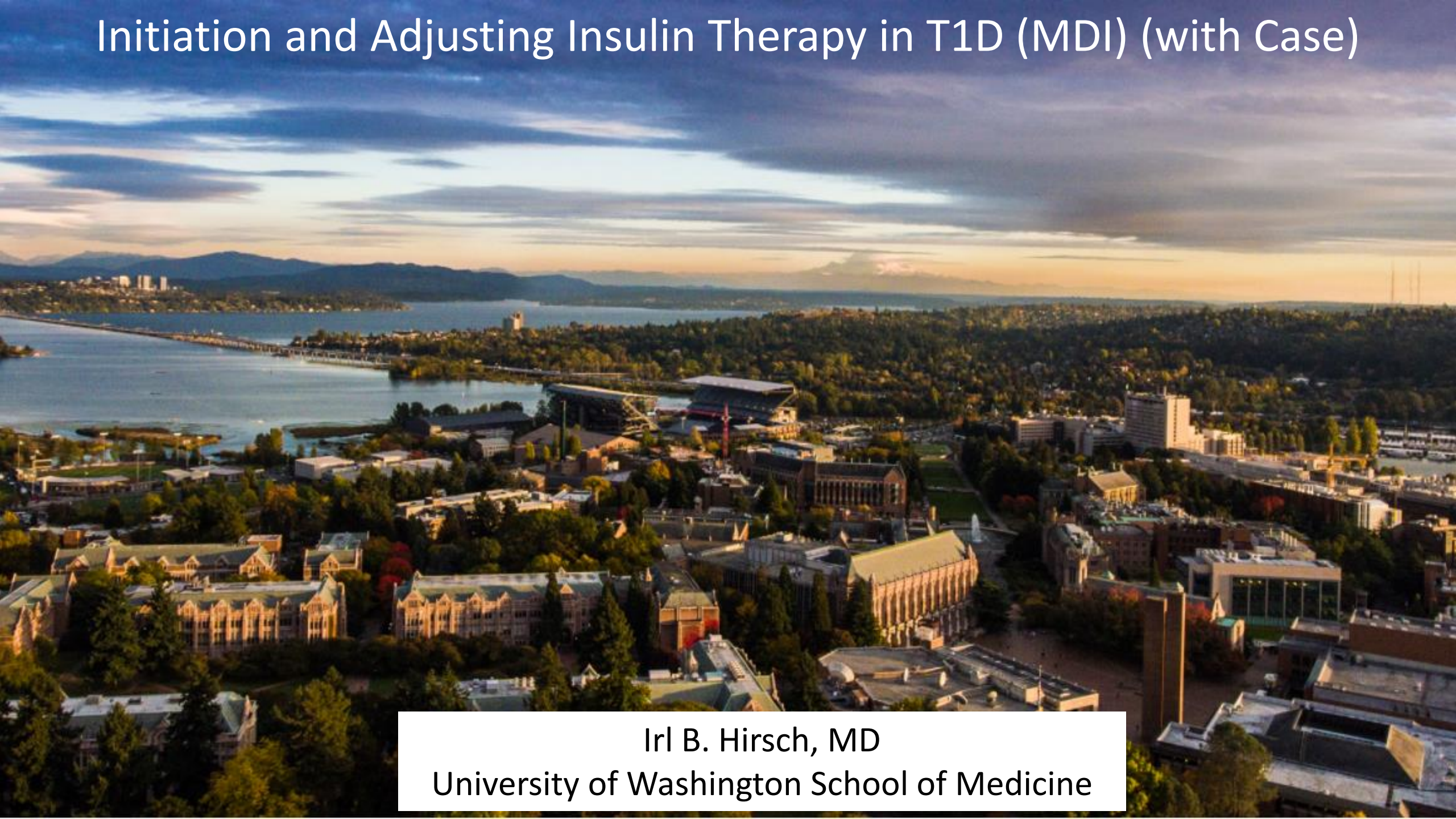
Initiation and Adjusting Insulin Therapy in T1D (MDI) (with Case)



Irl B. Hirsch, MD
University of Washington School of Medicine

Dualities

- Research: Medtronic, Insulet, Beta Bionics
- Consulting: Abbott Diabetes Care, Roche, Bigfoot, GWave

Diagnosis of T1D in Adults (“Initiation”)

- Mostly misdiagnosed as type 2 due to numbers
- Variable presentation: could be classic or “smoldering”- often difficult to tell from phenotype and presentation
- JDRF: 50% of T1D presents after the age of 18 years
- Need to ask about family history of other autoimmune diseases that are common with T1D: autoimmune thyroid disease, Addison Disease, celiac, vitiligo

