SESSION 4
PEDIATRIC SESSION

NOVEL AND UPCOMING INSULINS:
FASTER INSULINS, INHALED INSULIN, AND WEEKLY BASAL INSULINS

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EPIC DIABETES CONFERENCE

JUNE 1, 2024 CU ANSCHUTZ MEDICAL CAMPUS

EMPOWERING PATIENTS FOR INDIVIDUALIZED CARE

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DISCLOSURES: WADWA

- Research support: Dexcom, Eli Lilly & Co, Tandem Diabetes Care
- Consultant/ Speaker: Dexcom, Tandem Diabetes Care
- Advisory Board: Provention Bio, Sequel Med Tech

DISCLOSURES: TRIOLO

•None

OUTLINE

- Historical perspective
- Current insulins
- New insulins

HISTORICAL BACKGROUND OF INSULIN

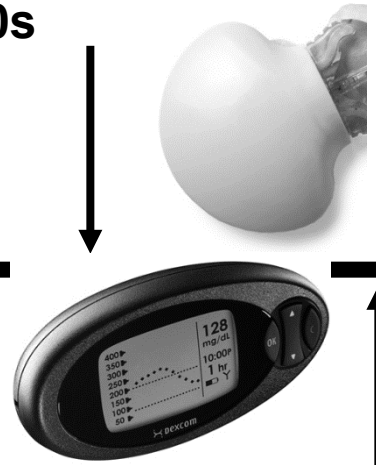
PROGRESS IN DIABETES CARE

Discovery of Insulin, 1920s

First portable Glucose monitors 1970s

DCCT 1993

Continuous Glucose Monitoring 2000s



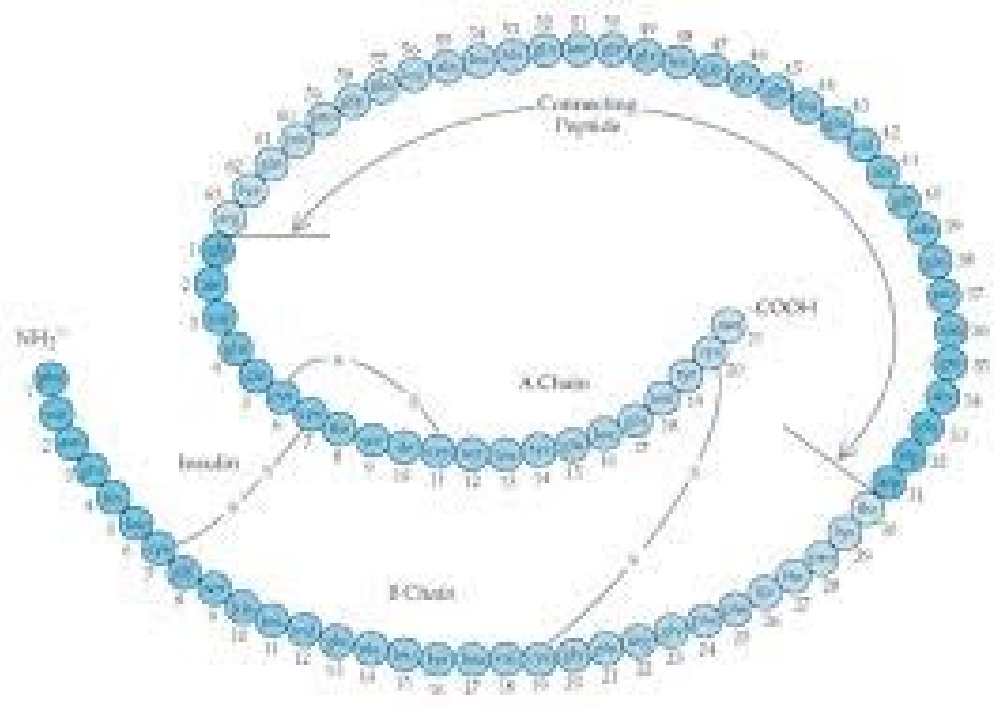
NPH insulin 1930s

Biosynthetic Human insulins 1980s

Rapid acting/Basal Insulins and CSII 1990s

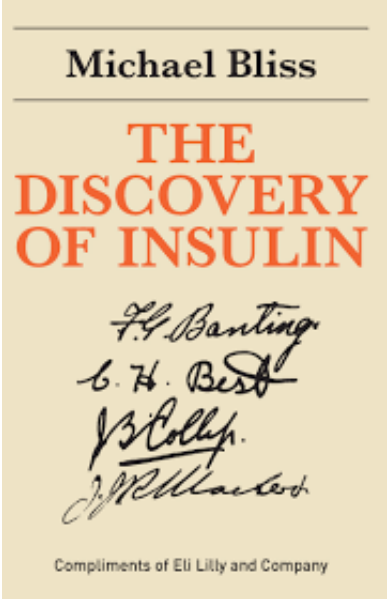
HCL

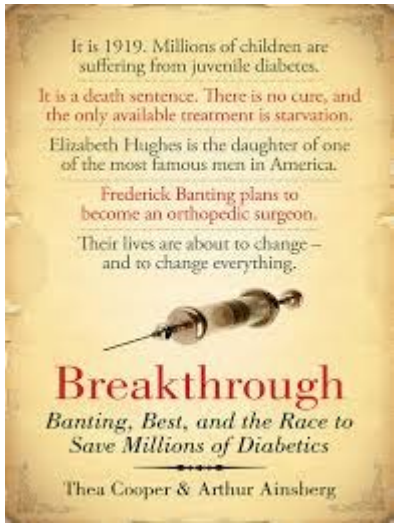
INSULIN MOLECULE



- Two peptide chains (A and B)
- Connected via a short C-domain acting as a hinge between the two
- Three disulfide bridges
  - A7-B7
  - A20-B19
  - A6-B11

https://pro.endocrineweb.com/conference-news/ada-2022-glucose-responsive-insulin-technology-a-future-available-to-all





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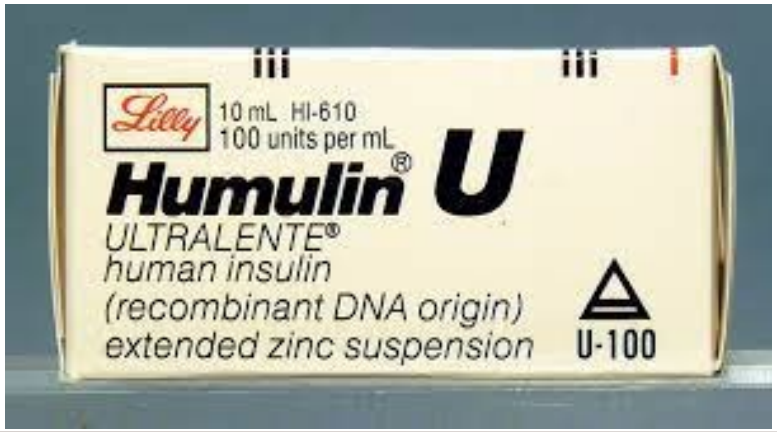
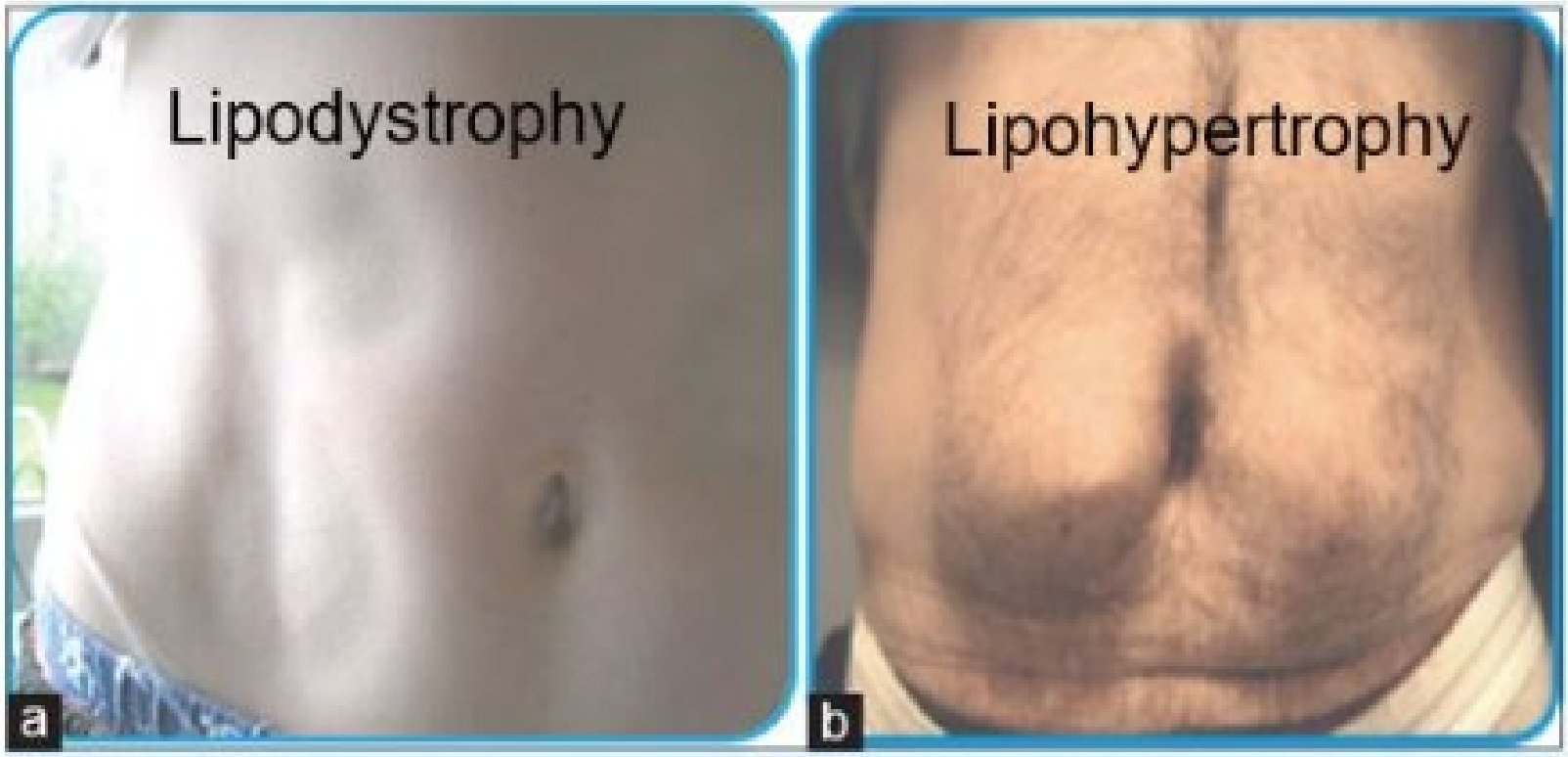
OLD INSULINS

