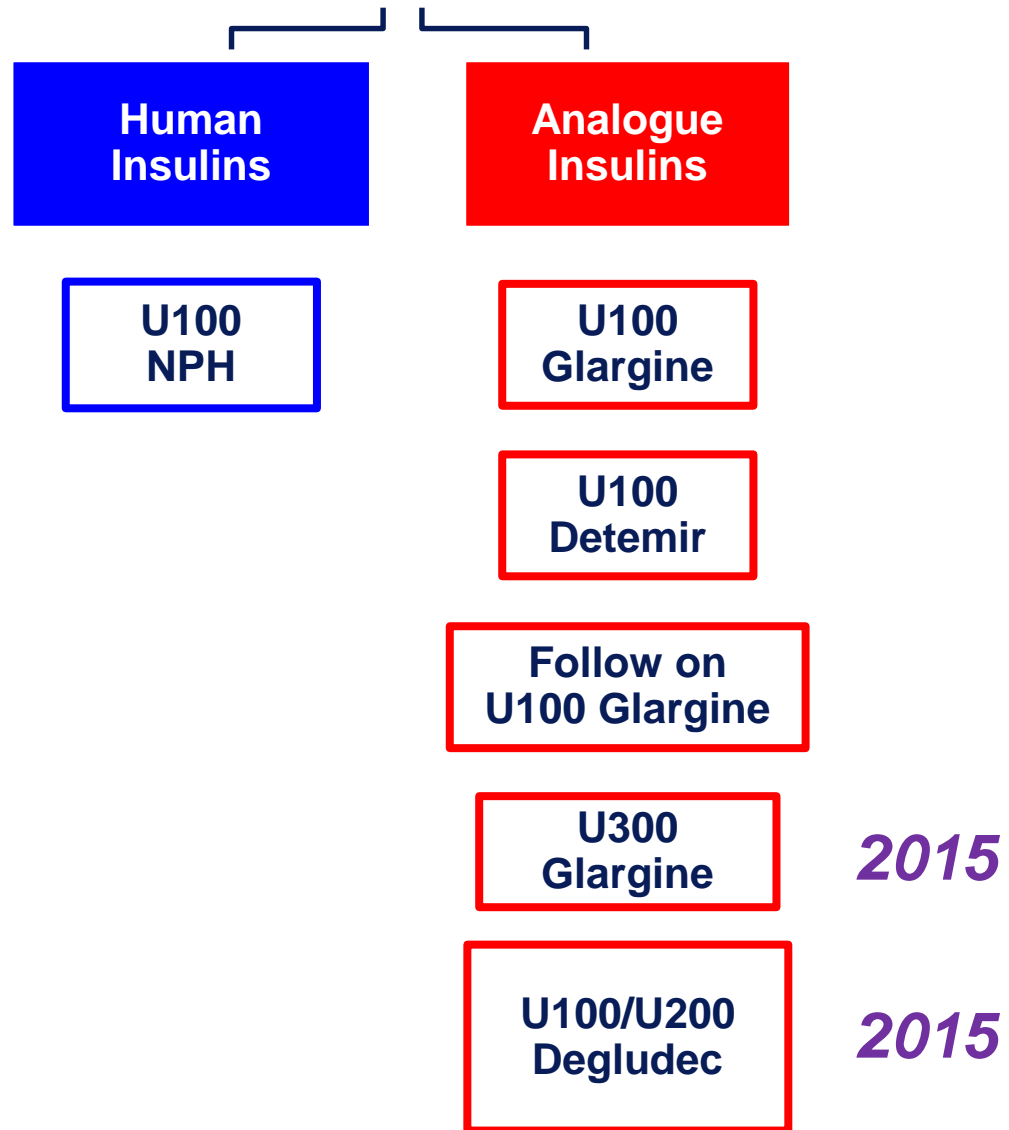
# FDA Definitions

- *Biological products* are generally large complex molecules that are produced through biotechnology in a living system.
- A *biosimilar* is a biologic product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product.
- Historically insulin was approved by the FDC (food, drug and cosmetic association). So no way to test and confirm similar to an FDA approved reference product. Complex approval pathway for approval of *follow on* insulins – have their own drug name, and pharmacy cannot substitute.
- Current follow-on insulins:
  - Glargine U-100 -- *Basaglar* (Eli Lilly).
  - Lispro -- *Admelog* (Sanofi).