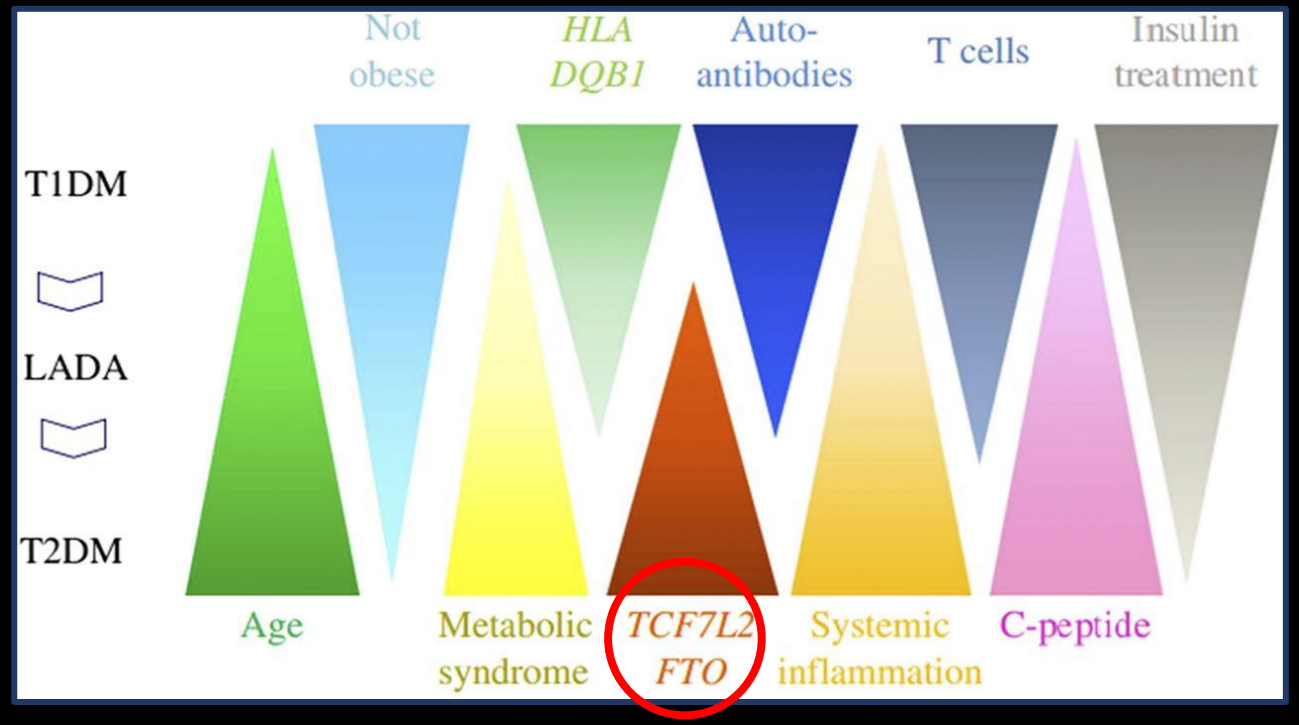
LADA: ADA Standards of Care, 2021

- “There is debate as to whether slowly progressive autoimmune diabetes with an adult onset should be termed latent autoimmune diabetes in adults (LADA) or whether the clinical priority is awareness that slow autoimmune β-cell destruction means there may be long duration of marginal insulin secretory capacity. For the purpose of this classification, all forms of diabetes mediated by autoimmune β-cell destruction are included under the rubric of type 1 diabetes.”

Diabetes Care 2021 Jan; 44(Supplement 1): S15-S33

“Use of the term LADA is common and acceptable in clinical practice and has the practical impact of heightening awareness of a population of adults likely to develop overt autoimmune β-cell destruction”

The Reality, We Know Our Current Classification Needs to Change as There is Much Overlap