Old insulins:

- Semilente, Lente, Ultralente
  - Early 1950's to 2011
- Porcine, Bovine, Regular insulins



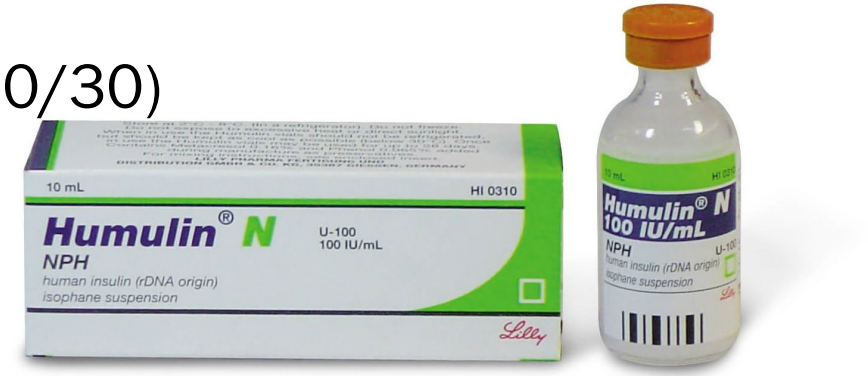
MORE LIPOATROPHY AND LIPOHYPERTROPHY WITH PREVIOUS INSULINS



NPH

NPH still used (“cloudy” insulin)

- Neutral Protamine Hagedorn insulin
- Draw in syringe
- Can mix with R, Humalog, Novolog
- Pre-mixed (70/30 (N/R), 75/25 (N/H), Novolog 70/30)
- Less expensive than newer analogs
- ($43 for 5 pens – GoodRx)



CURRENT INSULINS

Basal: long acting

- Glargine: Lantus, Basaglar, Semglee, Toujeo
- Detemir: Levemir

Bolus: short acting

- Lispro: Humalog
- Aspart: Novolog

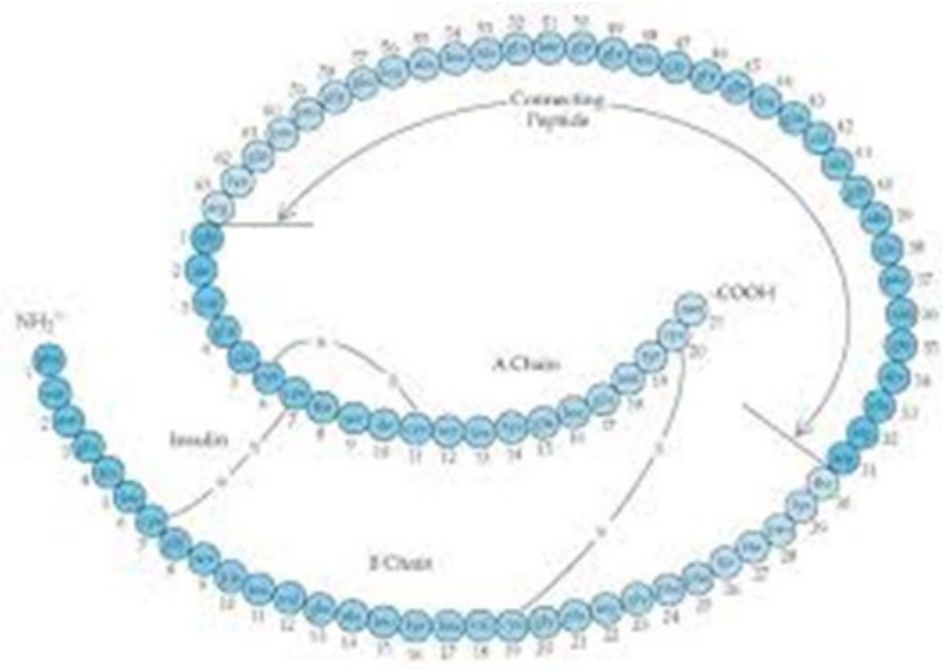
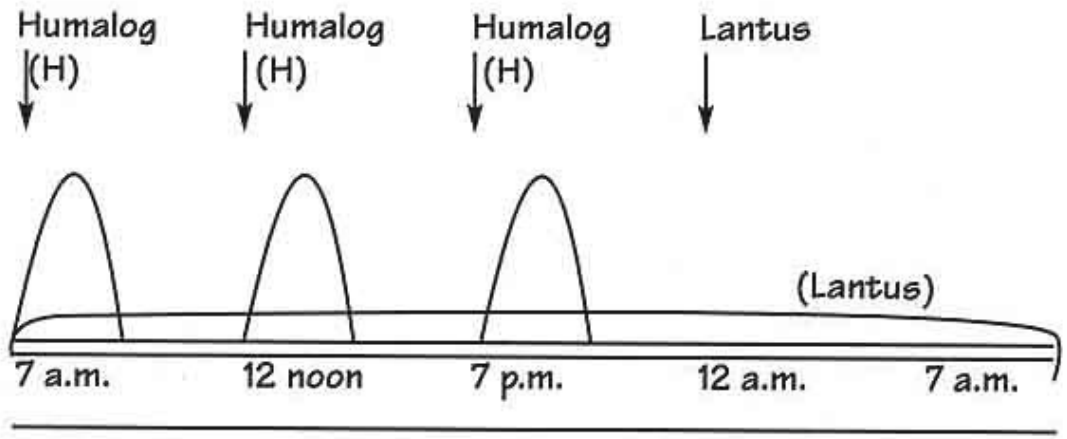


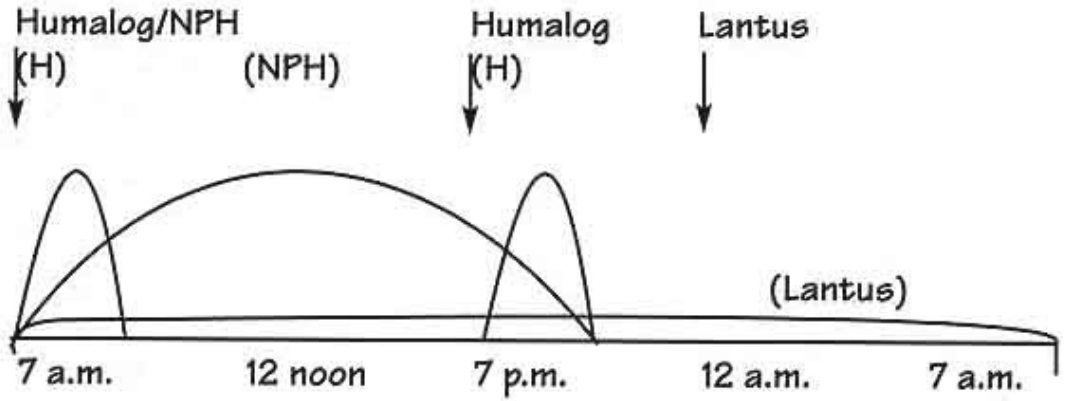
Figure 1: Use of Lantus Insulin

Two of the most common methods of using Lantus insulin:

In the first example, Lantus is used as the basal insulin and Humalog (H) or NovoLog is taken prior to meals.



