



100 Years of Insulin Therapy: A long Successful Path



Disclosures

- Dr Jorge De Jesús has received honorariums as speaker for the following pharmaceutical companies: Janssen
- Dr Jorge De Jesús has no conflicts of interests with any entity for the information included in this presentation



INSULIN IS INSULINOR Not?

Recombinant Human Insulin

Jorge De Jesús MD FACE



100 Years of Insulin Therapy: A long Successful Path



Objectives:

After this presentation the audience will be able to familiarize with the use of human insulins as an alternative to the high cost of insulin analogs

Regular human insulin

NPH insulin (Neutral Protamine Hagedorn)

70/30 (NPH/ Regular) pre- mix combination

Regular concentrated insulin U500

Concept of “overbasalization” and insulin stacking



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Back to the Future: Relearning How to Use Human Insulin

Jay H. Shubrook, DO; Anne L. Peters, MD

DISCLOSURES | April 15, 2019



www.webmd.com

A vial of insulin analog costs about \$200 to \$300, compared with \$25 for a vial of human insulin. In the Unit...



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Switching to Human Insulin Not Harmful in Type 2 Diabetes

Miriam E. Tucker

January 29, 2019

5 Read Comments



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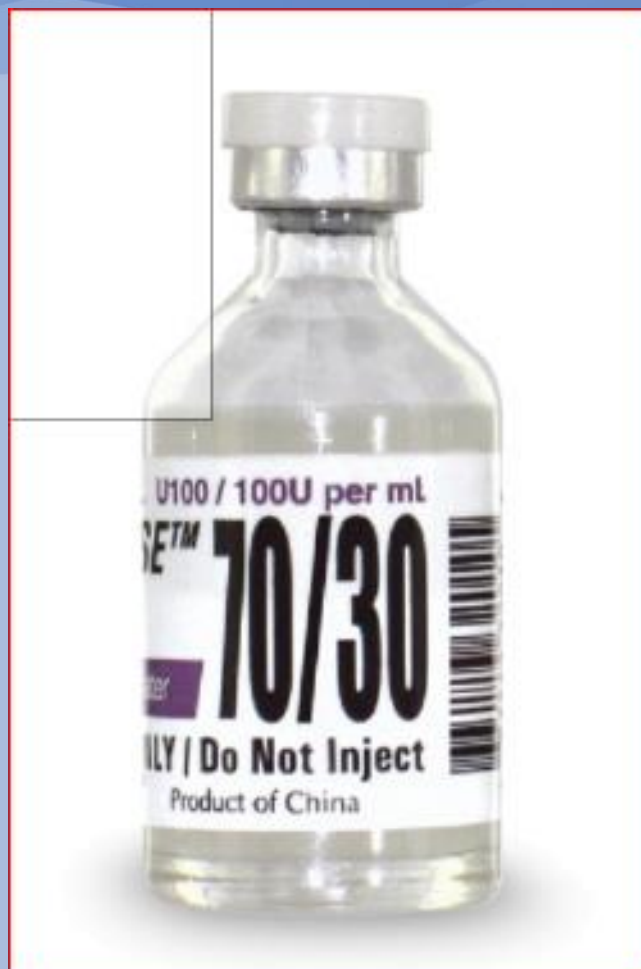
Switching patients with type 2 diabetes from insulin analogs to human insulin could save a lot of money, without causing harm, new research suggests.

Findings from the large retrospective cohort study of Medicare beneficiaries were [published](#) in this week's issue of *JAMA* by Jing Luo, MD, of the Program on Regulation, Therapeutics, and Law, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, and colleagues.

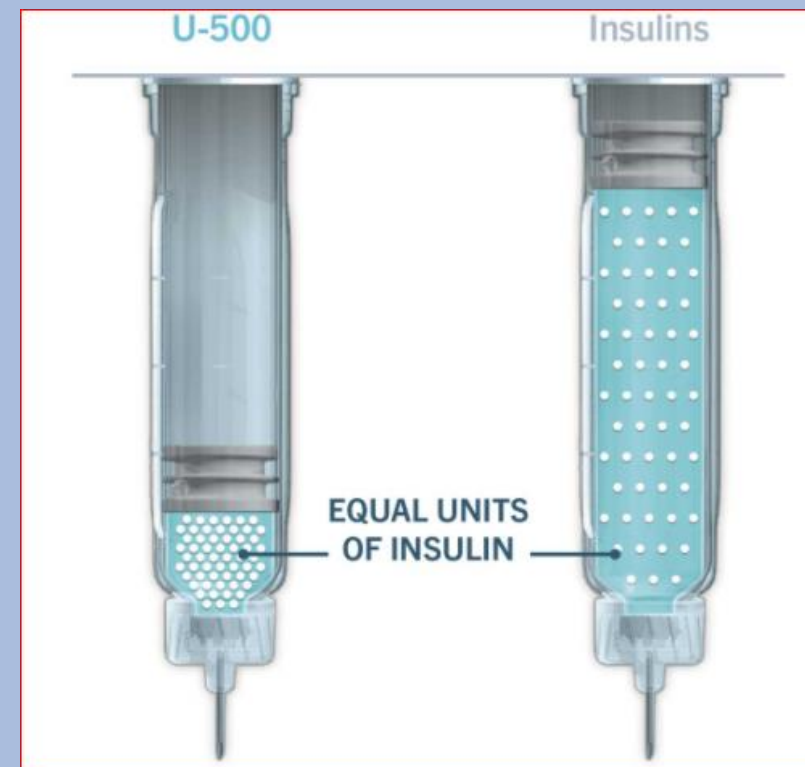


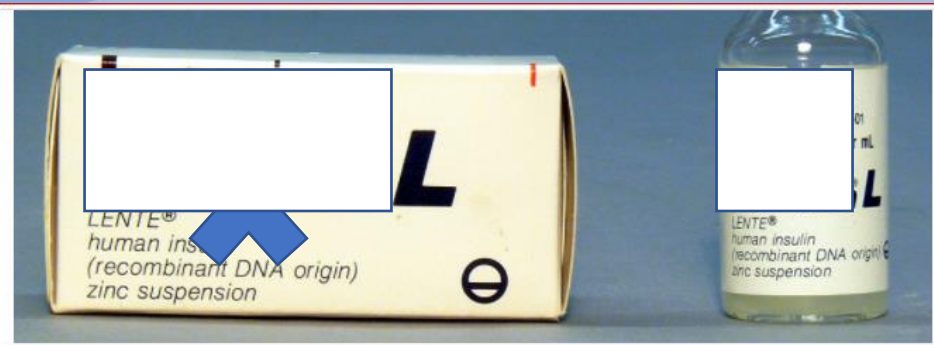
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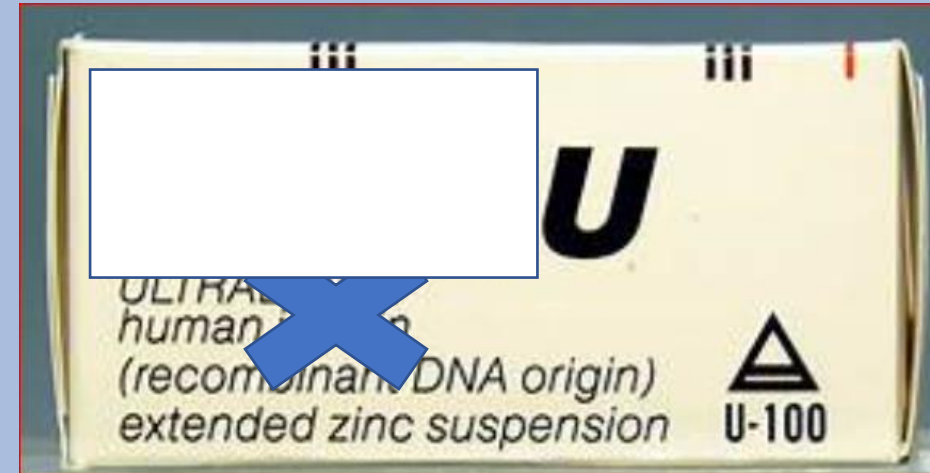


Regular Insulin U-500





Humulin L is an intermediate-acting insulin with a slower onset of action than regular insulin and a longer duration of activity (up to 24 hours). Due to declining use of longer-acting insulins, Humulin L was discontinued in 2005.