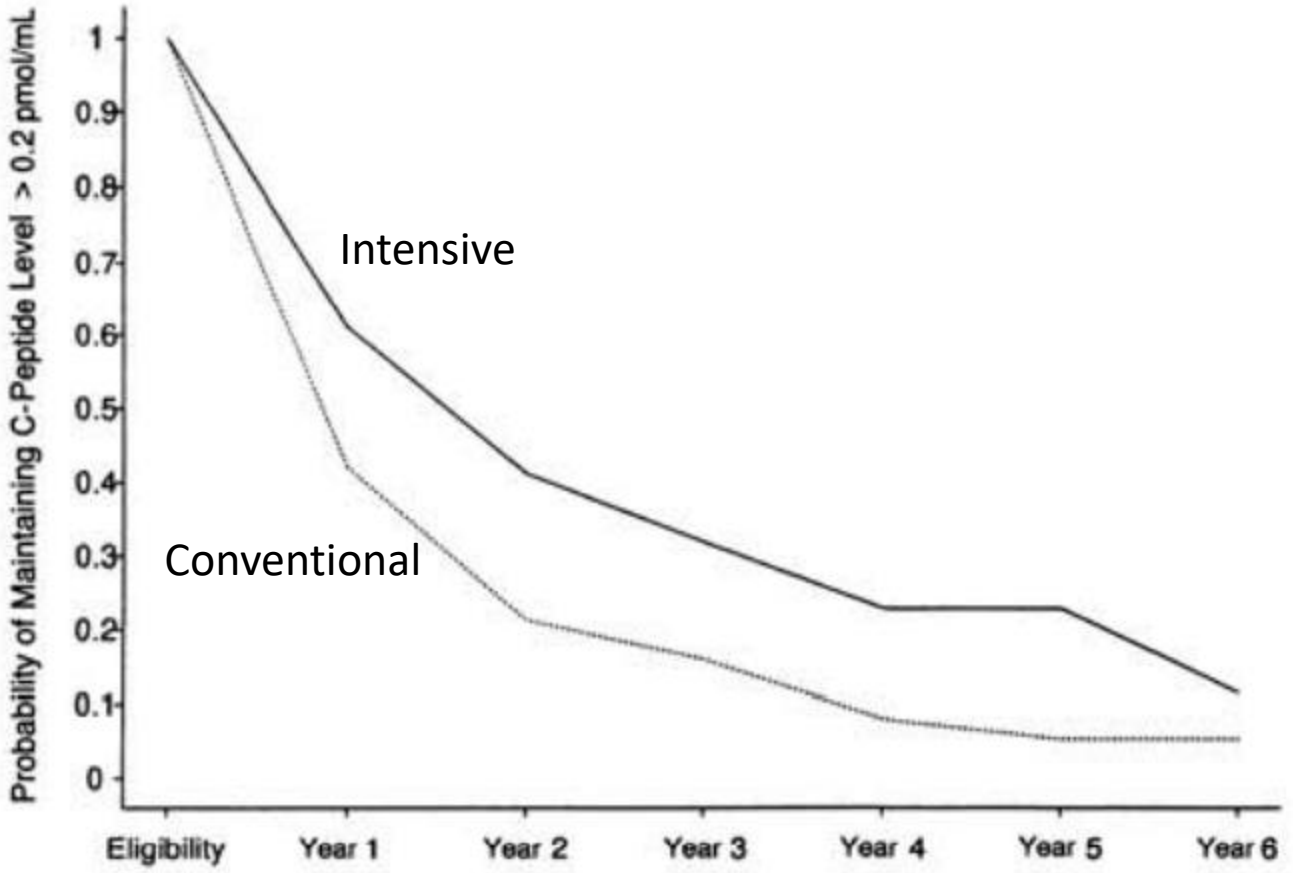
Qualitative factors associated with associated with different forms of diabetes

Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin JR 3rd, Aguilar RB. Diabetes Care. 2016 Feb;39(2):179-86.

Treatment Strategies: “LADA”

- INSULIN (“intensive therapy”)

Other therapies (available but not proven):
1. GLP1 RAs (most work with liraglutide)
2. TNFά blockers



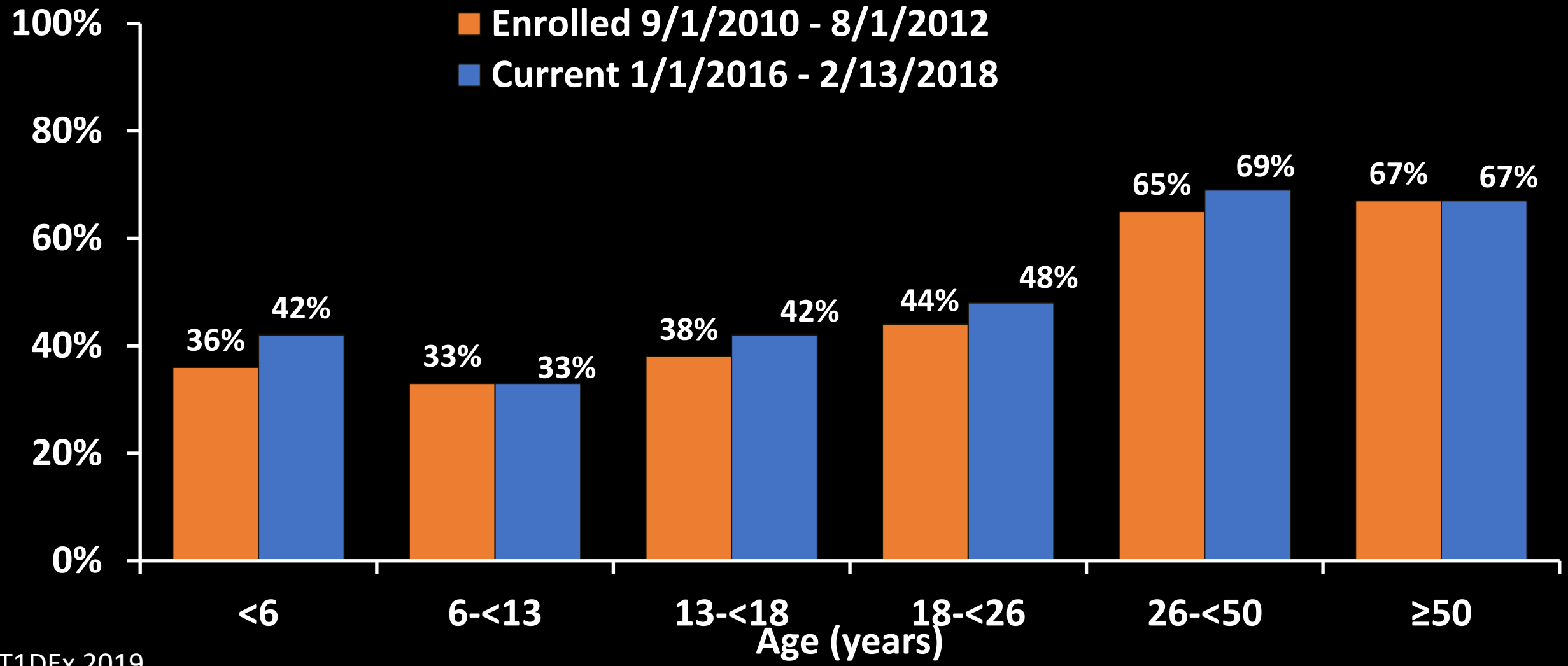
Number of patients in each treatment group who were evaluated