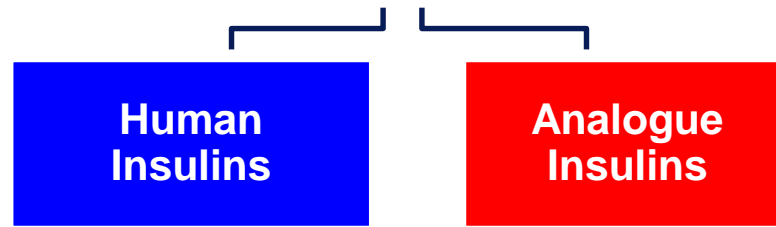
# March 23, 2020 – New FDA Approval Process for Insulins

- Insulin is now designated as a biological product – all insulin on the market is now labeled as biologics by the FDA.
- Insulin approval is now officially moved to the biologic regulatory framework - much more stream-lined process for submission of insulins to the FDA.
- *“Paving the way for biosimilar and interchangeable insulins.”*
- *“Expected to increase patient access, adding more choices and potentially reducing costs of these vital therapies.”*

# Basal Insulins



# Basal Insulins



U100  
NPH

U100  
Glargine

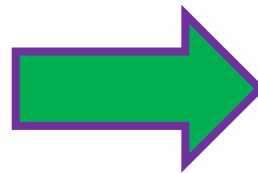
U100  
Detemir

Follow on  
U100 Glargine

U300  
Glargine

U100/U200  
Degludec

Ultralong analogues



*Toujeo*

*Tresiba*

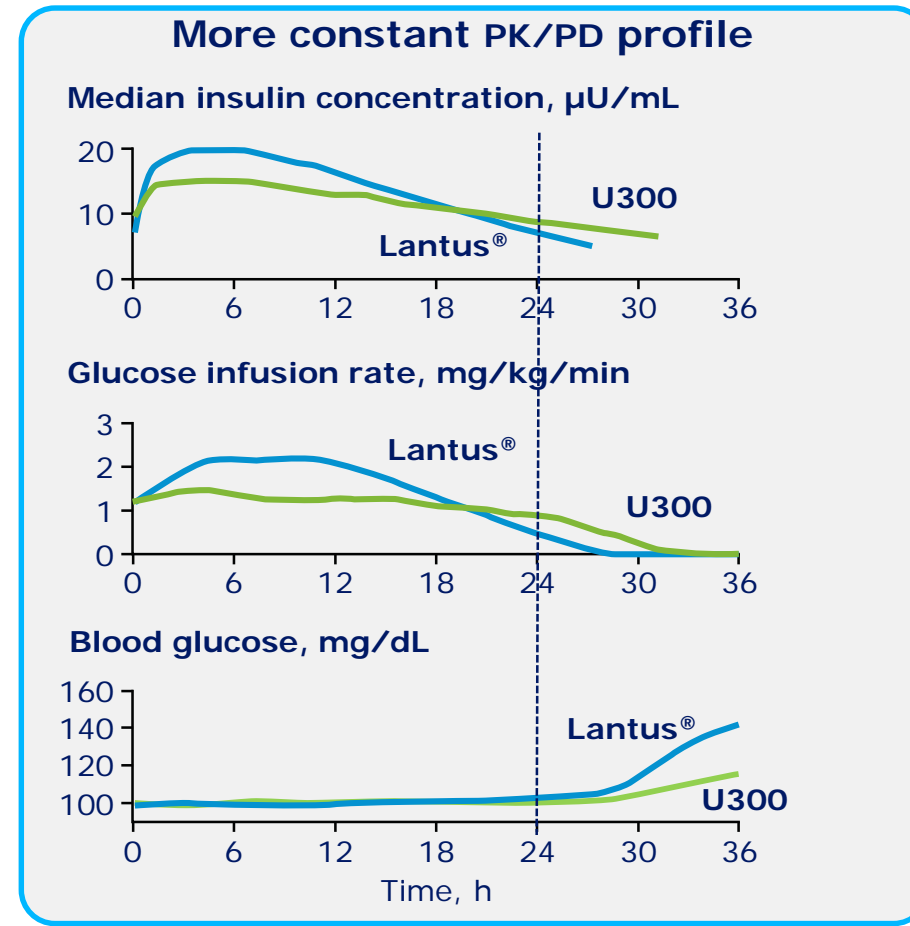
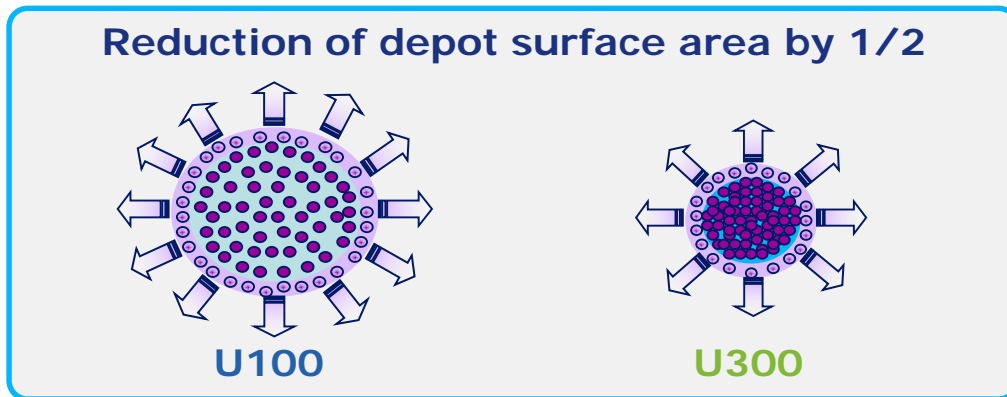
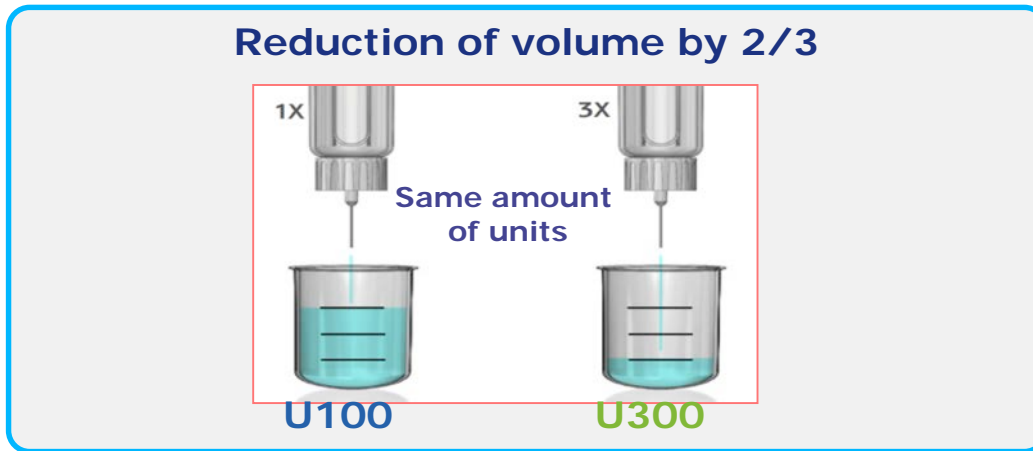
**What are U numbers?**



# U Numbers

- U numbers designate an insulin's concentration – units per mL of volume.
- Historically most insulins in the US are U100, with syringes and other calibrated devices.
- U500 insulin has been available in the US since 1994. Originally in 20 mL vials without dedicated syringes. Now specific syringes and pens available – show real insulin doses.
- Many concentrated insulins now available.
  - Alter PK/PD – create a new insulin.
  - Convenience – larger volume pens and maximal injections.

# Different PK/PD profile Glargine U-100 vs. Glargine U-300 (Toujeo)



# Insulin Degludec Mode of Action

Insulin degludec for injection is a zinc/phenol formulation in the T3R3 conformation as di-hexamers (~69 kDa)

- Phenol ↓

Rapid phenol depletion (after injection) changes the conformation to a T6-state exposing the core and Zinc ions and multi-hexamer chains are formed