Commercially available human Insulins are now virtually free of contaminants

Porcine (one aminoacid)



No longer available in US

Bovine(3 aminoacids)



Older preparations would contain :

Islet cell peptides

Proinsulin

C-peptide

Pancreatic Polypeptides

Glucagon , Somastostatin

→ Antibody formation



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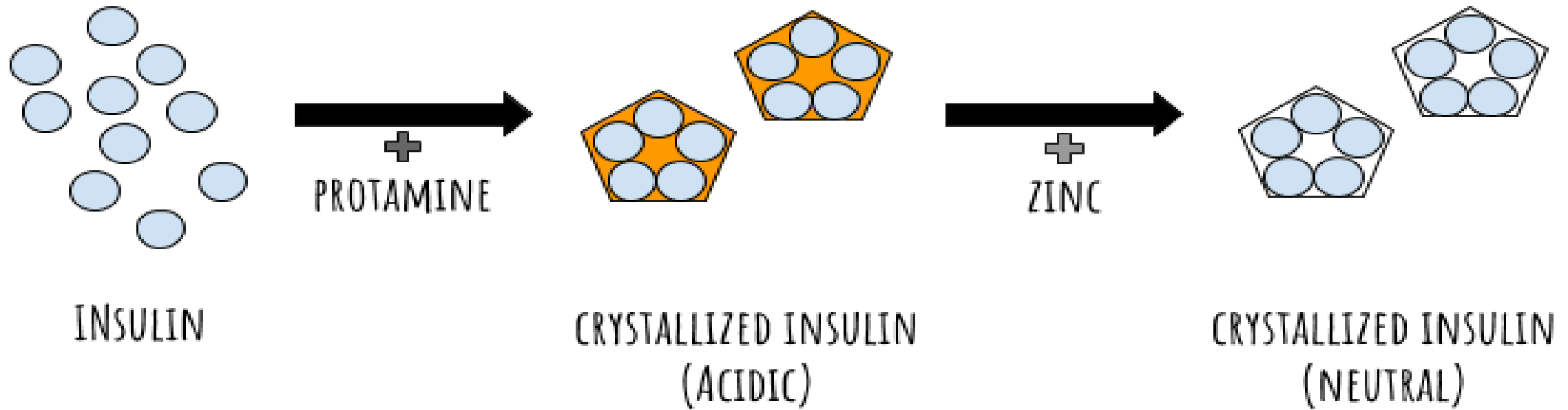
PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Initiation of insulin therapy in DM2

Pharmacologic Therapy for Type 2 Diabetes

- 9.4 Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. **A**
- 9.5 Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. **A**
- 9.6 Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. **A**
- 9.7 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels ($>10\%$ [86 mmol/mol]) or blood glucose levels ($\geq 300\text{ mg/dL}$ [16.7 mmol/L]) are very high. **A**

NPH ACTS AS A BASAL INSULIN
GRADUAL RELEASE FROM S/C AREA OF INJECTION
THIS ACTION IS VARIABLE BETWEEN INDIVIDUALS AND EVEN IN THE SAME
INDIVIDUAL



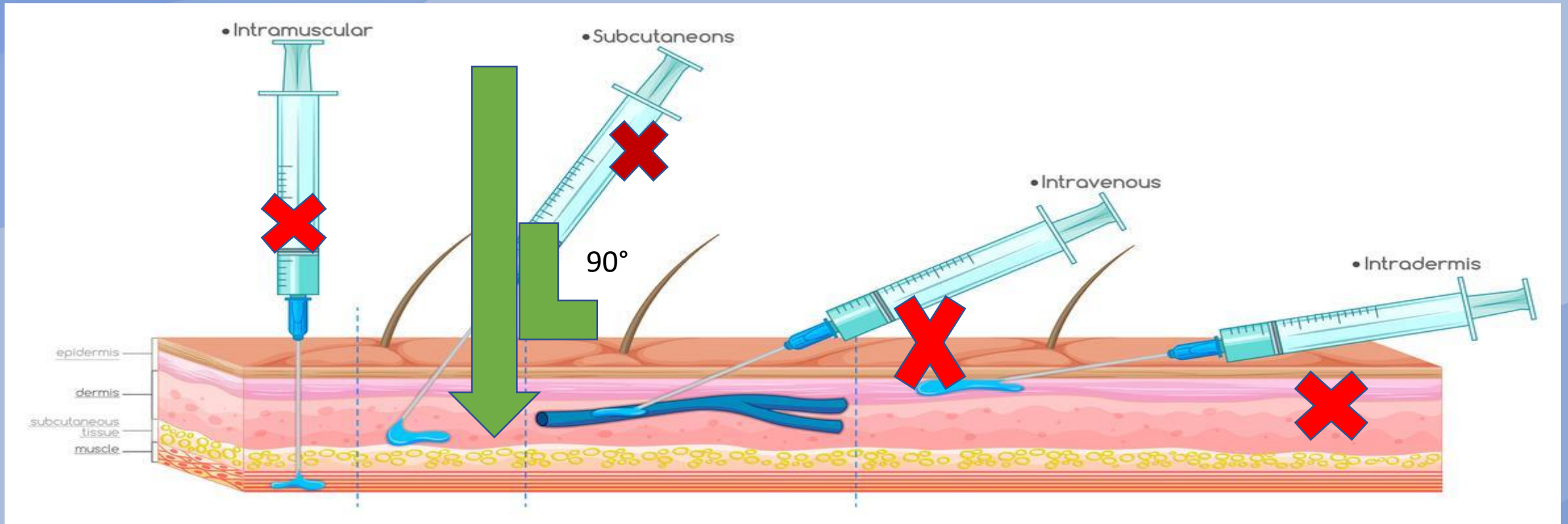
NPH CAN BE GIVEN ONCE OR TWICE A DAY PRIOR TO MEALS
OR AT BEDTIME

- If insulin is a suspension (NPH, Lente) roll and agitate the vial to mix it well.
- Regular (Actrapid) insulin should never be contaminated with NPH or any insulin modified with added protein (medium and long-acting insulins).
- Inject air into both vials when they are sitting flat, so that the insulin doesn't touch the needle tip.



NPH

90 degree angle of s/c injection



Basal Insulins

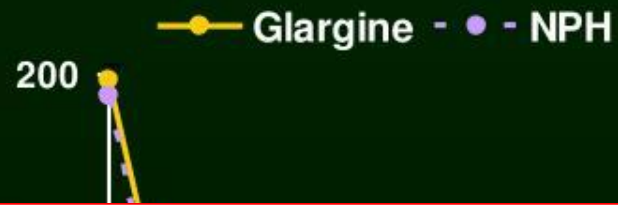


Insulin	Type	Onset of action	Peak of action	Duration of action
NPH	Intermediate acting	1-2 hours	5-7 hours	13-18 hours
Glargine (Lantus) Aventis	Long acting	1-2 hours	Relatively flat	Upto 24 hours
Detemir (Levimir)Novo	Long acting	2-4 hours	8-12 hours	16-20 hours

The time course of action of any insulin may vary in different individuals, or at different times in the same individual. Because of this variation, time periods indicated here should be considered general guidelines only.



Treat-to-Target Trial: Oral Agents + Glargine or NPH at Bedtime (n=756): Efficacy Results



Less Risk of Severe Hypoglycemia With Long-Acting Insulin Analogs in Elderly

By Reuters Staff

March 02, 2021

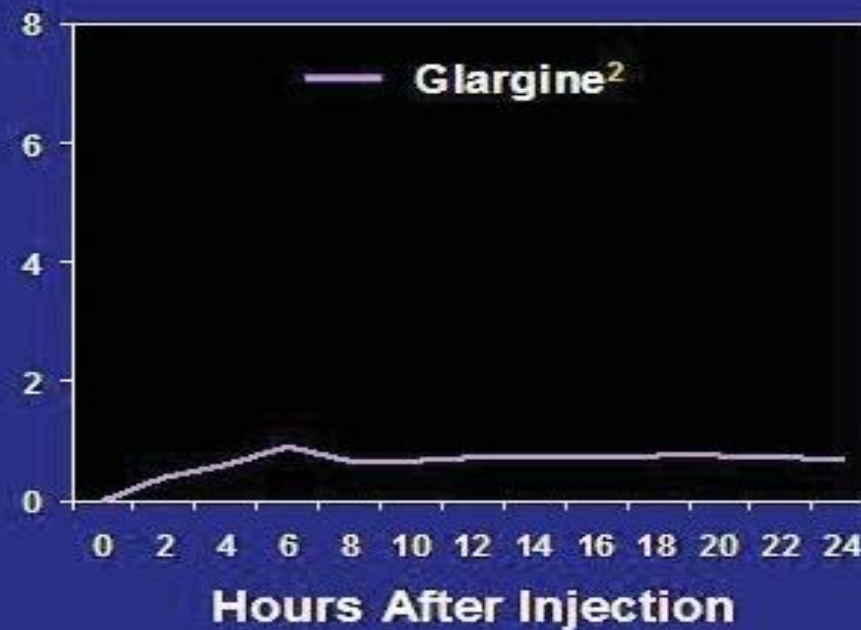
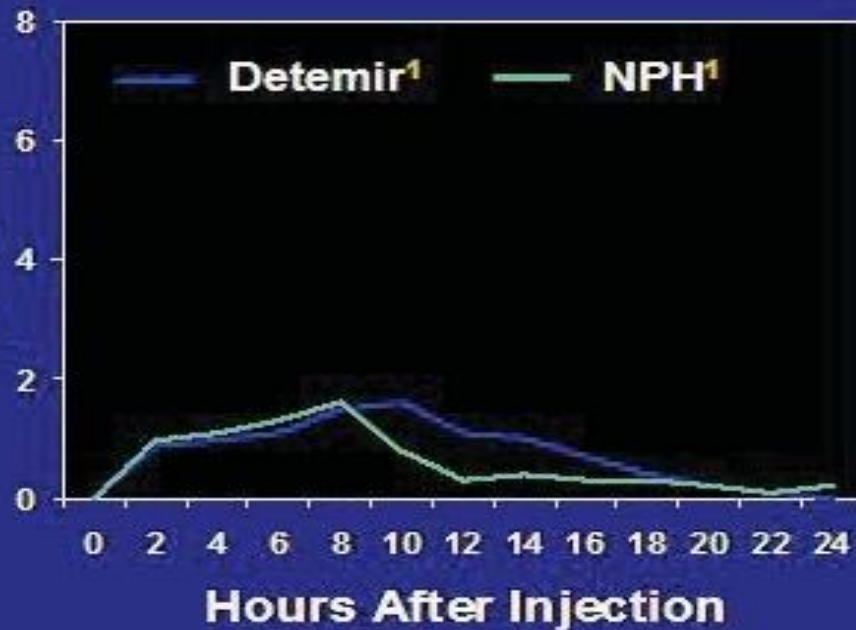


*In both groups, FPG decreased from 194 or 198 mg/dL to 117 or 130 mg/dL, respectively, by study end, and A1C decreased from 8.6% to 6.9% by 18 weeks.