Intensive	138	131	80	53	32	8	2
Conventional	165	150	63	32	22	3	0

Ann Intern Med
1998;128:517-523

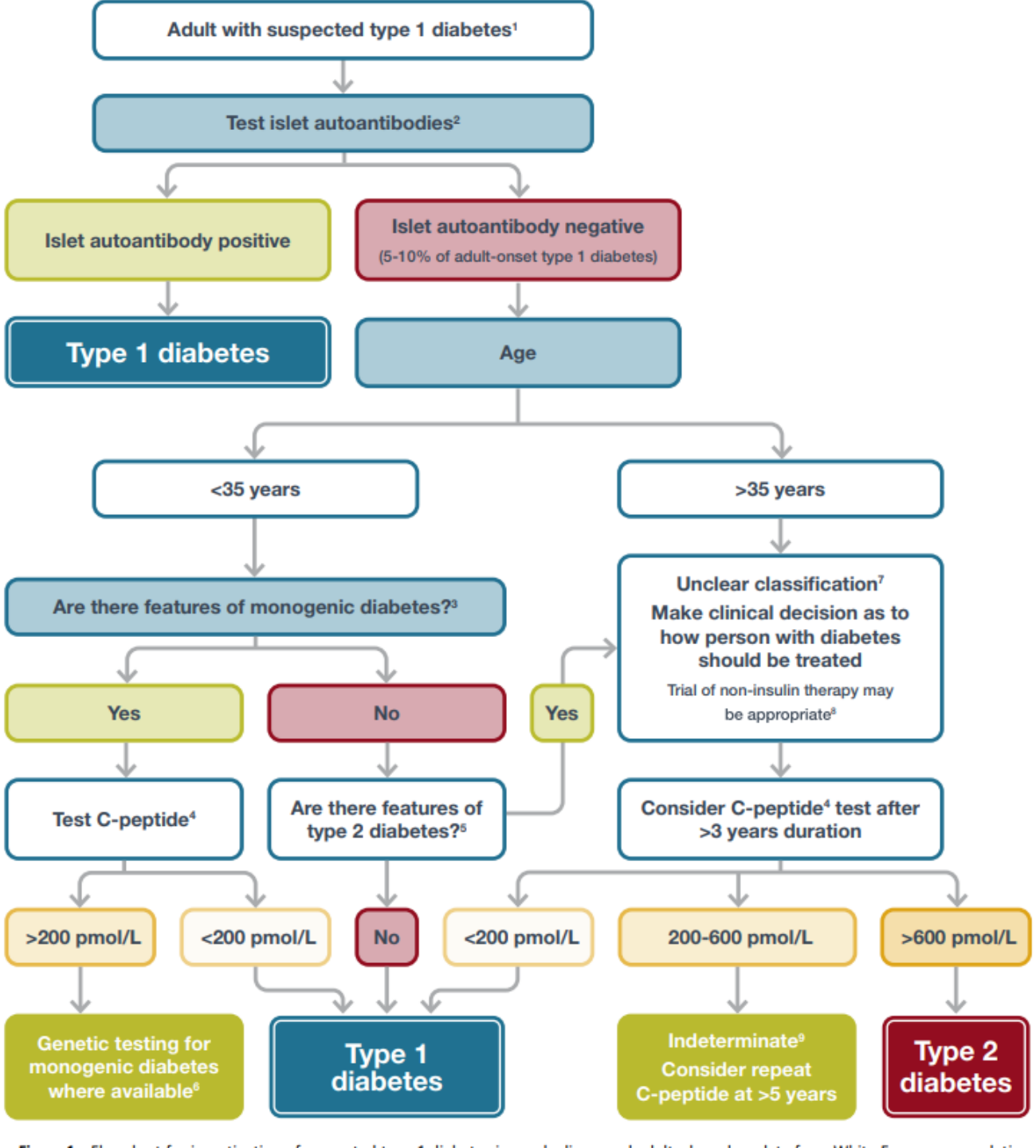
Many with T1D Are Overweight /Obese

Difficult to use obesity as a criterion for T1D



T1DEx 2019