In this second example, NPH and Humalog (H) or NovoLog are taken in one syringe in the a.m. Humalog is taken alone at dinner. Lantus (alone in the syringe) is taken either at dinner, at bedtime or in the a.m.



Frohnert BI and Chase HP, Insulin: Types and Activities, Understanding Diabetes

INSULIN CONCENTRATIONS

Standard concentration = U100 (100 units/ ml)

- Regular available as U500
- Glargine available as U300
- Degludec available as U200

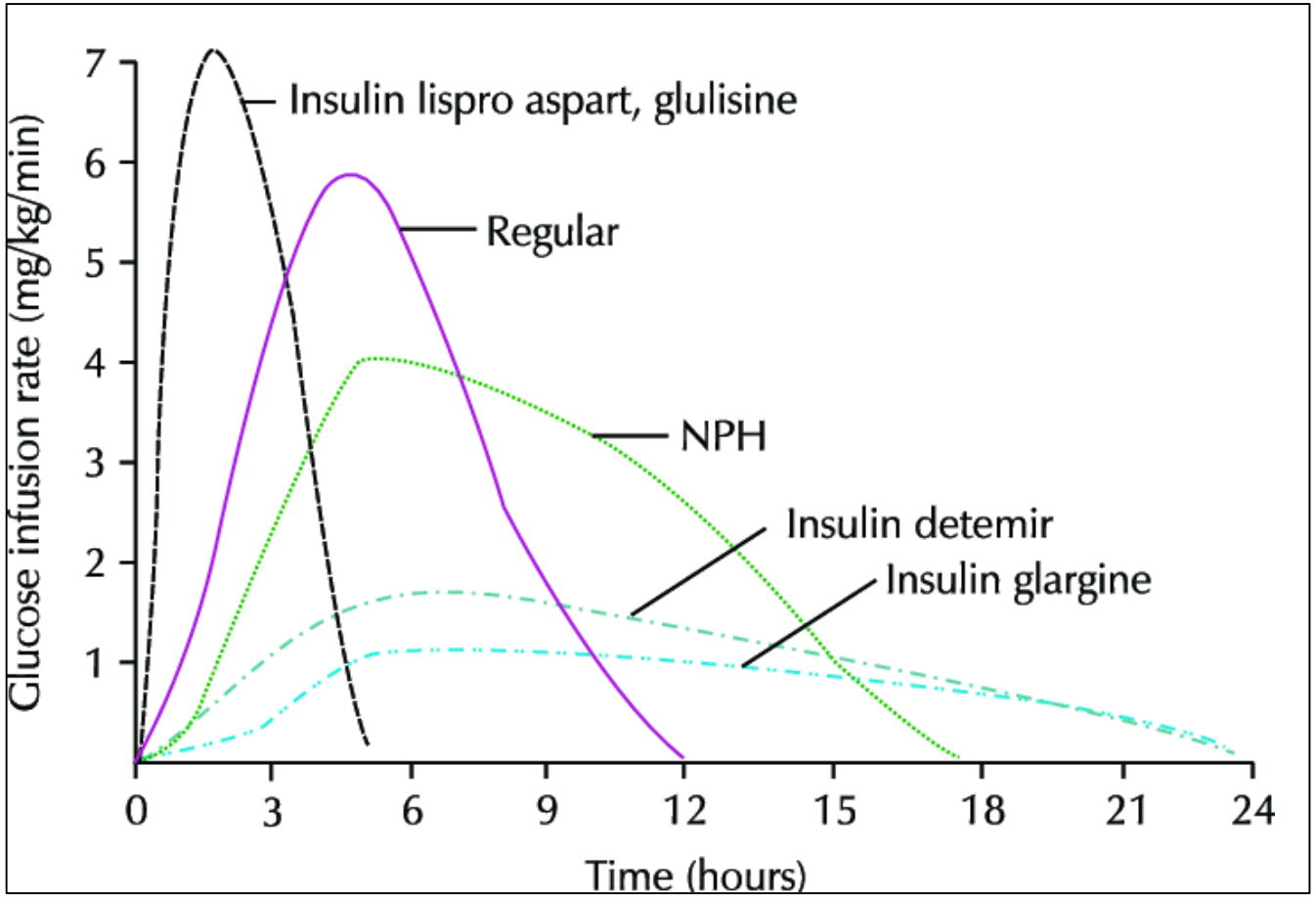
Diluted insulins

- Not standard
- U10, U50, U25, etc…
- Compounding pharmacy vs. other prep

Insulins	Onset	Peak	Duration
Lispro (Humalog, Lyumjev) Aspart (Novolog, Fiasp) Glulisine (Apidra)	10-15 min	60-90 min	2-4 hours
Regular (Humulin R, Novolin R, Myxredlin)	30-60 min	2-4 hrs	6-8 hrs
NPH	60-90 min	4-8 hrs	10-15 hrs*
Glargine (Lantus, Basaglar, Toujeo, Semglee)	1-2 hours	none	22-24 hrs
Detemir (Levemir)	1-2 hours	none	12-24 hrs*
Degludec (Tresiba)	1-2 hours	None	24-36 hrs

* Dose dependent duration

TIME-ACTIVITY CURVES FOR AVAILABLE INSULIN FORMULATIONS



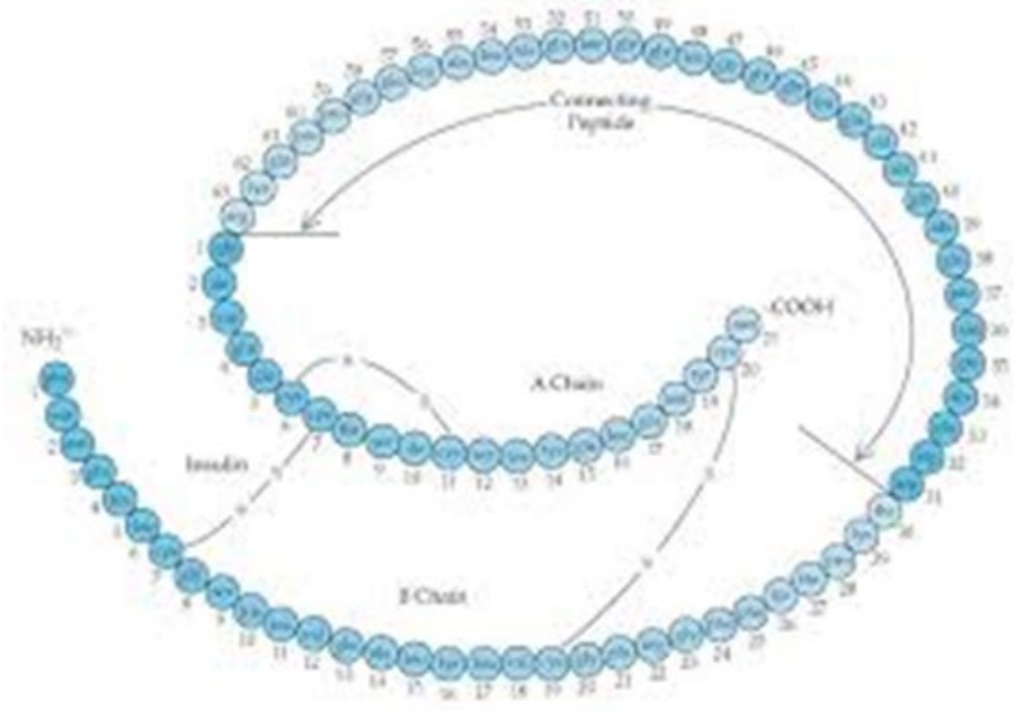
NEWER INSULINS

Basal

- Insulin degludec (Tresiba)

Bolus

- Inhaled insulin (Afrezza)
- Faster insulin aspart (Fiasp)
- Ultra rapid insulin lispro (Lyumjev)