Riddle MC et al. *Diabetes Care*. 2003;26:3080-3086.



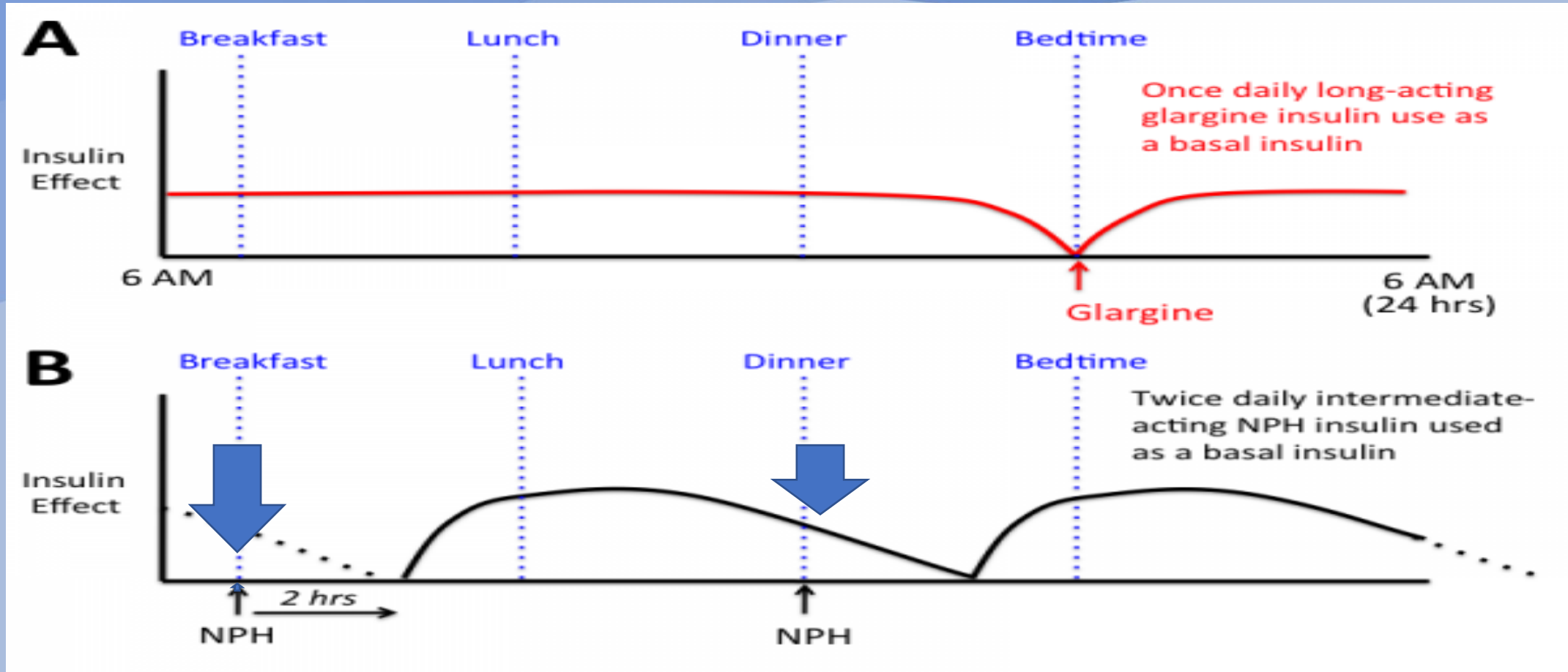
Glucose Infusion Rate
(mg/kg/min)



- Type 1 diabetic patients (N=12)¹, Type 1 diabetic patients (n=20)²
- NPH and Glargine dose = 0.3 U/kg; Detemir dose = 0.4 U/kg



NPH as BASAL INSULIN



Usually 2/3 TDD prior to BKFST and 1/3 PRIOR dinner



'Overbasalization' Common in Type 2 Diabetes Management

Miriam E. Tucker

May 27, 2021

A1c >8% despite more than
.5units/kg per day of basal insulin



Such 'overbasalization,' defined as a [hemoglobin A1c](#) of greater than 8% despite use of more than 0.5 units/kg per day of basal insulin, was identified in about 40% of patients seen in a Florida primary care clinic during 2015-2018. The [findings](#) were published in the April 2021 issue of Clinical Diabetes by Kevin Cowart, PharmD, a diabetes care and education specialist at the University of South Florida, Tampa, and colleagues.



Consider overbasalization if:

TABLE 1 When to Consider Treatment Intensification Beyond Basal Insulin

Definition of overbasalization: the titration of basal insulin beyond an appropriate dose in an attempt to achieve glycemic targets

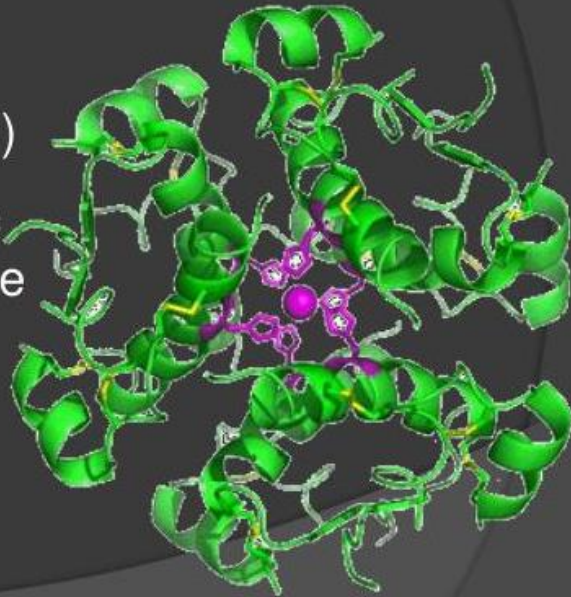
How to identify overbasalization:

- Basal insulin dose >0.5 units/kg/day
- Postmeal blood glucose >180 mg/dL
- A1C not at goal despite target fasting blood glucose level being achieved
- BeAM differential ≥ 50 mg/dL