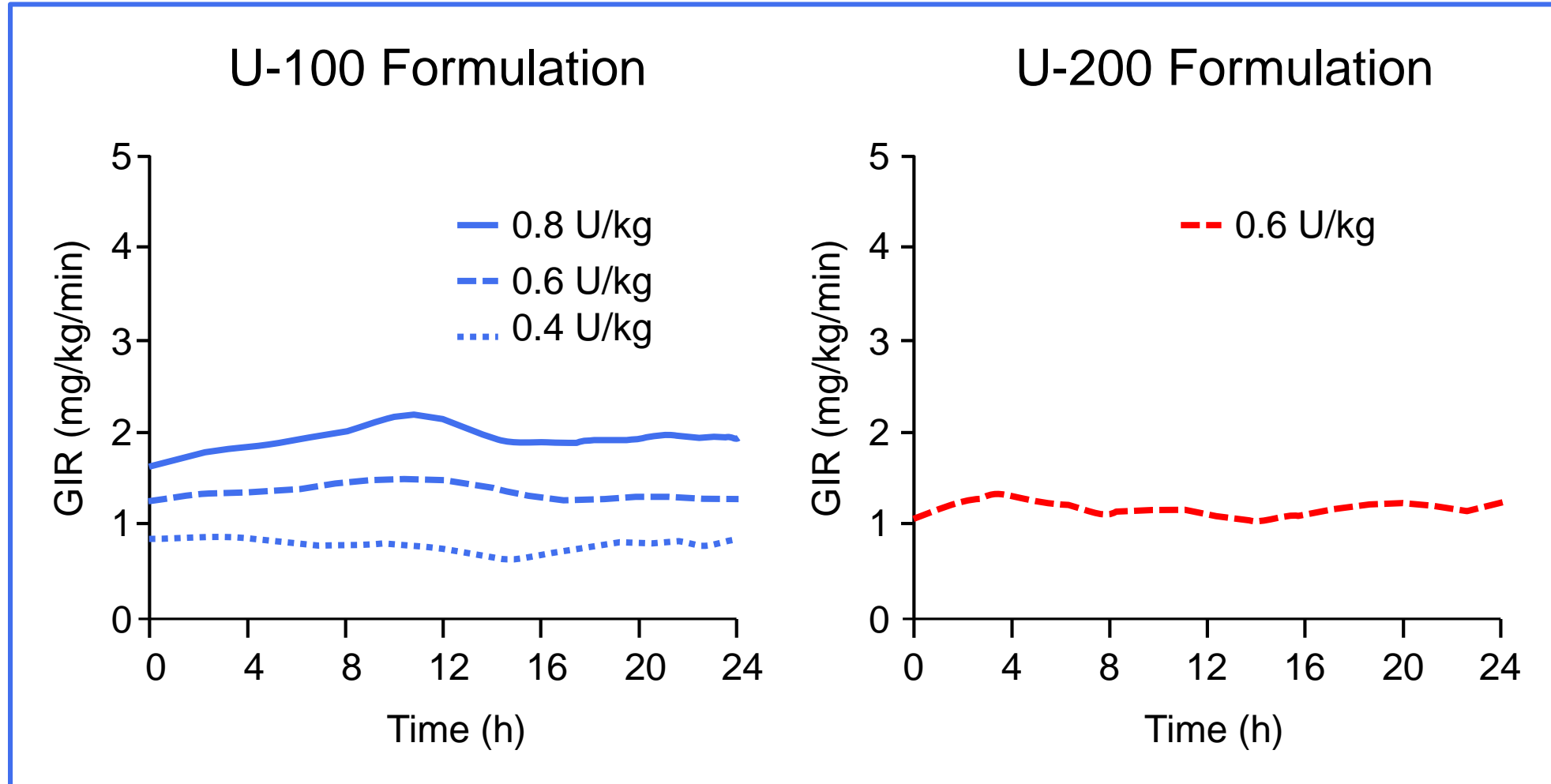
- Zinc ↓

Zinc diffuses slowly causing individual hexamers to disassemble, releasing dimers and then monomers

↓  
Monomers are absorbed from the depot into the circulation

↓  
Monomers bound to albumin  
(protein-bound depot)

# Pharmacodynamics of U-100 and U-200 Degludec – 24.5 Hour Half-life



Heise T, et al. *Diabetes Obes Metab.* 2012;14:944-950.

Heise T, et al. *Diabetes.* 2012;61(suppl 1):A91 [abstract 349-OR].

# Summary of Ultralong Basal insulins

- Clinical characteristics:
  - Longer duration – once daily dosing, and much wider window for varying injection time. No “best” time to inject.
  - Flatter overall profile – less within day variability.
  - Less day to day variability – fasting BG.
  - Less nocturnal and severe hypoglycemia.
- No major clinical advantage of Glargine U300 or Degludec over the other insulin.