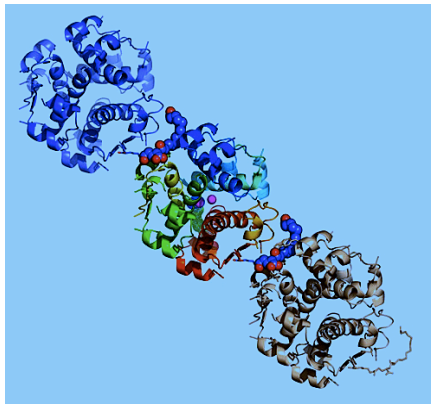


NEWER BASAL INSULINS

INSULIN DEGLUDEC (TRESIBA)

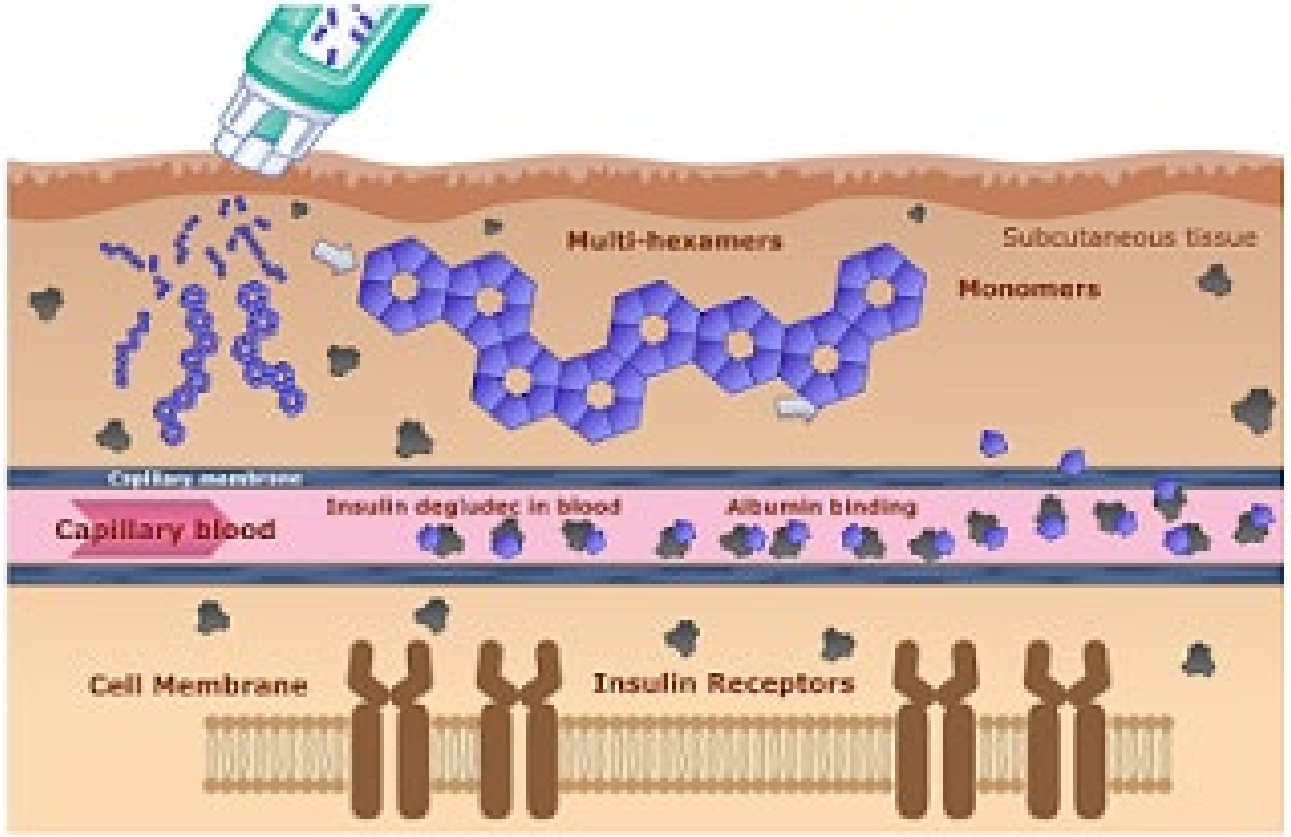
Insulin Degludec (Tresiba, Novo Nordisk)

- Clinical trials completed in 2011 in adults with T1D and T2D
  - T2D: Lancet, March 2011
  - T1D: Diabetes Care, March 2011
- **Pediatric clinical trial data published in 2015**
  - Thalange, Klingensmith et al, *Pediatr Diabetes* 2015



- *Approved by FDA in 2016*
- Covered by some insurance, some require prior authorization and/or documentation of failure with other long-acting insulins

Protraction mechanism for Degludec



Hexamers formed leading to duration of action > 24 hours

Advantages

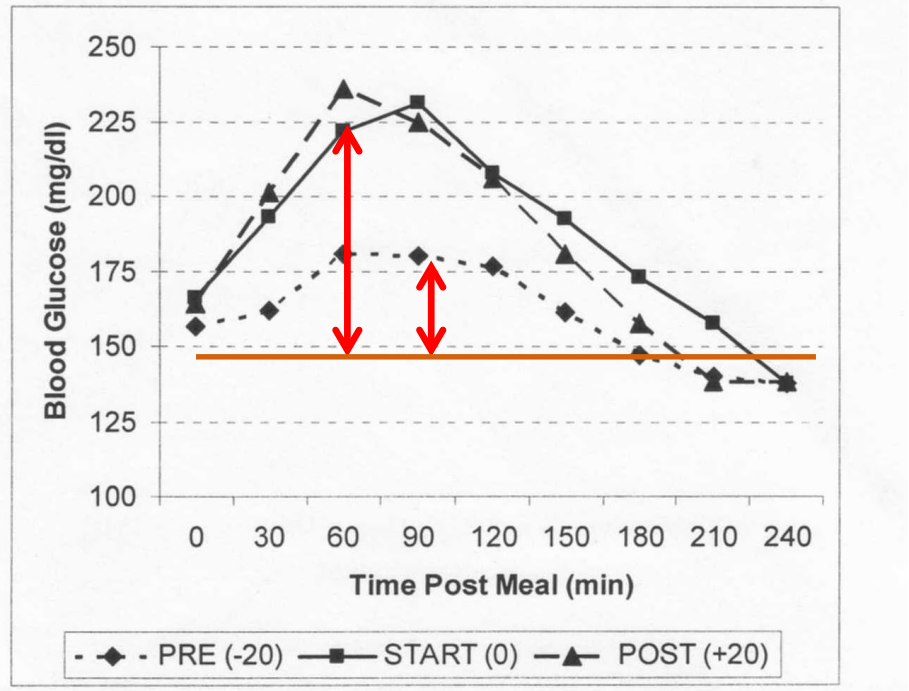
- Flexible dose timing
- More stable basal action
- Decrease risk for severe hypoglycemia and possibly for ketoacidosis

Disadvantages

- Newer insulin
  - Access difficult for some
- Longer half life
  - Takes more time to see impact of adjustments

NEWER RAPID ACTING INSULINS

EFFECT OF BOLUS TIMING ON BG EXCURSIONS



p<0.05 for PRE vs START for 60, 90, and 120 minutes and PRE vs POST for 150 minutes

- Insulin pump boluses given at, pre and post meal time
- Area under curve is TOO LARGE for CURRENT rapid acting insulin analogs given at meal time
- Differences in glycemic excursions significant when bolus given 20 min before meal