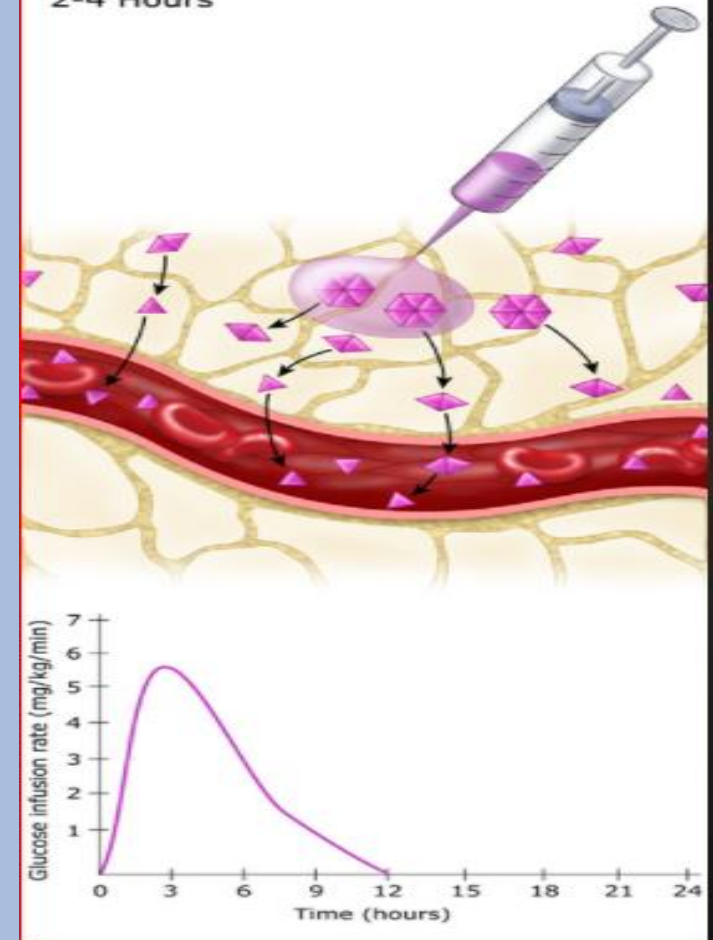


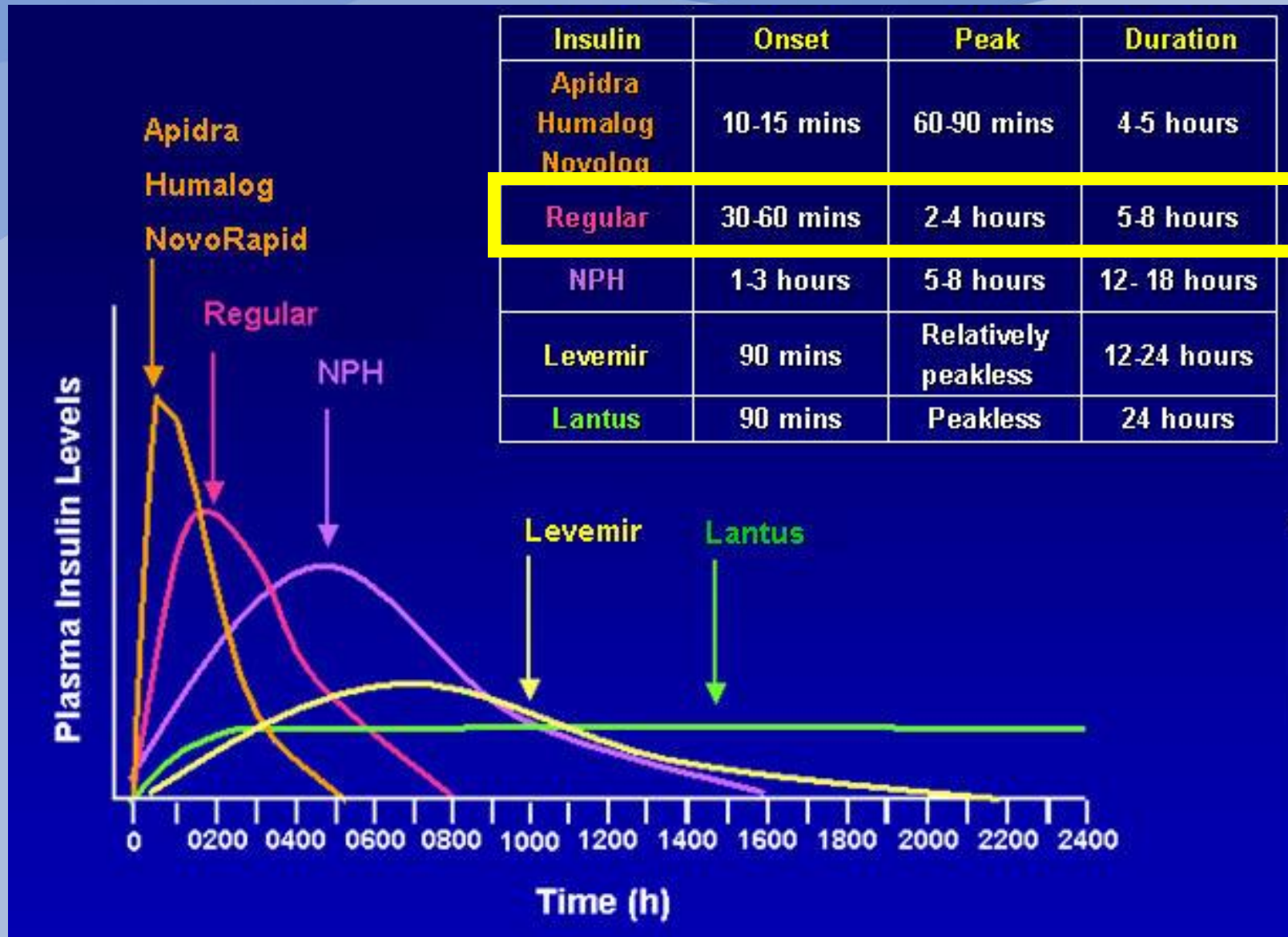
Quaternary Structures of Stored Insulin

- Insulin is stored in pancreas cells as “hexamers” (6-units)
- Stabilized by a Zinc atom at center of the cluster



Regular Human Insulin Peak Time:
2-4 Hours



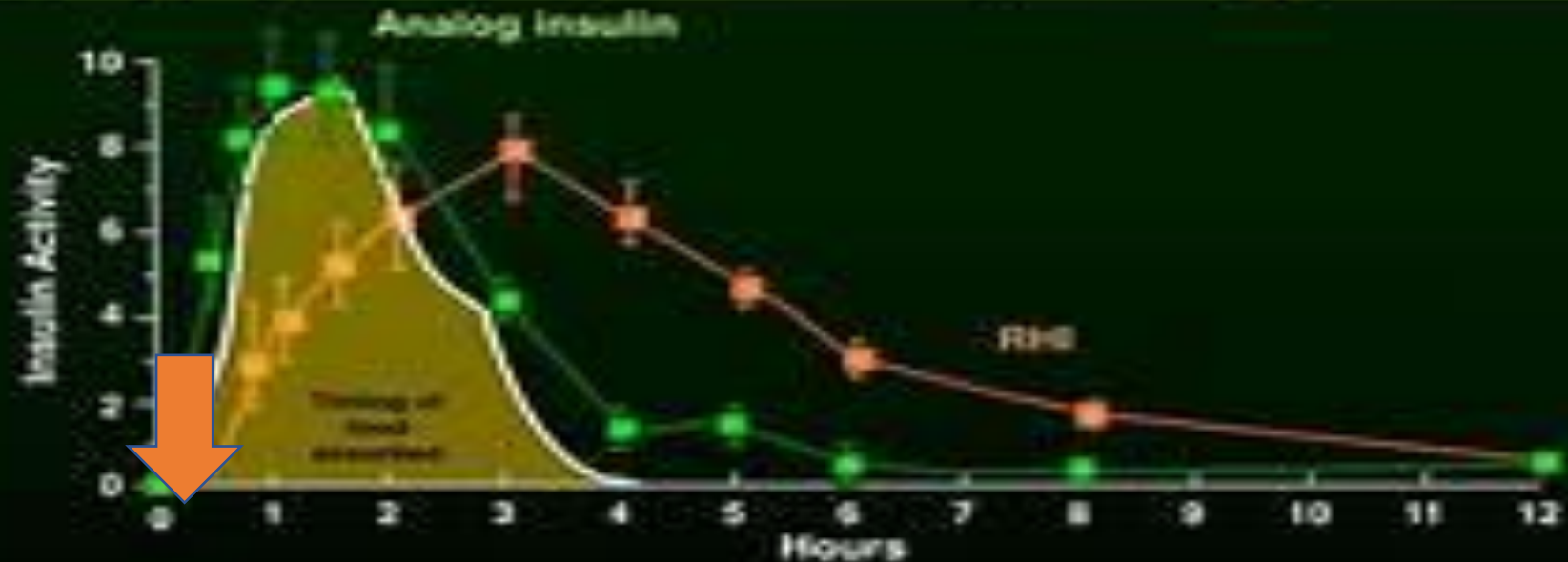


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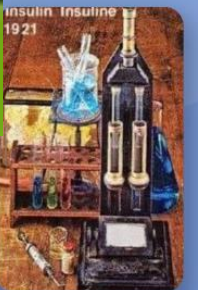
When using regular insulin prior a meal advise administration aprox 20-30 minutes prior the selected meal . This could vary from patient to patient and must be individualized.

Meal Insulin: Rapid-Acting Analogs (Lispro, Aspart, Glulisine) vs Regular

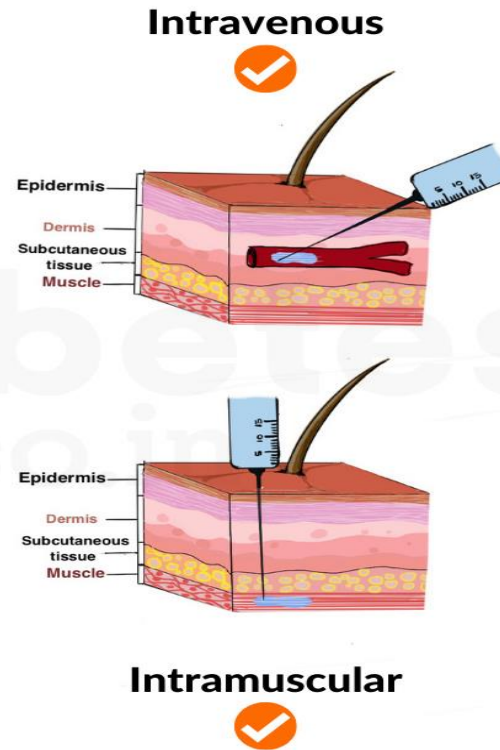
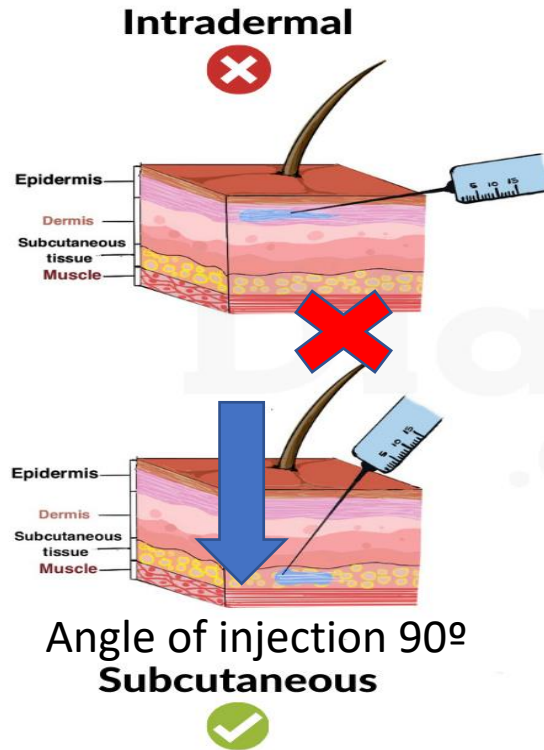


RHI = regular human insulin.