Unclear Diabetes Type: Based on White European Populations



Diabetes Care 2021 Sep; dci210043
On-line Sept 29, 2021

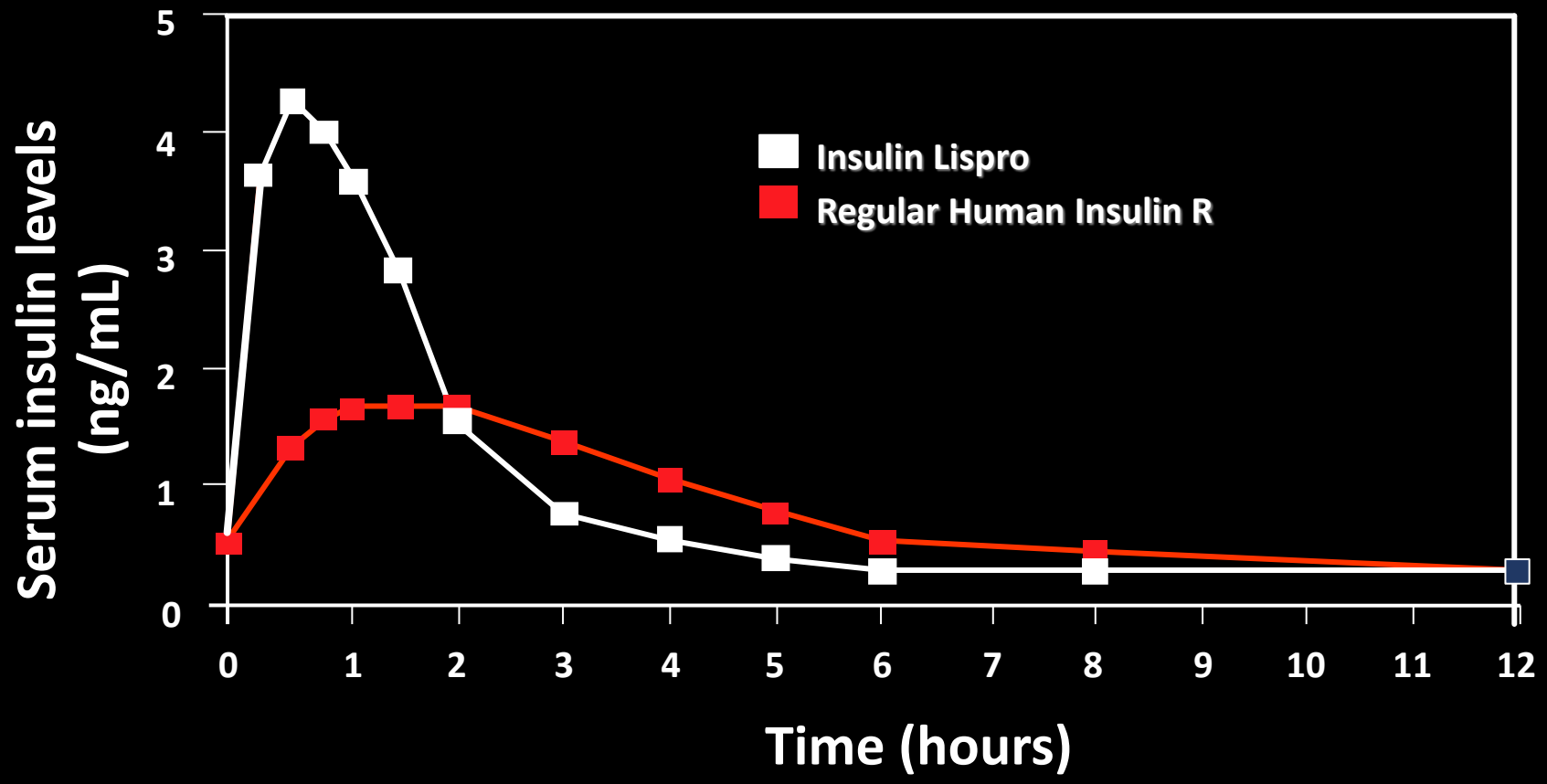
Understanding Prandial Vs. Basal Insulin

- Prandial insulin
  - Postprandially, 30% taken up by liver, the rest by skeletal muscle