Cobry, Chase et al, Diabetes Technol Ther. 2010 Mar

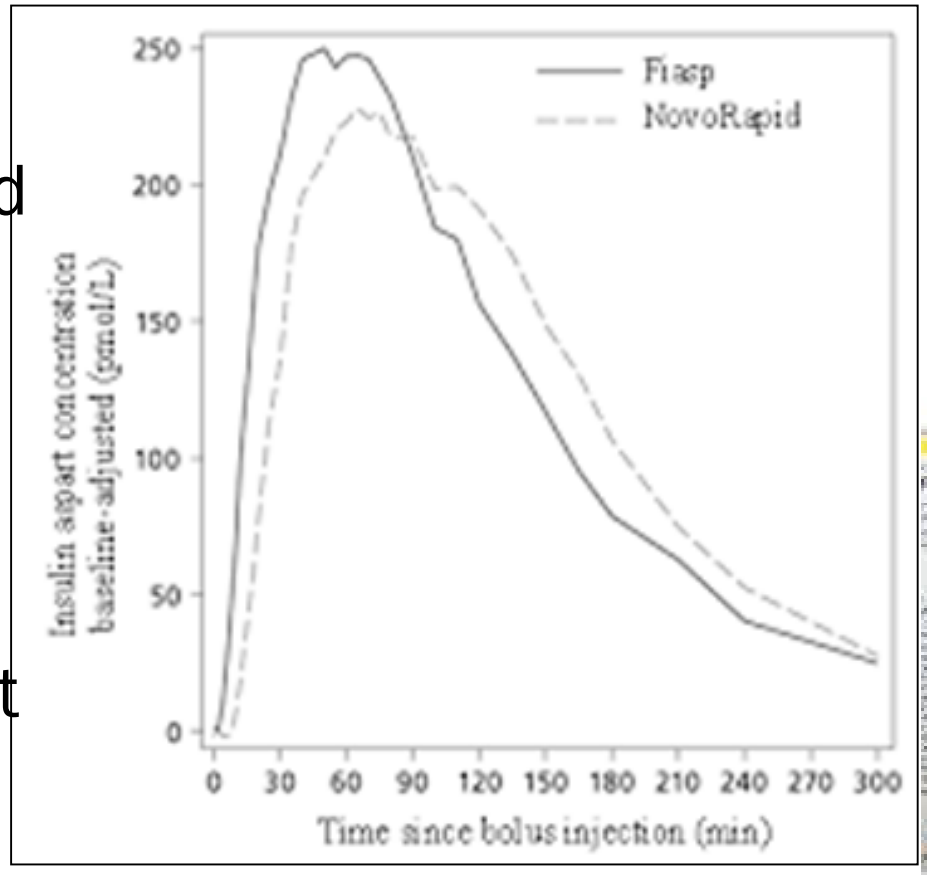
NEWEST RAPID ACTING INSULINS

Ultra-rapid Insulins

- New insulins with more rapid onset
  - Inhaled insulin (Afrezza)
  - Faster acting insulin aspart (Fiasp)
  - Ultra rapid insulin lispro (Lyumjev)

FASTER INSULIN ASPART (FIASP)

- Addition of niacinamide (vitamin B3) to current insulin aspart to increase speed of absorption
- L-arginine also added for stability
- More rapid onset than aspart (NovoRapid/ Novolog)
- FDA approved for ages 2 & over but not in HCL*



FASTER INSULIN ASPART (FIASP)

- Onset 1 and onset 2 studies: non-inferior to aspart in adults with T1D, T2D
- Onset1
  - Randomized, 3-arm 26-week study in adults with T1D (n=1043)
    - Pre-meal use double blinded
    - Post-meal use open-label (n=382)
  - Change in HbA1c non-inferior
    - 7.6% to 7.3% (pre-meal faster aspart), 7.4% (aspart), 7.5% (post-meal faster aspart)

Russell-Jones et al, Diabetes Care July 2017

FASTER INSULIN ASPART (FIASP)

- Onset2
  - Randomized 26 week study in adults with type 2 diabetes (n=689)
    - Mealtime use of aspart vs. faster aspart
  - Change in HbA1c non-inferior
    - A1c 6.6% at end of trial for both groups
  - Overall safety equal but more 0-2 hr postmeal hypoglycemia in faster aspart group

Bowering et al, Diabetes Care July 2017

FASTER INSULIN ASPART (FIASP)

- Global Pediatric trial: Onset 7
  - Ages 2-17 years (n=777)
  - Participants on Multiple Daily Injections
  - 3-arm, 26 week randomized, double blinded study (similar to trials in adults with T1D)
  - Pre and post-meal faster aspart non-inferior to pre-meal aspart
  - Lower A1c with pre-meal vs. post-meal faster aspart (-0.17% (-0.30,-0.03), p=0.014)

Bode BW et al, Diabetes Care July 2019

FASTER INSULIN ASPART (FIASP)

- Caveats
  - Not approved for pediatric patients with T2D
  - Anecdotal data on pump occlusions
    - No published data
  - Now approved for use in Omnipod (but not OP5)

  - Insurance coverage improved in 2024 but may still need prior authorization

LYUMJEV (INSULIN LISPRO-AABC)

Ultra-rapid lispro insulin (Eli Lilly)

Excipients:

- Treprostinil – prostaglandin analogue
- Citrate – increases absorption rate, increases vascular permeability

FDA approved

- For adults with T1D, T2D in June 2020
- For use in insulin pumps in August 2021
- For pediatric T1D in October 2022
- Not approved in HCL systems (yet…)

Bode BW et al. Diabetes Technol Ther. 2021 Jan;23(1):41-50.
Warren M et al, Diabetes Obes Metab. 2021 Jul;23(7):1552-1561.

LYUMJEV (INSULIN LISPRO-AABC)

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

ORIGINAL ARTICLE | Open Access

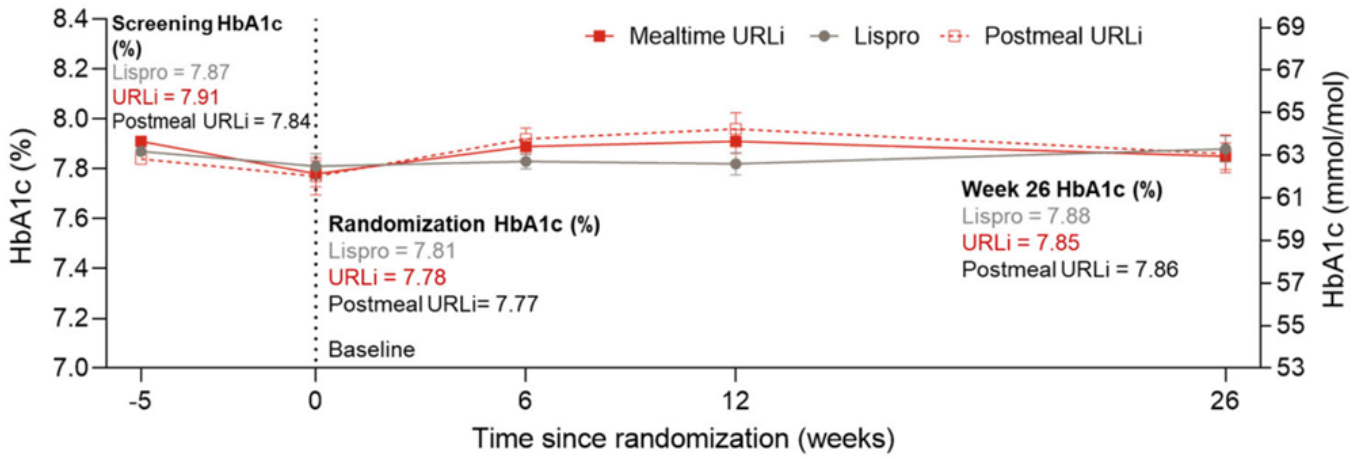
Efficacy and safety of ultra-rapid lispro versus lispro in children and adolescents with type 1 diabetes: The PRONTO-Peds trial

R. Paul Wadwa MD, Lori M. Laffel MD, Denise R. Franco MD, Mary Anne Dellva MS, Alastair W. Knights PhD, Robyn K. Pollom ANP

First published: 24 August 2022 | https://doi.org/10.1111/dom.14849

LYUMJEV (INSULIN LISPRO-AABC)

FIGURE 1 Mean glycated haemoglobin (HbA1c) from study entry to Week 26. Data are mean at screening and least squares mean ± standard error at all other timepoints and based on the mixed-effects model for repeated measurements analysis in the efficacy estimand. Abbreviations: HbA1c, glycated haemoglobin haemoglobin; URLi, ultra-rapid lispro



3 arm, 26 week treat to target study in 716 pediatric T1D participants age 1-<18 yrs (12.3 yrs)

Mealtime lispro vs. mealtime URLi vs. postmeal URLi

Change in HbA1c baseline to 26 weeks noninferior

LYUMJEV IN HYBRID CLOSED LOOP SYSTEMS

Studies done using Lyumjev in HCL:

- Tandem Control IQ NCT05403502
- Medtronic 780G NCT05325294

ClinicalTrials.gov

ULTRA-RAPID LISPRO INSULIN WITH CONTROL-IQ

Published May 24, 2024!