Adapted with permission from Hower DG et al. Diabetes. 1994;43:306-327



TYPES OF INJECTIONS



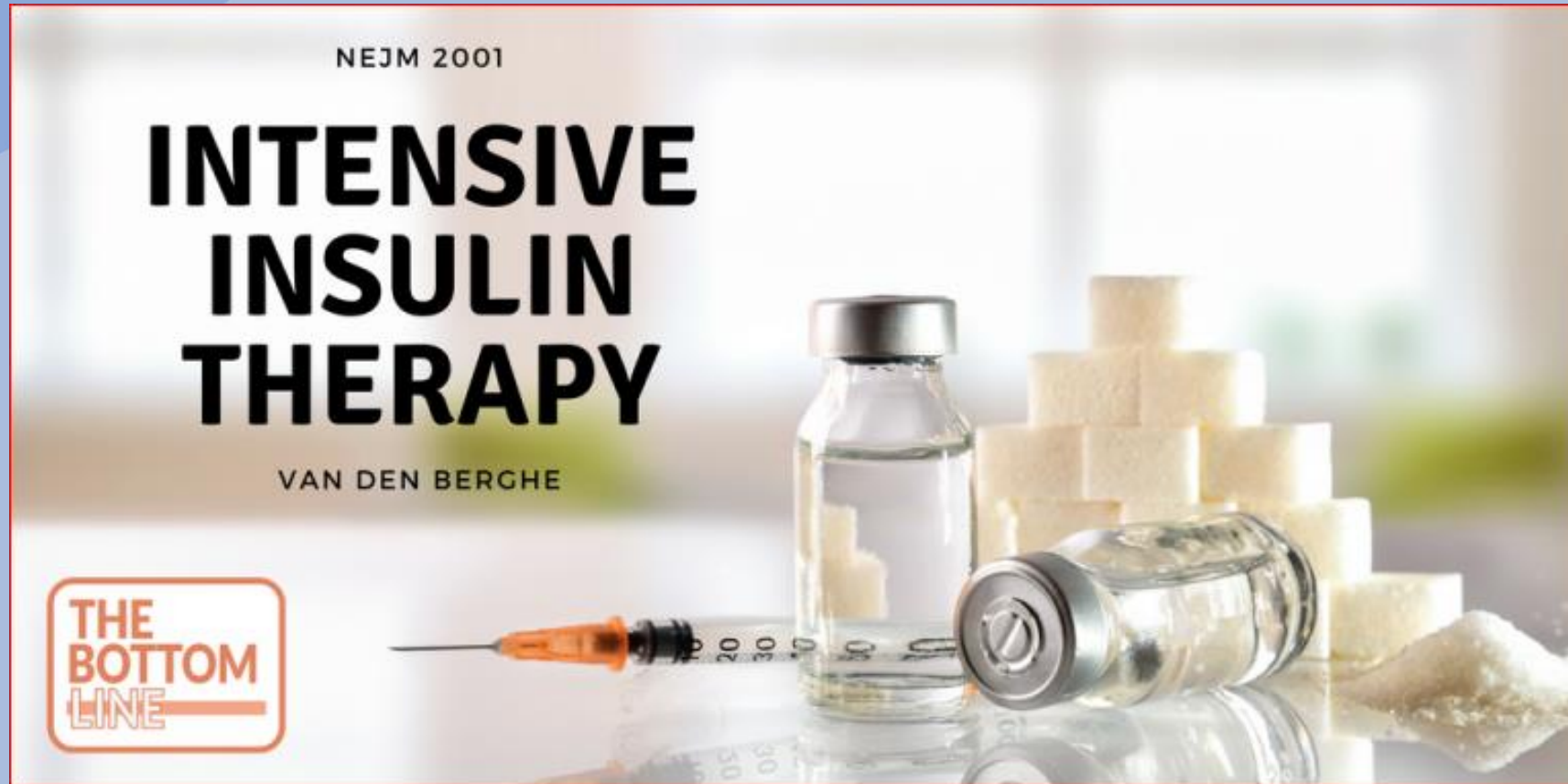
Only in infusions as described in next slide

- ✗ DO NOT USE THIS
- ✓ ROUTINELY DONE
- ✓ IN EMERGENCIES

Diabetes
.co.in



Intravenous regular human insulin: onset of action in minutes. Half life of 9-10 minutes



Potential Indications for IV Insulin Therapy

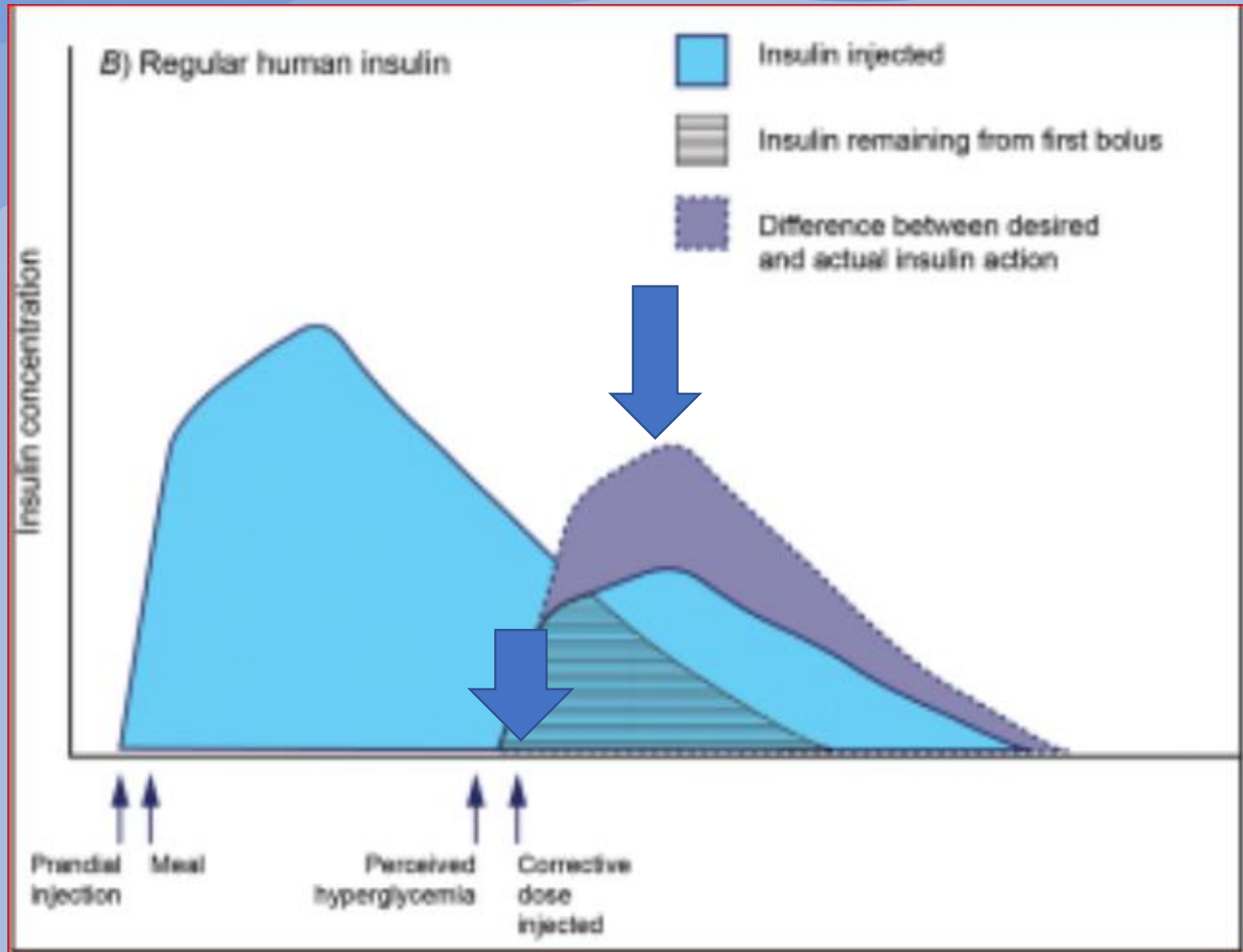
Table 1.