Prandial Insulin

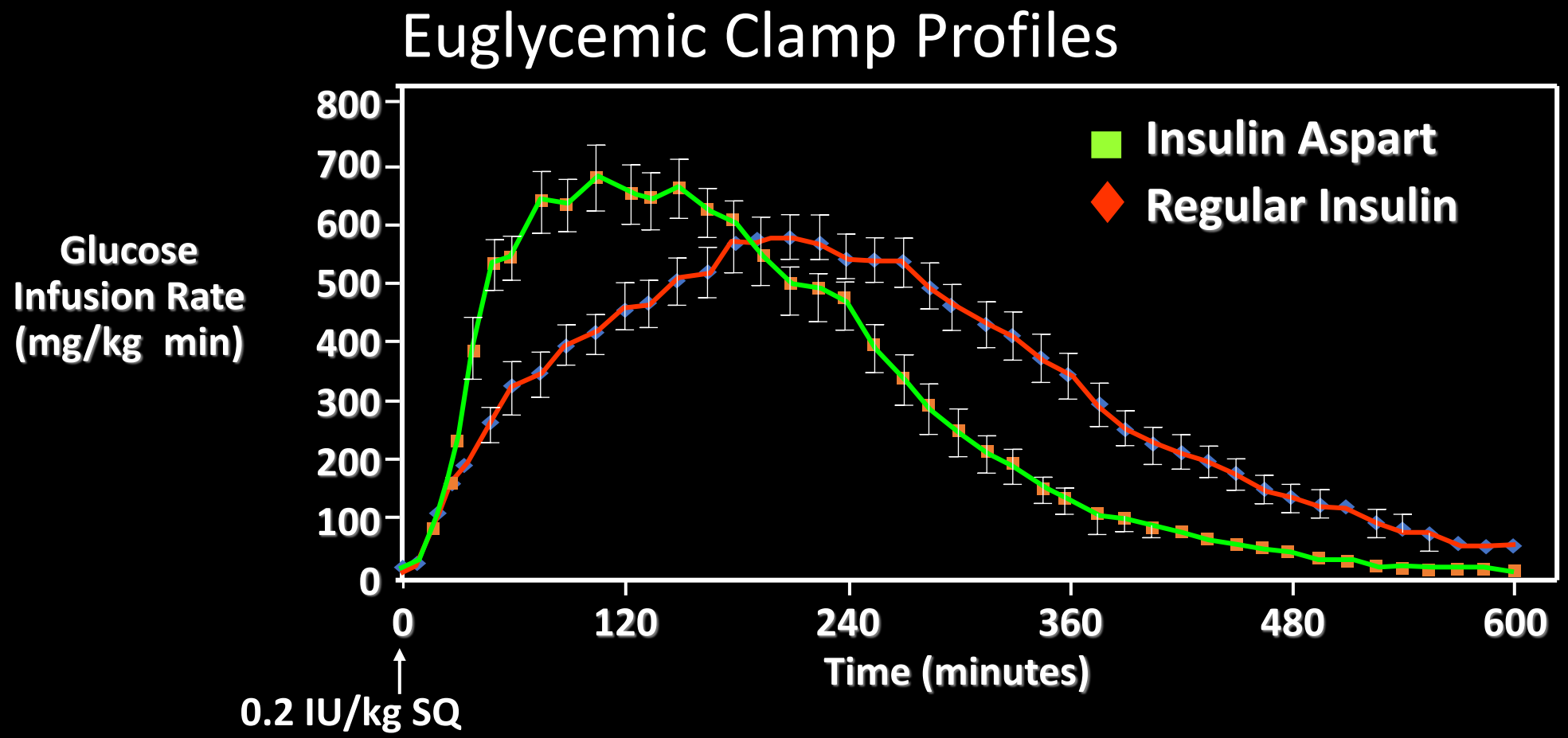
The basic principles of bolus insulin therapy are identical for pumps or multiple injections

Understand PK vs. PD (lispro)