- Study at 14 US sites (including BDC Pediatric & Adult clinics)
- N=179, age 6-75 yrs (109 pediatric (avg age 12 yrs), 70 adult (avg age 43 yrs)
- 173 completed study
- Lispro (Humalog) for 16 day lead-in,
- 13 weeks on Ultra-rapid lispro (URLi)
- Time in target range (70-180 mg/dl) increased from 65% to 67%
- Satisfaction on URLi higher than with lispro (questionnaire data)

DIABETES TECHNOLOGY & THERAPEUTICS
Vol 0 Iss 0, May 22, 2024

https://doi.org/10.1089/dia.2024.0048

DTT

Multicenter Evaluation of Ultra-Rapid Lispro Insulin with Control-IQ Technology in Adults, Adolescents, and Children with Type 1 Diabetes

Carol J. Levy, MD [1], Ryan Bailey, MS [2], Lori M. Laffel, MD [3], Gregory Forlenza, MD [4], Linda A. DiMeglio, MD [5], Michael S. Hughes, MD [6], Sue A. Brown, MD [7], Grazia Aleppo, MD [8], Anuj Bhargava, MD [9], Viral N. Shah, MD [4], Mark A. Clements, MDPhD [10], Mark Kipnes, MD [11], Brittany Bruggeman, MD [12], Mark Daniels, MD [13], Henry Rodriguez, MD [14], Peter Calhoun, PhD [2], John W. Lum, MS [2], Ravid Sasson-Katchalski, MD [15], Jordan E. Pinsker, MD [15], Robyn Pollom, NP [16], and Roy W. Beck, MD, PhD [2] for the TL1 Study Group

Abstract

Objective: To evaluate the safety and explore the efficacy of use of ultra-rapid lispro (URLi, Lyumjev) insulin in the Tandem t:slim X2 insulin pump with Control-IQ 1.5 technology in children, teenagers, and adults living with type 1 diabetes (T1D).

Methods: At 14 U.S. diabetes centers, youth and adults with T1D completed a 16-day lead-in period using lispro in a t:slim X2 insulin pump with Control-IQ 1.5 technology, followed by a 13-week period in which URLi insulin was used in the pump.

Results: The trial included 179 individuals with T1D (age 6–75 years). With URLi, 1.7% (3 participants) had a severe hypoglycemia event over 13 weeks attributed to override boluses or a missed meal. No diabetic ketoacidosis events occurred. Two participants stopped URLi use because of infusion-site discomfort, and one stopped after developing a rash. Mean time 70–180 mg/dL increased

Levy CJ, Forlenza G et al, *Diabetes Technol Ther*, 2024 May

ULTRA-RAPID LISPRO INSULIN WITH CONTROL-IQ

TABLE 3. CGM METRICS DURING THE URLi AND LISPRO PERIODS

	Lispro Period (n = *179*) Mean ± SD	*URLi Period* (n = *179*) Mean ± SD	*Mean Difference (95% CI) (P value)*[b]
Time < 54 mg/dL (%)[a]	0.27% ± 0.35%	0.26% ± 0.27%	−0.02% (−0.05%, 0.02%) (0.41)
Time < 70 mg/dL (%)[a]	1.4% ± 1.3%	1.2% ± 1.0%	−0.2% (−0.3%, −0.1%) (<0.001)
CGM hypoglycemic event rate per week[a,c]	0.46 ± 0.75	0.49 ± 0.55	0.01 (−0.09, 0.10) (0.88)
Time in range 70–180 mg/dL (%)	65% ± 15%	67% ± 13%	2% (1%, 3%) (0.004)
Time in range 70–140 mg/dL (%)	40% ± 14%	42% ± 13%	2% (1%, 3%) (0.005)
Time >180 mg/dL (%)	34% ± 15%	32% ± 13%	−2% (−3%, 0%) (0.01)
Time >250 mg/dL (%)	12% ± 10%	11% ± 8%	−1% (−2%, 0%) (0.01)
Mean glucose (mg/dL)	167 ± 26	165 ± 23	−2 (−4, 0) (0.03)
Glucose SD (mg/dL)	61 ± 15	60 ± 14	−1 (−2, 0) (0.08)
Glucose CV (%)	36% ± 5%	36% ± 5%	0% (−1%, 0%) (0.51)
CGM hyperglycemic event rate per week[d]	1.8 ± 1.9	1.6 ± 1.6	−0.1 (−0.3, 0.1) (0.17)

- Higher time in target range was statistically significant
- No increase in time below target range

Levy CJ, Forlenza G et al, *Diabetes Technol Ther*, 2024 May

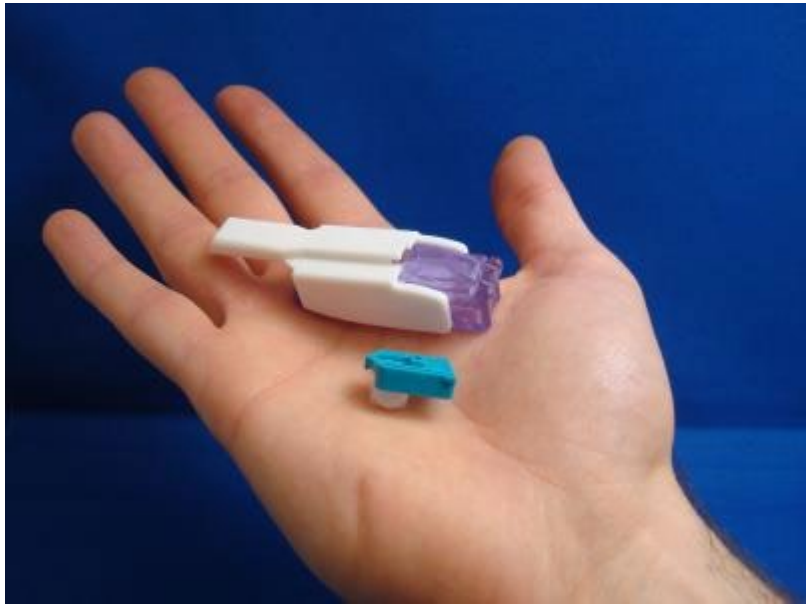
LYUMJEV IN HYBRID CLOSED LOOP SYSTEMS

Evaluation of the Advanced Hybrid Closed Loop (AHCL) System in Type 1 Adults and Pediatrics Utilizing Lyumjev®

- Medtronic 780G clinical trial
  - 1 arm study in participants ages 7-80 years with T1D
  - Completed in 2024
  - No results available yet

ClinicalTrials.gov NCT05325294

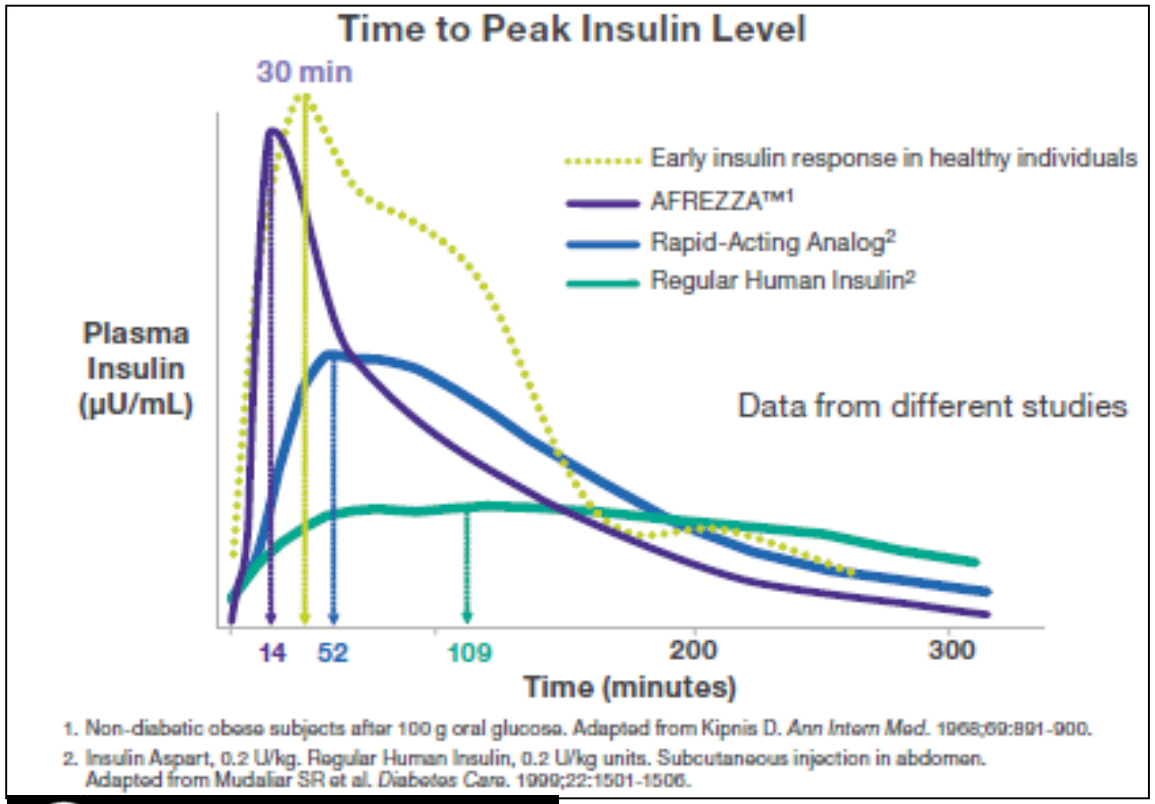
INHALED INSULIN (AFREZZA)



Afrezza (MannKind Corp)