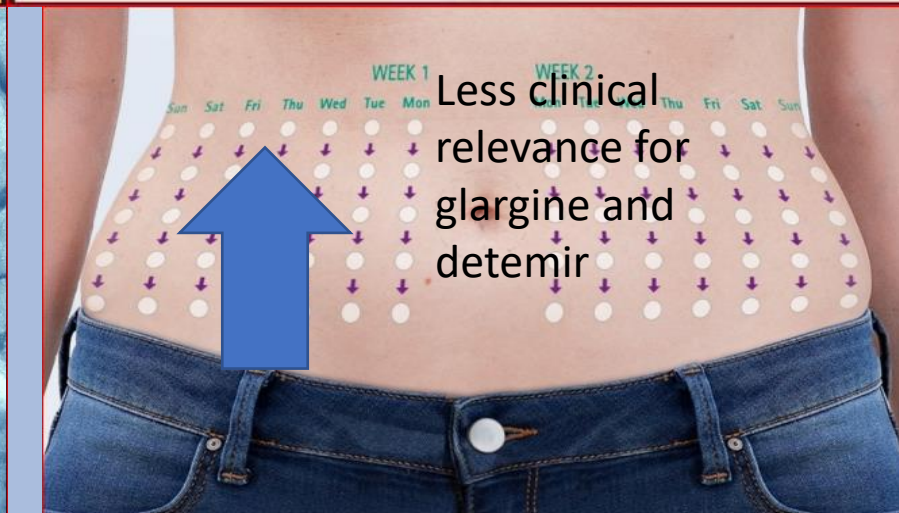
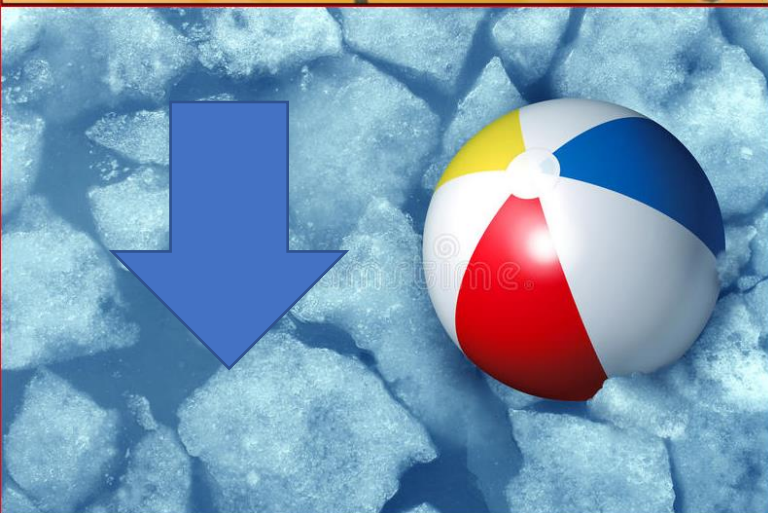
Potential Indications for IV Insulin Therapy²⁰

- Diabetic ketoacidosis
- Hyperglycemic, hyperosmolar state
- Critical care illness (medical/surgical)
- Post-cardiac surgery
- Myocardial infarction or cardiogenic shock
- Prolonged NPO status in patients who are insulin deficient
- Labor and delivery
- Uncontrolled hyperglycemia during high-dose glucocorticoid therapy
- Perioperative period
- Post-organ transplantation
- Stroke
- Total parenteral nutrition therapy
- Dose-finding strategy before converting a patient to subcutaneous insulin



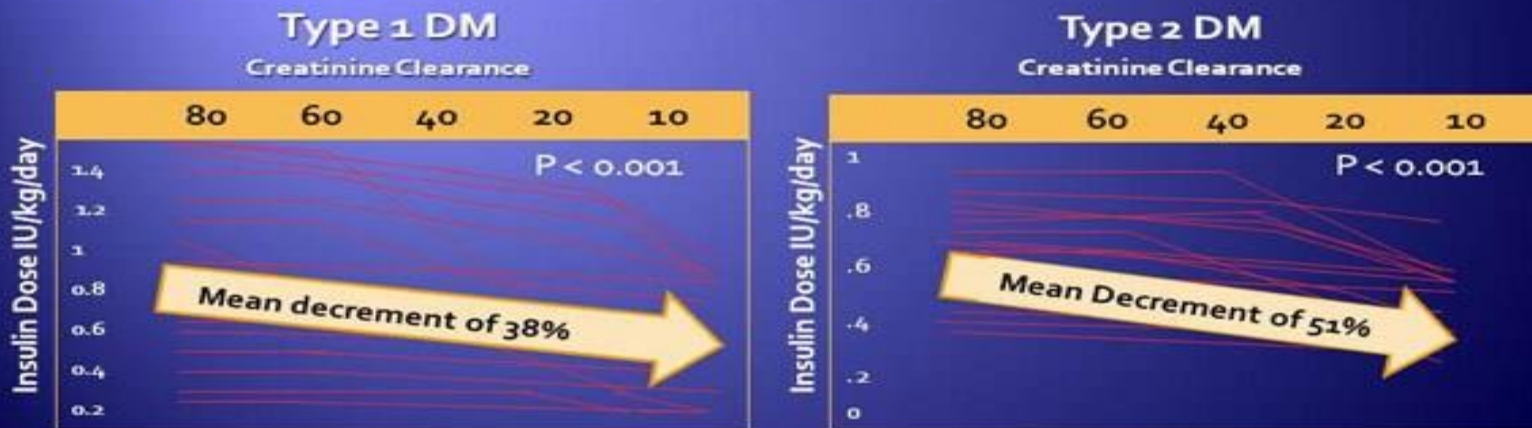
Stacking:" the practice of providing correctional doses of insulin before a prior dose of prandial or the peak action of NPH has had its full effect" Hirsch





Declining Kidney Function = Declining Insulin Requirement

The insulin requirement of patients with Type 1 and Type 2 diabetes was found to be reduced as creatinine clearance rate declined. However, there was considerable inter-individual variation.

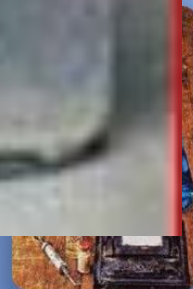


Adapted from Biesenbach G, et al. *Diabet Med.* 2003;20:642-645.





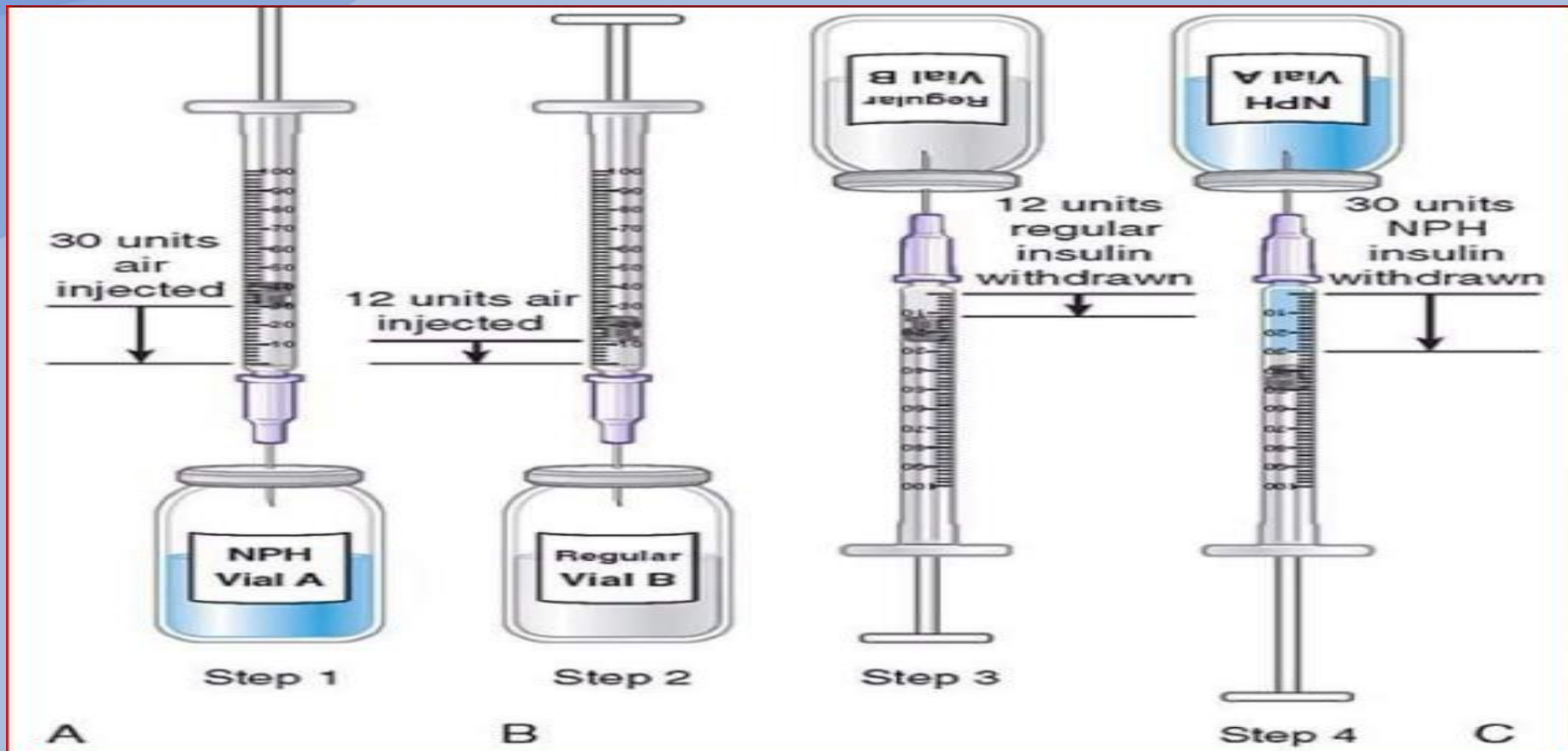
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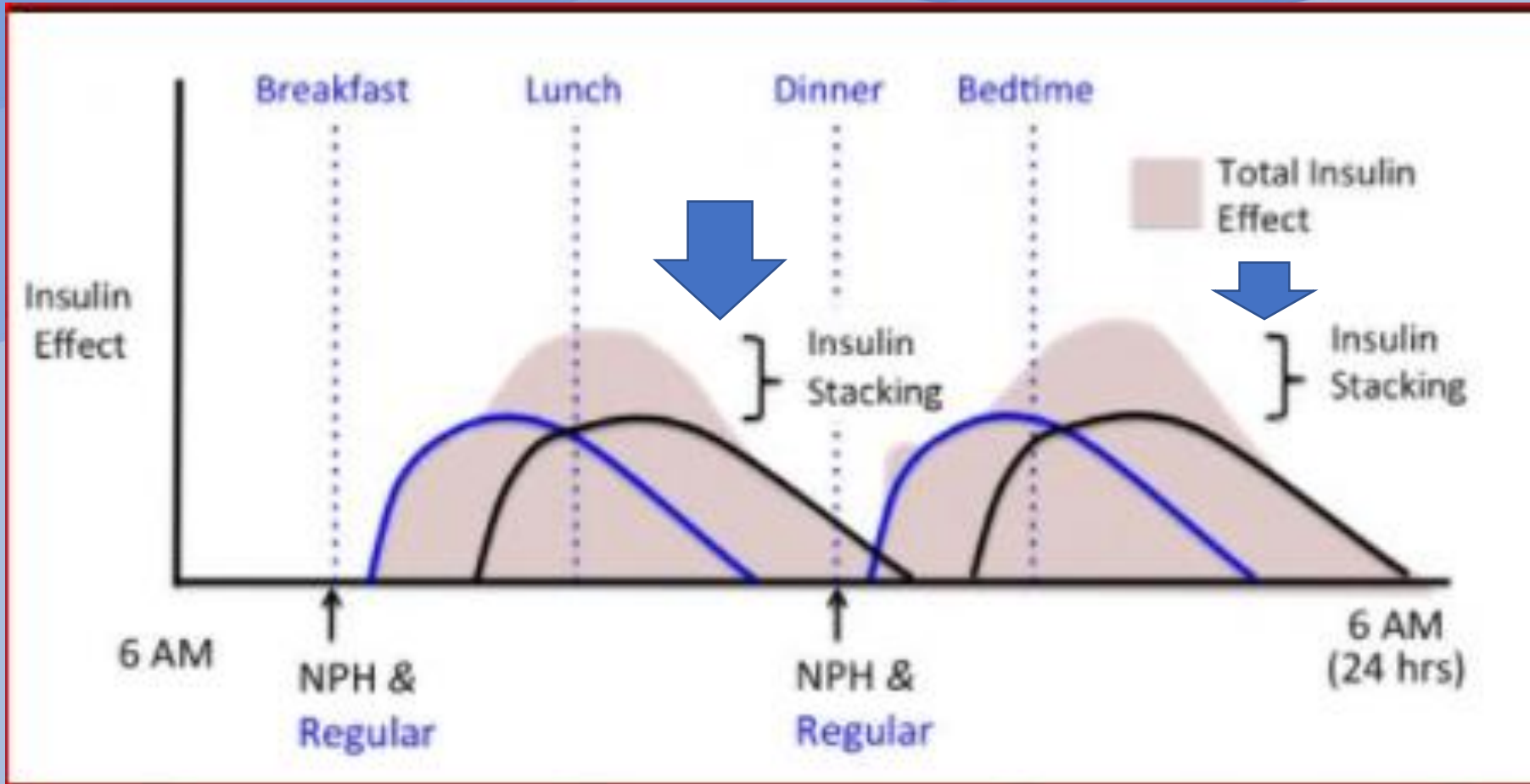
NPH PLUS REGULAR IN SAME SYRINGE