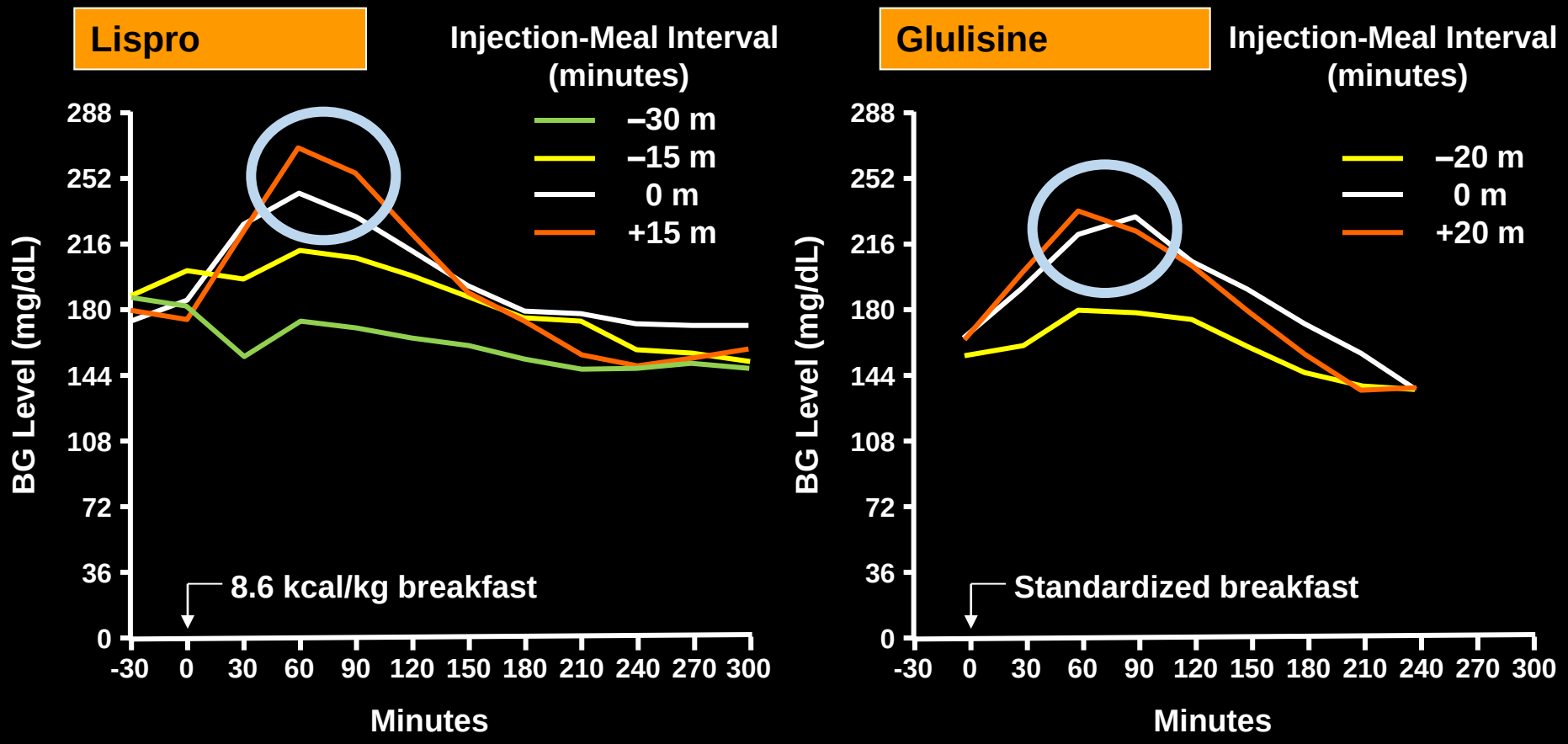
Diabetes 43: 396-402, 1994

Glucodynamic Principles (Analogue Pearl): Prandial Insulin: not as rapid acting as we thought



Diabetes Care 1999;22:1501-1506

PEARL 1: Timing (lag time) of Rapid-Acting Analog Insulin Injection Alters PPG in Type 1 Diabetes Mellitus