- ‘ultra-rapid’
- Approved by FDA in United States **for adults**
- Clinical trials in pediatrics (still) in progress
- Dry powder using “technosphere” technology
- Requires monitoring of spirometry
- Not for use in patients with COPD or asthma

INHALED INSULIN (AFREZZA)



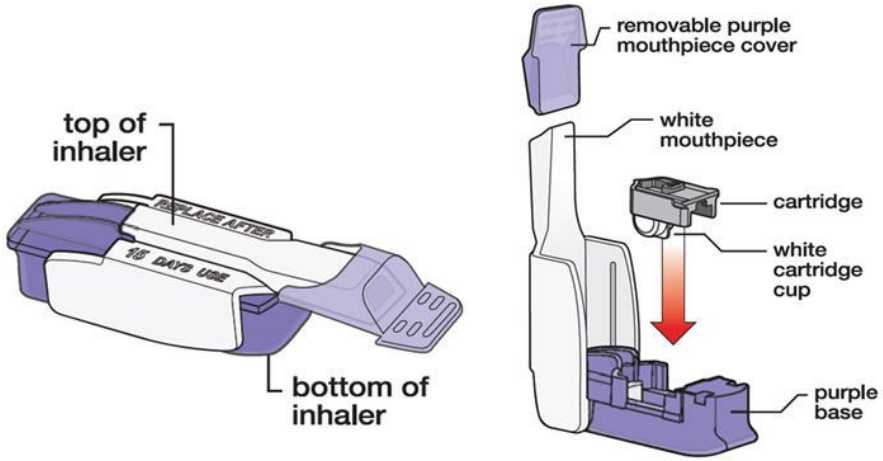
1. Non-diabetic obese subjects after 100 g oral glucose. Adapted from Kipnis D. *Ann Intern Med.* 1968;69:891-900.
2. Insulin Aspart, 0.2 U/kg. Regular Human Insulin, 0.2 U/kg units. Subcutaneous injection in abdomen. Adapted from Mudaliar SR et al. *Diabetes Care.* 1999;22:1501-1506.

The NEW ENGLAND JOURNAL of MEDICINE

- Very rapid onset of action
- Faster than current rapid acting insulin analogs

AFREZZA INSULIN CARTRIDGES & DELIVERY

Injected Mealtime Insulin Dose	AFREZZA® Dose	# of cartridges needed: 4 unit (blue)	8 unit (green)	12 unit (yellow)
up to 4 units	4 units			
5-8 units	8 units			
9-12 units	12 units		+	or
13-16 units	16 units			
17-20 units	20 units		+	
21-24 units	24 units			



https://www.drugs.com/pro/afrezza.html

- Fewer needles but may take several puffs (and more time) for one meal

IN THE PIPELINE...

INSULIN ICODEC

NOT FDA APPROVED

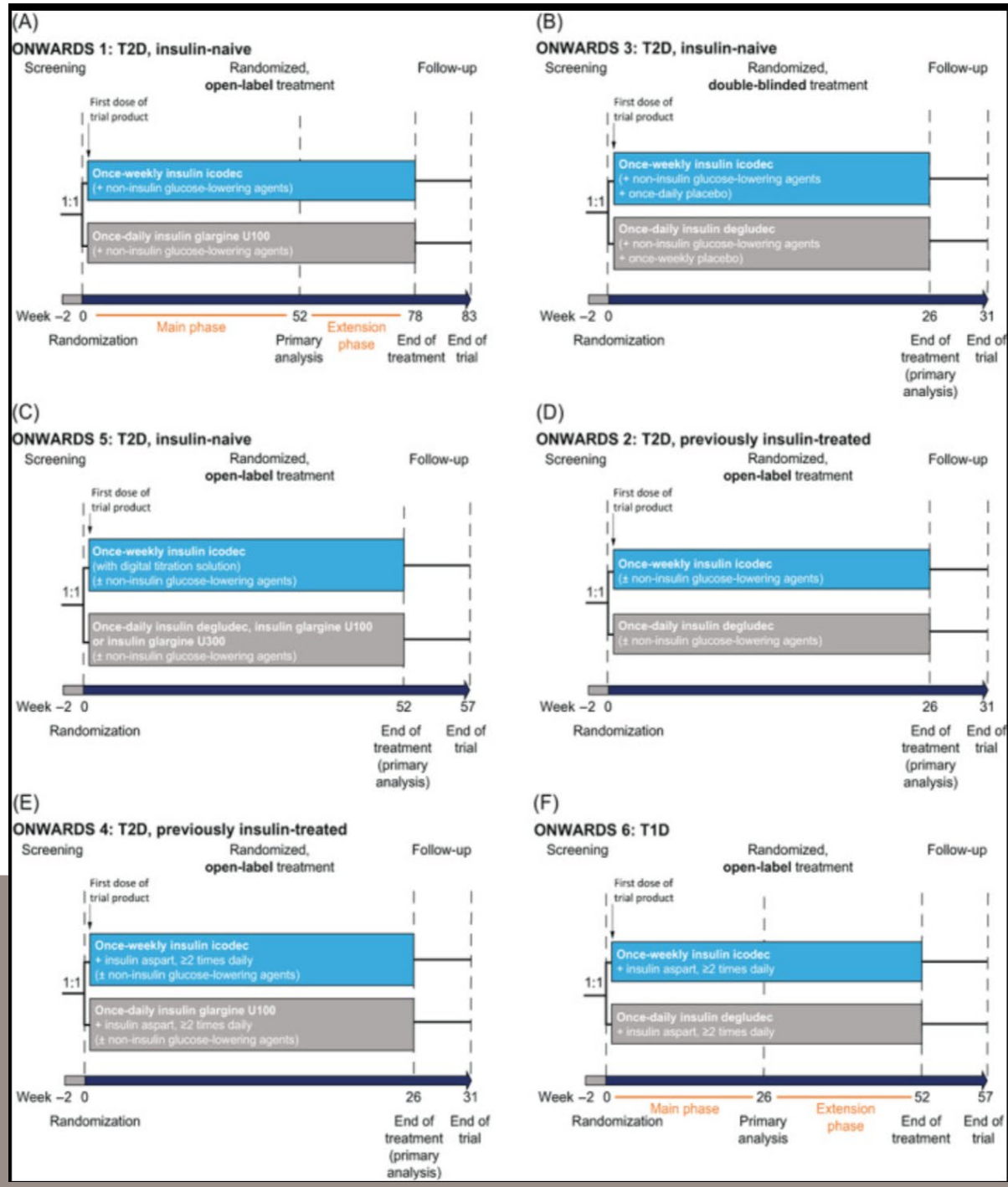
- Once-weekly injectable insulin analog to be used as long-acting insulin
- Modified aa structure; binds with albumin
- Half-life 196 hours (aprox 7 days), steady state after 3-4 injections
- Dosing = 7 x daily dose, given once weekly (ex: adult on glargine 20 units/ day would take 140 units icodec once/ week)
- Trials completed mostly in T2D, one study in T1D (ONWARDS 6)
- Submitted by Novo Nordisk for FDA review in April 2023

ONWARDS TRIALS FOR INSULIN ICODEC

- Phase 3a trials for non-inferiority and superiority vs. approved long-acting insulins (glargine, degludec)
- ONWARDS 1-5 in T2D
- ONWARDS 6 in adults with T1D

Rosenstock J et al, N Engl J Med. 2023 Jul 27;389(4):297-308. PMID: 37356066.
Lingvay I et al. JAMA. 2023 Jul 18;330(3):228-237. PMID: 37354562.
https://www.novonordisk-us.com/media/news-archive, June 2023