NPH MIX WITH REGULAR DOES NOT AFFECT POTENCY OR TIME ACTION

PROFILE OF REGULAR INSULIN



PATIENT EDUCATION: USE AVAILABLE EDUCATIONAL
VIDEOS | E : INTERNET



Insulin NPH And Regular Human Suspension

COMMON BRAND(S): HUMULIN 70-30, NOVOLIN 70-30

GENERIC NAME(S): INSULIN NPH AND REGULAR HUMAN

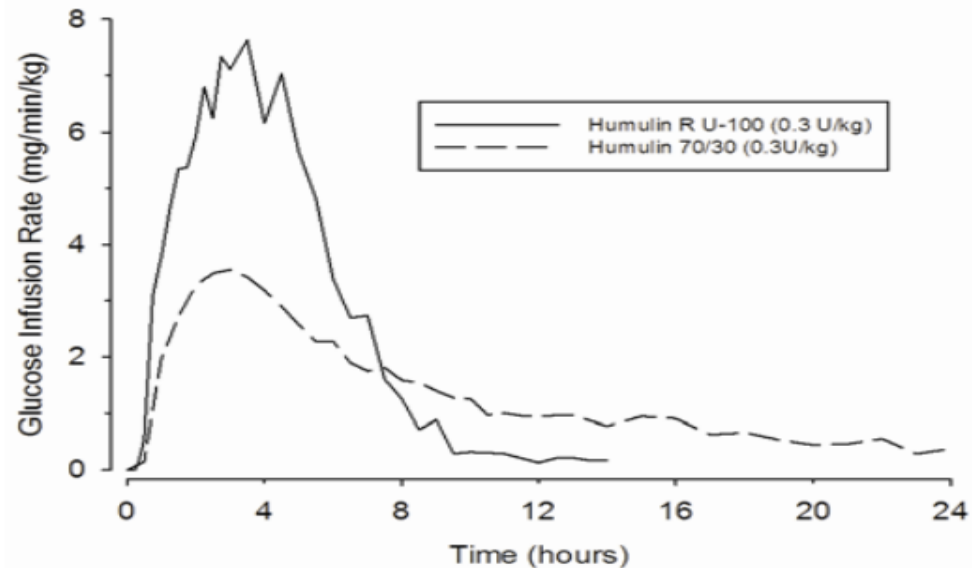


Figure 1: Mean Insulin Activity Versus Time Profiles After Subcutaneous Injection of HUMULIN 70/30 or HUMULIN[®] R U-100 (0.3 unit/kg) in Healthy Subjects.



CONSIDER ADDING REGULAR INSULIN TO NPH IF BASAL > .5U/kg/DAY
POSTPRANDIAL HYPERGLYCEMIA still PRESENT

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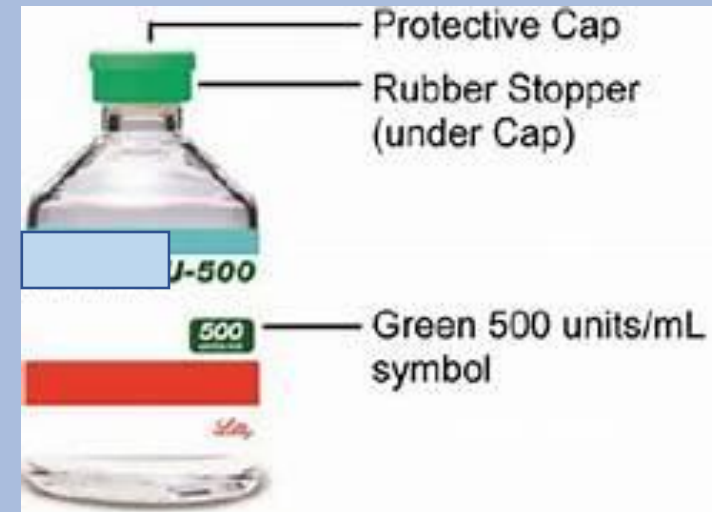
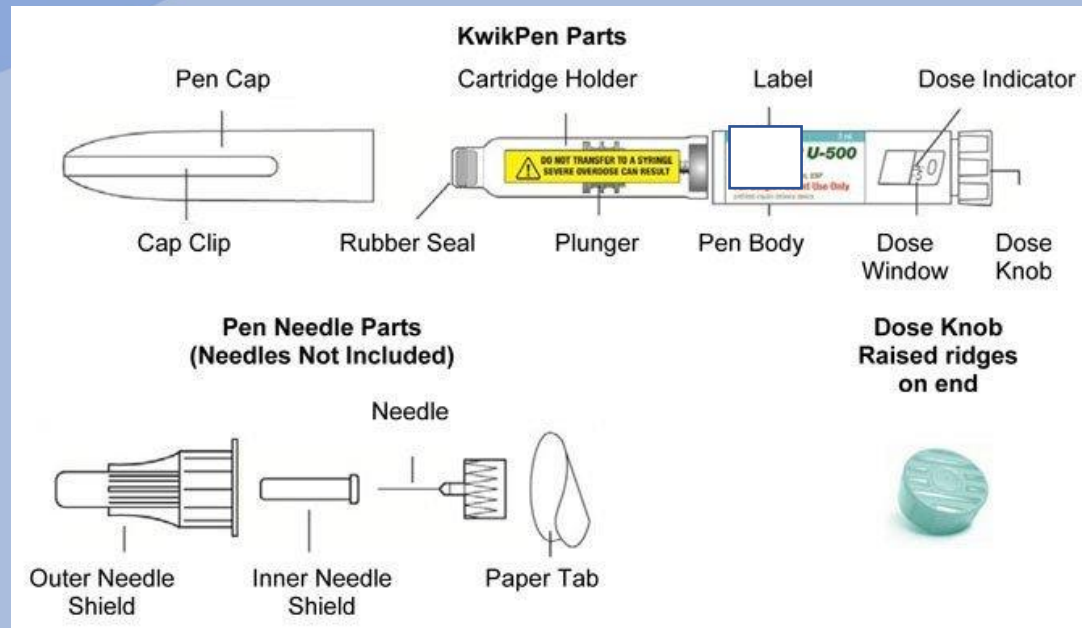
Premixed Insulin

Premixed insulin (e.g., NPH/regular 70/30) is administered either before the **largest** meal of the day or, more commonly, as two injections per day before breakfast and dinner (31). Therefore, its use allows for less flexibility in dosing than a basal-bolus insulin regimen. Although premixed insulin is less costly than insulin analogs, patients must eat regular meals and may be at greater risk for hypoglycemia than with a basal-bolus regimen (31,32). The choice of whether to initiate a basal-bolus or premixed insulin regimen should be patient specific, accounting for eating habits, preferences, convenience, and cost (13).