# When to Use Ultralong Basal insulins

1. Patients with nocturnal or severe hypoglycemia with traditional basal analogues.
2. Patients who use >80 units of basal insulin - both Glargine U300 and Degludec U200 can give maximum 160 units as a single injection.
3. Patients with erratic schedules or lifestyles in terms of sticking to time of administration.
4. As a starting insulin – why not?

Note clinical studies DO NOT show better A1c than standard analogues – just better safety.

**How to start and optimize basal insulin?**

Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals



If injectable therapy is needed to reduce A1C<sup>1</sup>

Consider GLP-1 RA in most patients prior to insulin<sup>2</sup>

**INITIATION:** Initiate appropriate starting dose for agent selected (varies within class)  
**TITRATION:** Gradual titration to maintenance dose (varies within class)

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred

If above A1C target

Add basal insulin<sup>3</sup>

Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to **Table 9.3** for insulin cost information.

Add basal analog or bedtime NPH insulin

**INITIATION:** Start 10 IU a day OR 0.1-0.2 IU/kg a day

**TITRATION:**

- Set FPG target (see Section 6: Glycemic Targets)
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10-20%





Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals



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# Few Added Steps

1. Instructions to call clinic if not available or affordable.
2. Typically do not stop other DM meds – may alter doses.
  - Historically insulin and TZD not considered good combination because of heart failure, edema, and weight.
3. Choose a maximal dose – typically  $<0.5$  u/kg.
4. BG testing – my favorite is twice daily. Always fasting (using to titrate insulin). Then alternate pre-supper and bedtime.
5. Follow up by phone or in person in 1 month.

## 2020/2021 PROGRAM SCHEDULE

DATES (All Thursdays, 12pm to 1pm)	SESSION	DIDACTIC TOPICS (in addition to case review)
<b>August 13</b>	TeleECHO Session #1	<ul style="list-style-type: none"> <li>• Project ECHO Orientation</li> <li>• Anatomy of an ECHO session</li> <li>• Newly diagnosed DM2                             <ul style="list-style-type: none"> <li>• Types of diabetes</li> </ul> </li> </ul>
<b>August 27</b>	TeleECHO Session #2	<ul style="list-style-type: none"> <li>• Overview of Diabetic Care                             <ul style="list-style-type: none"> <li>• ADA guidelines</li> </ul> </li> </ul>
<b>September 10</b>	TeleECHO Session #3	<ul style="list-style-type: none"> <li>• Approach to glycemic control                             <ul style="list-style-type: none"> <li>• Sulfonylureas, metformin</li> <li>• Continuous Glucose Monitors (CGM)</li> </ul> </li> </ul>
<b>September 24</b>	TeleECHO Session #4	<ul style="list-style-type: none"> <li>• GLP1 agonists/DPP4 inhibitors</li> </ul>
<b>October 8</b>	TeleECHO Session #5	<ul style="list-style-type: none"> <li>• SGLT 2 inhibitors</li> </ul>
<b>October 22</b>	TeleECHO Session #6	<ul style="list-style-type: none"> <li>• Insulin 101</li> </ul>
<b>November 12</b>	TeleECHO Session #7	<ul style="list-style-type: none"> <li>• Advanced insulin</li> </ul>
<b>December 10</b>	TeleECHO Session #8	<ul style="list-style-type: none"> <li>• ASCVD prevention:                             <ul style="list-style-type: none"> <li>• Lipids, HTN, ASA</li> </ul> </li> </ul>
<b>January 14</b>	TeleECHO Session #9	<ul style="list-style-type: none"> <li>• Complications:                             <ul style="list-style-type: none"> <li>• Screening</li> <li>• Prevention</li> </ul> </li> </ul>
<b>January 28</b>	TeleECHO Session #10	<ul style="list-style-type: none"> <li>• Special Populations:                             <ul style="list-style-type: none"> <li>• Elderly, pregnancy</li> <li>• Adherence</li> </ul> </li> </ul>



# ECHO Reminders

- Volunteers to present cases
- Please complete evaluation forms for each session
  - CME will be processed once session evaluation form is received at UVM
- UVM Project ECHO materials available at [www.vtahec.org](http://www.vtahec.org)
- Please contact us with any questions/suggestions
  - [Mark.Pasanen@uvmhealth.org](mailto:Mark.Pasanen@uvmhealth.org)
  - [Elizabeth.Cote@uvm.edu](mailto:Elizabeth.Cote@uvm.edu)
  - [ahec@uvm.edu](mailto:ahec@uvm.edu)