NOT FDA APPROVED

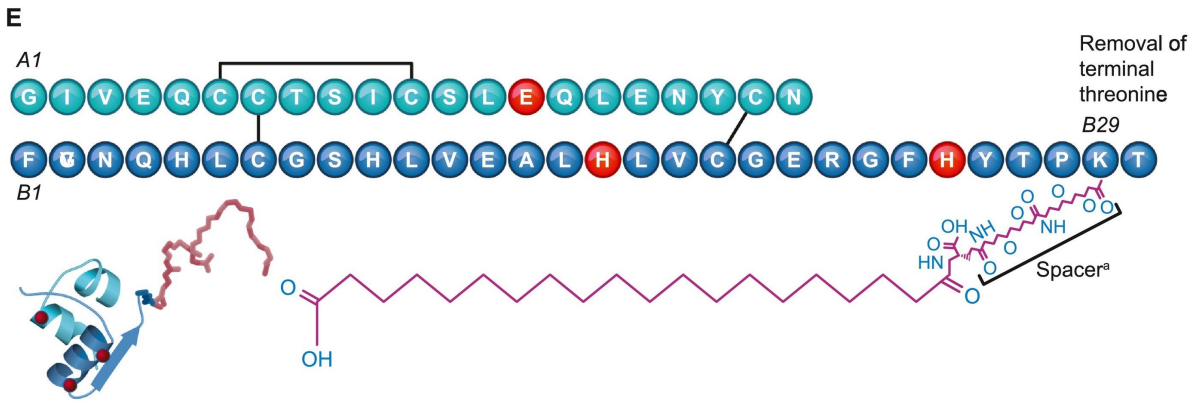


INSULIN ICODEC

NOT FDA APPROVED

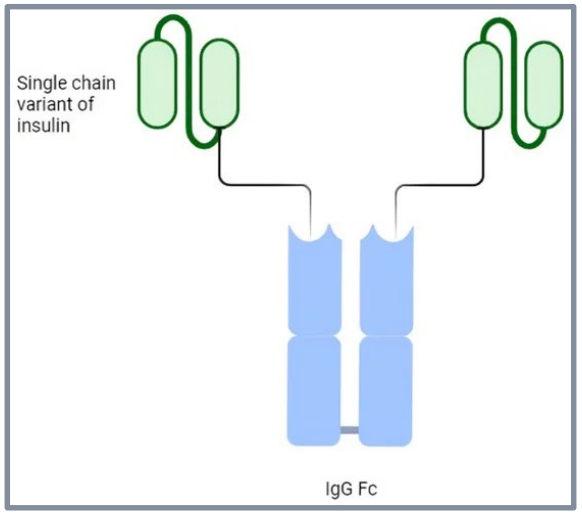
Data from ONWARDS studies:

- Non-inferiority for HbA1c in adults with T1D and T2D
- More severe hypoglycemia in T1D cohort (ONWARDS 6)
- FDA Advisory committee voted AGAINST approval for use in T1D due to hypoglycemia risk
- Unclear what this will mean for use in T2D



https://www.medpagetoday.com/endocrinology/type1diabetes/110337

INSULIN EFSITORA ALFA



Once weekly long-acting insulin in clinical trials; NOT FDA APPROVED

"Fusion protein" made up of single chain insulin variant combined with a human IgG fragment

Phase 2 studies (for efficacy) in adults with T1D and T2D published in 2023

In T1D study with 265 participants:

- Non-inferior to insulin degludec over 26 weeks for change in HbA1c and percent time in range (56.1% vs 58.9%).
- No significant difference in hypoglycemia (CGM) and similar rates of adverse events (including skin reactions)

Argano C et al, *Biomedicines*. 2024; 12(4):900. https://doi.org/10.3390/biomedicines12040900
Kazda CM et al, *Diabetes Care*. 2023 May 1;46(5):1052-1059. PMID: 36920867

INSULIN EFSITORA ALFA

NOT FDA APPROVED

2024

- Large Phase 3 studies (efficacy and safety) in T2D completed (QWINT-2, QWINT-4)
  - QWINT-2: 52 week study in 928 participants (NCT05362058)
  - QWINT-4: 26 week study in 730 participants (NCT05462756)
- Press release May 16 re: topline results reported “safe and well tolerated”
- Non-inferior HbA1c reduction vs. degludec (QWINT-2) and glargine (QWINT-4)
- QWINT-2 data to be presented in September 2024 at EASD meeting

http://investor.lilly.com/news-releases/news-release-details/once-week-dosing-insulin-efsitora-alfa-delivers-a1c-reduction

OTHER INSULINS

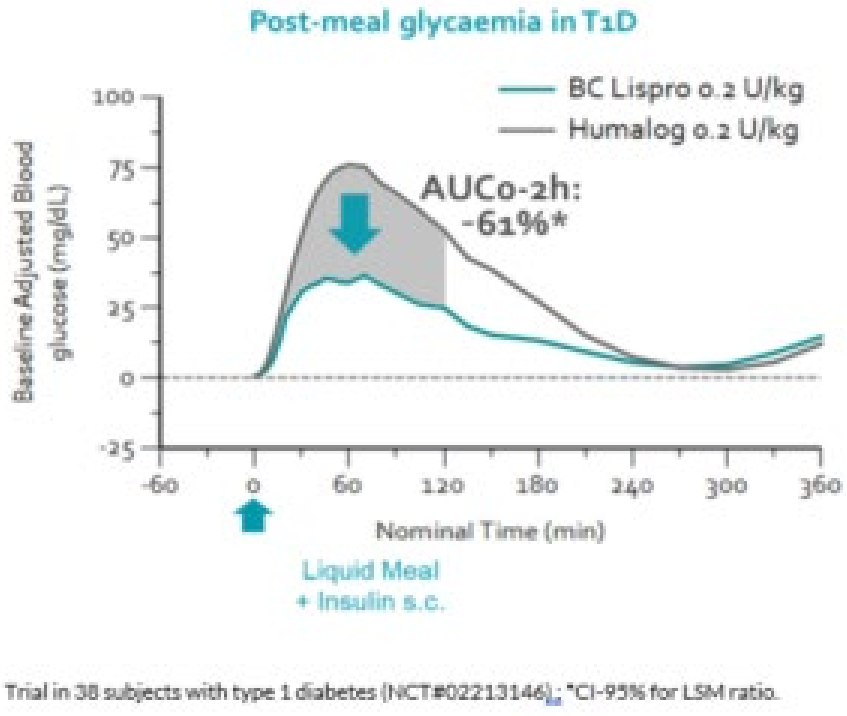
Several methods to decrease time to onset have been tried with little success

- E.g. warming site, hyaluronidase

Adocia biochaperone lispro

- Biochaperone designed to attach and increase absorption of lispro
- Phase 1 study completed in 2022
- Phase 3 trials ongoing in China in 2024
- No current trials in Europe and US

https://www.adocia.com/medias-publications



“SMART” INSULIN PENS

InPen (Medtronic)

Set up app on phone

Consider:

- Out of pocket expense – improved
- “starter” kits now available in clinic
- See data in Carelink, Clarity

Other smart pens coming

- Bigfoot Unity (pen caps)- now in some markets in US
- Novo Nordisk in UK

BIOSIMILARS AND GENERICS

www.fda.gov/drugs/biosimilars/health-care-provider-materials

Example:

Semglee (insulin glargine-yfgn, Mylon) similar to glargine (Lantus)

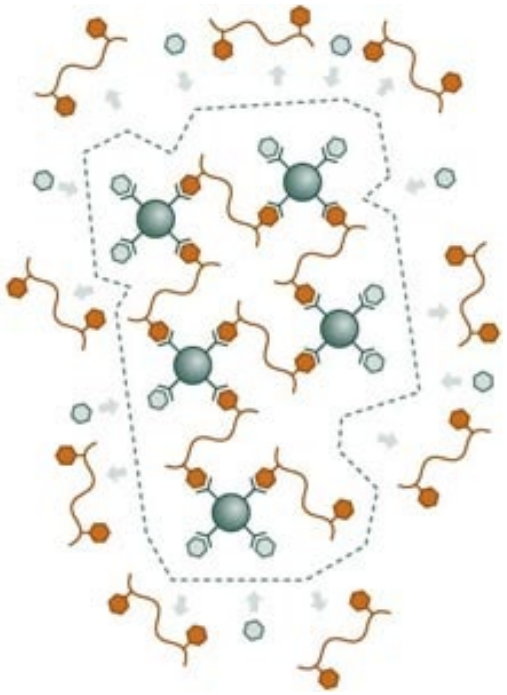
FDA approved July 2021

CLOSING THOUGHTS

- Options for long acting and rapid acting insulin have increased
- New and interesting options in the pipeline
- Cost is still a major barriers for some
- It is important to know about the options (“tools”) available to put together the right regimen for clinical care

QUESTIONS?

“SMART” INSULIN



Glucose-Responsive Insulins (GRIs)

Various strategies

Animal studies:

- J Yu et al, Glucose-responsive insulin patch for the regulation of blood glucose in mice and minipigs. *Nat Biomed Eng* **4,** 499–506 (2020). https://doi.org/10.1038/s41551-019-0508-y
- Zhou, X., Wu, H., Long, R. *et al.* Oral delivery of insulin with intelligent glucose-responsive switch for blood glucose regulation. *J Nanobiotechnol* **18,** 96 (2020). https://doi.org/10.1186/s12951-020-00652-z

In silico models/ testing:

- Yang JF, Yang S, Gong X, Bakh NA, Zhang G, Wang AB, Cherrington AD, Weiss MA, Strano MS. In Silico Investigation of the Clinical Translatability of Competitive Clearance Glucose-Responsive Insulins. ACS Pharmacol Transl Sci. 2023 Sep 18;6(10):1382-1395. PMID: 37854621