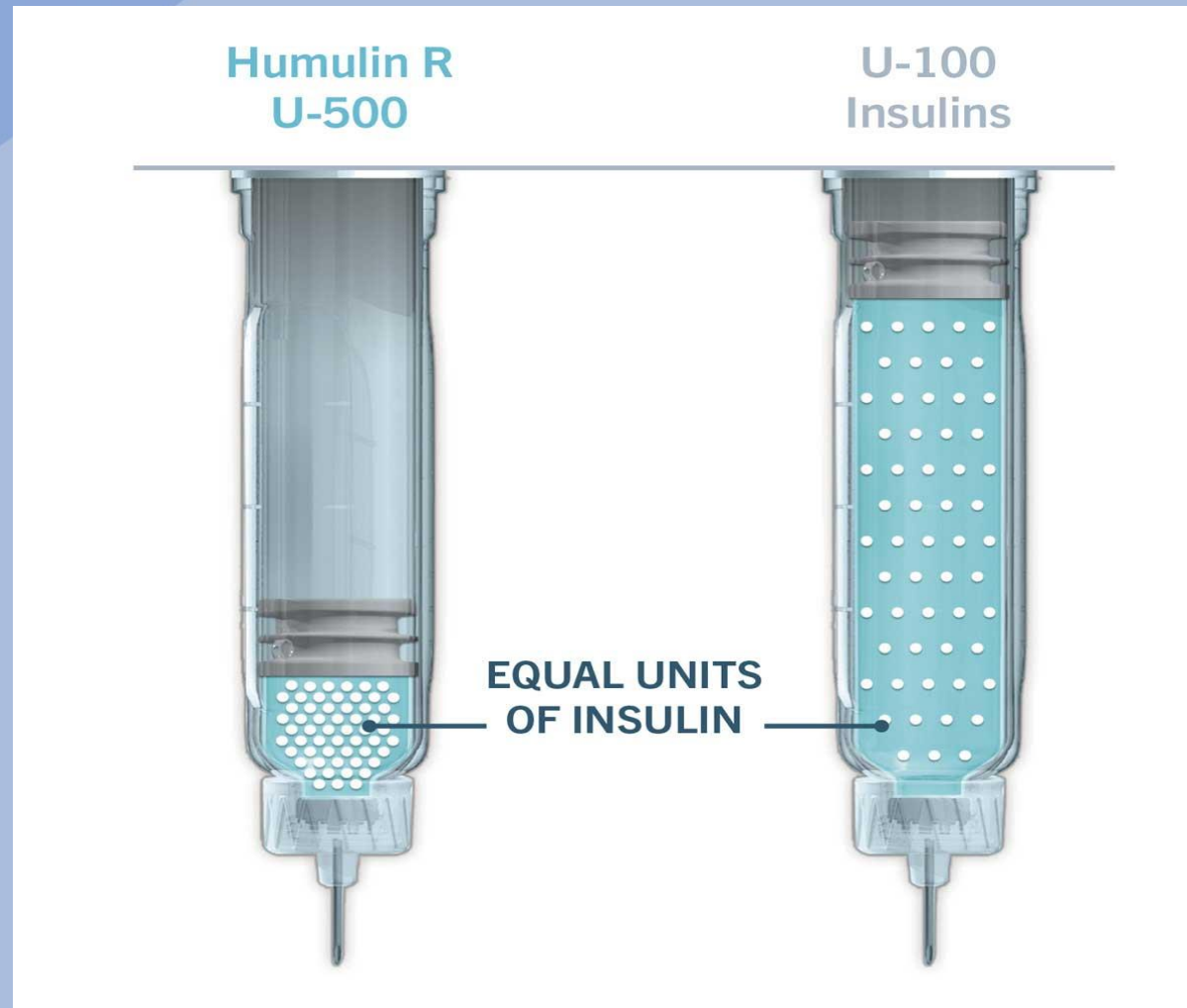


Regular insulin u 500

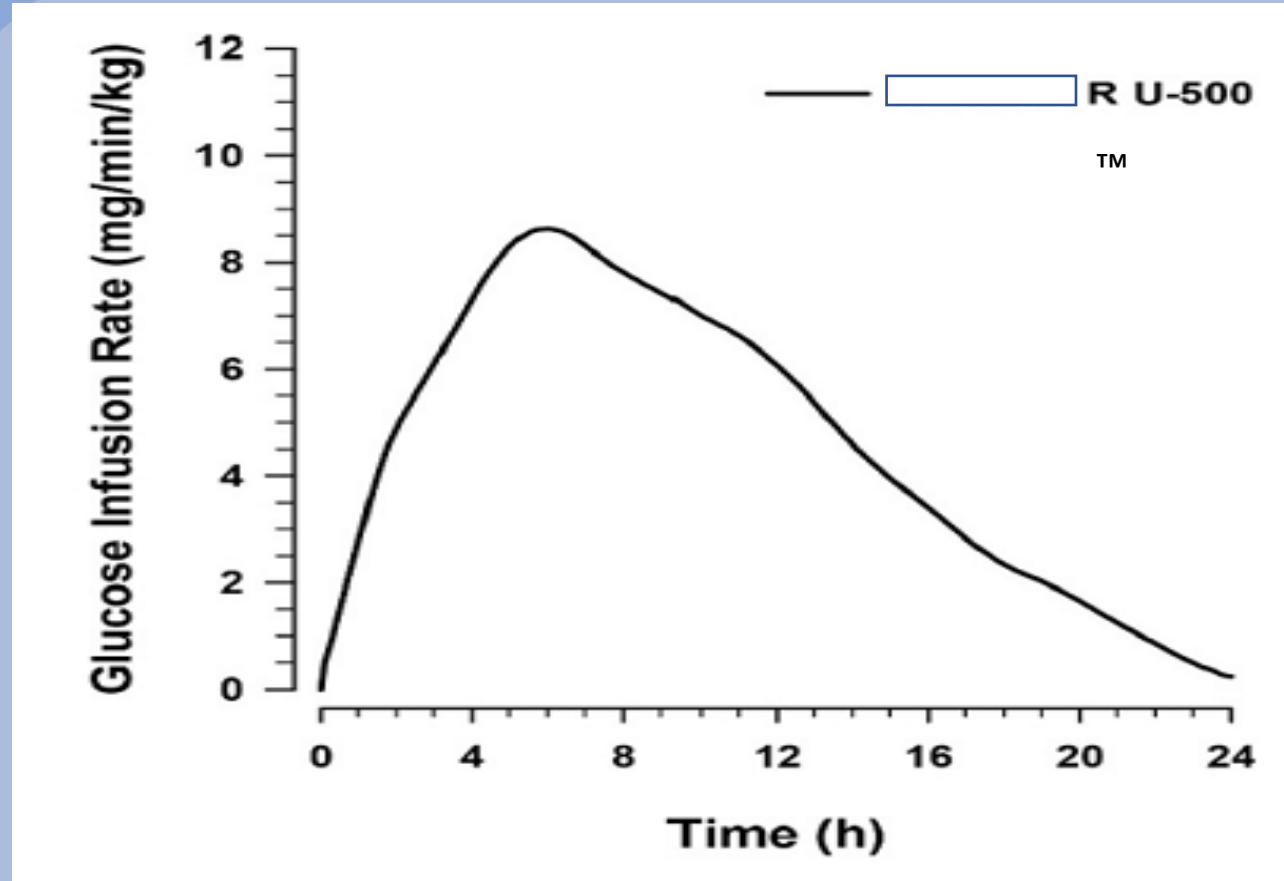
Considered for highly resistant insulin individuals who use more than 200 units of insulin per day



Extreme caution when calculating dose “ it is a concentrated regular insulin

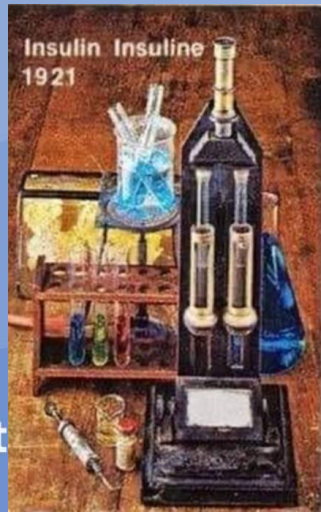


R u 500



package insert information on file

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Importance of patient education



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Take- away points:

Human insulin is a cost -effective alternative for the treatment of diabetes mellitus

Importance of mode of action of each preparation is important for appropriate therapy in the individual to be treated to avoid stacking and risk of hypoglycemia

Regular insulin should be used by subcutaneous route but can be used in IV infusions in certain clinical scenarios described

NPH insulin can be an alternative to analog basal insulin. Be familiar with onset of action ; peak of action and duration of action. Get familiar with over-basalization concept

NPH insulin can be divided in twice a day dose to achieve 24 hr cover of “basal insulin” needs

Regular insulin and NPH insulin can be mixed in order to achieve pre-prandial and postprandial blood glucose control . Avoid insulin stacking

Pre- mixed insulin use has particular characteristics for the use in certain individuals but with less flexibility in dose modification

Regular u 500 should be used for individuals using more than 200 units of insulin per day . Should be used with extreme caution



g Successful Path

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2021