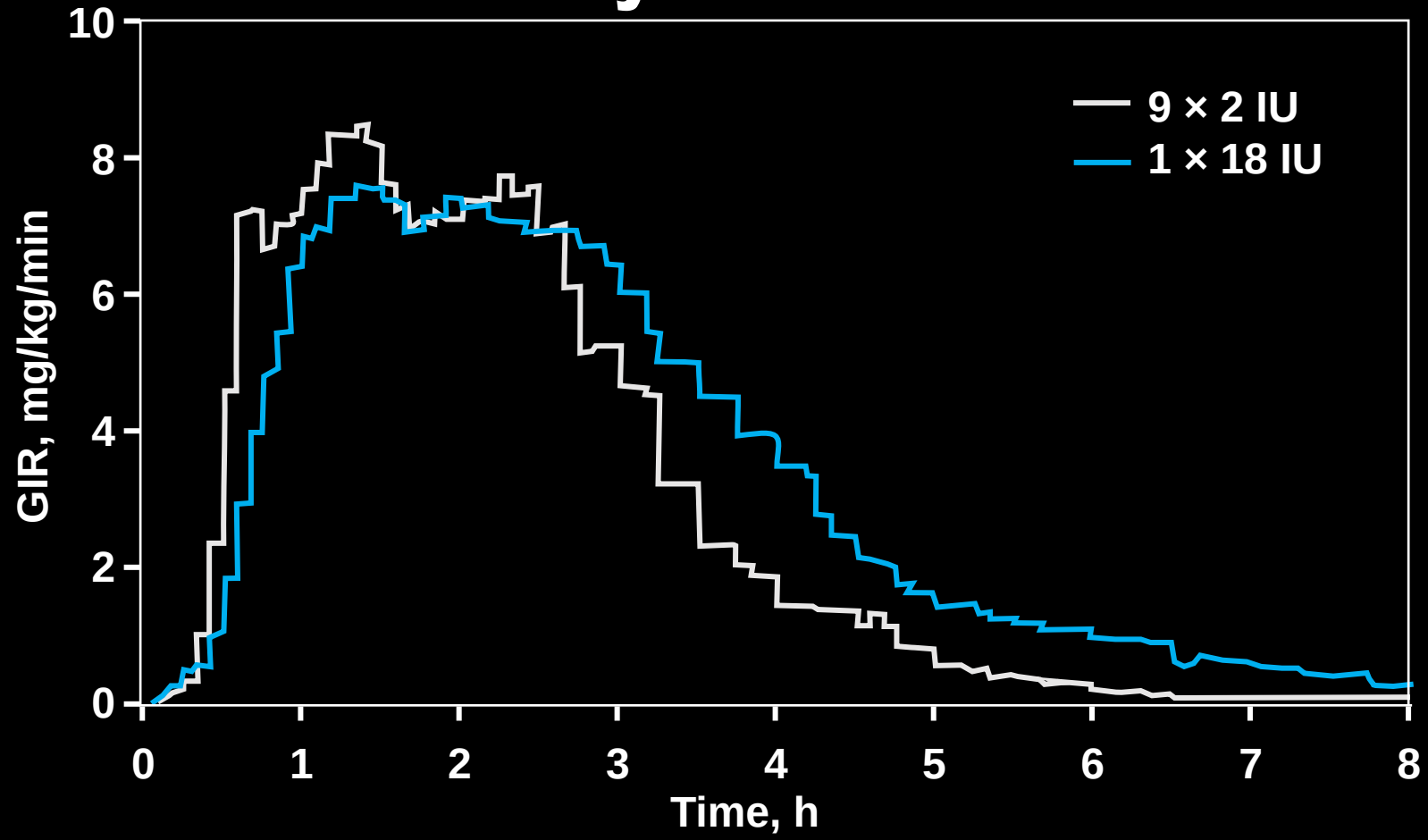


Rassam AG, et al. *Diabetes Care*. 1999;22:133-136.
Cobry E, et al. *Diabetes Technol Ther*. 2010;12:173-177.

Pearl 2: What About Giving Many Small Doses Instead of One Large Depot (Analogue Pearl)?

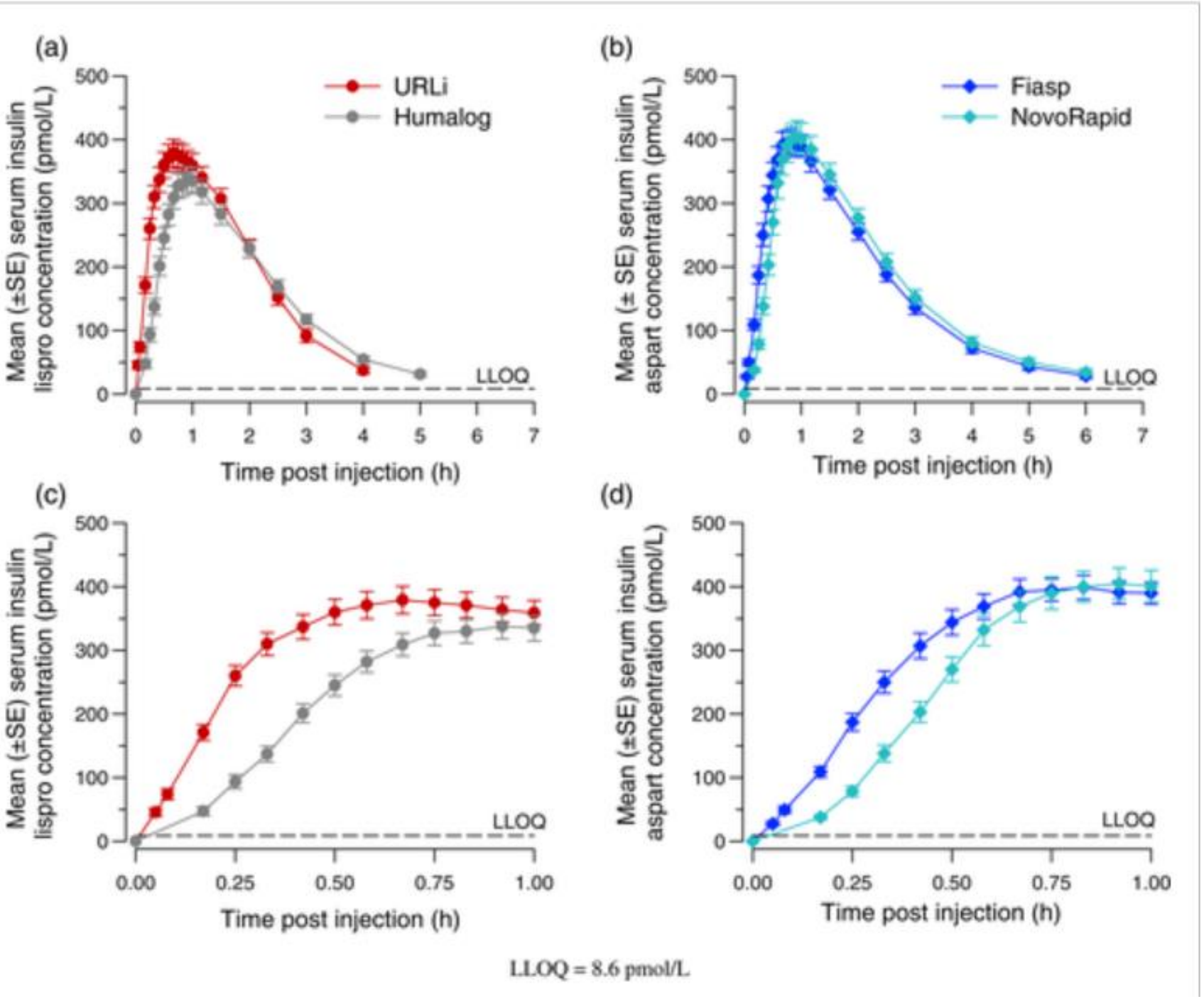
Insulin Aspart PK/PD: Dispersed Injection vs Single Injection, AP@home Consortium

Pharmacodynamics in T1D



Clamp study of 12 patients with T1D.

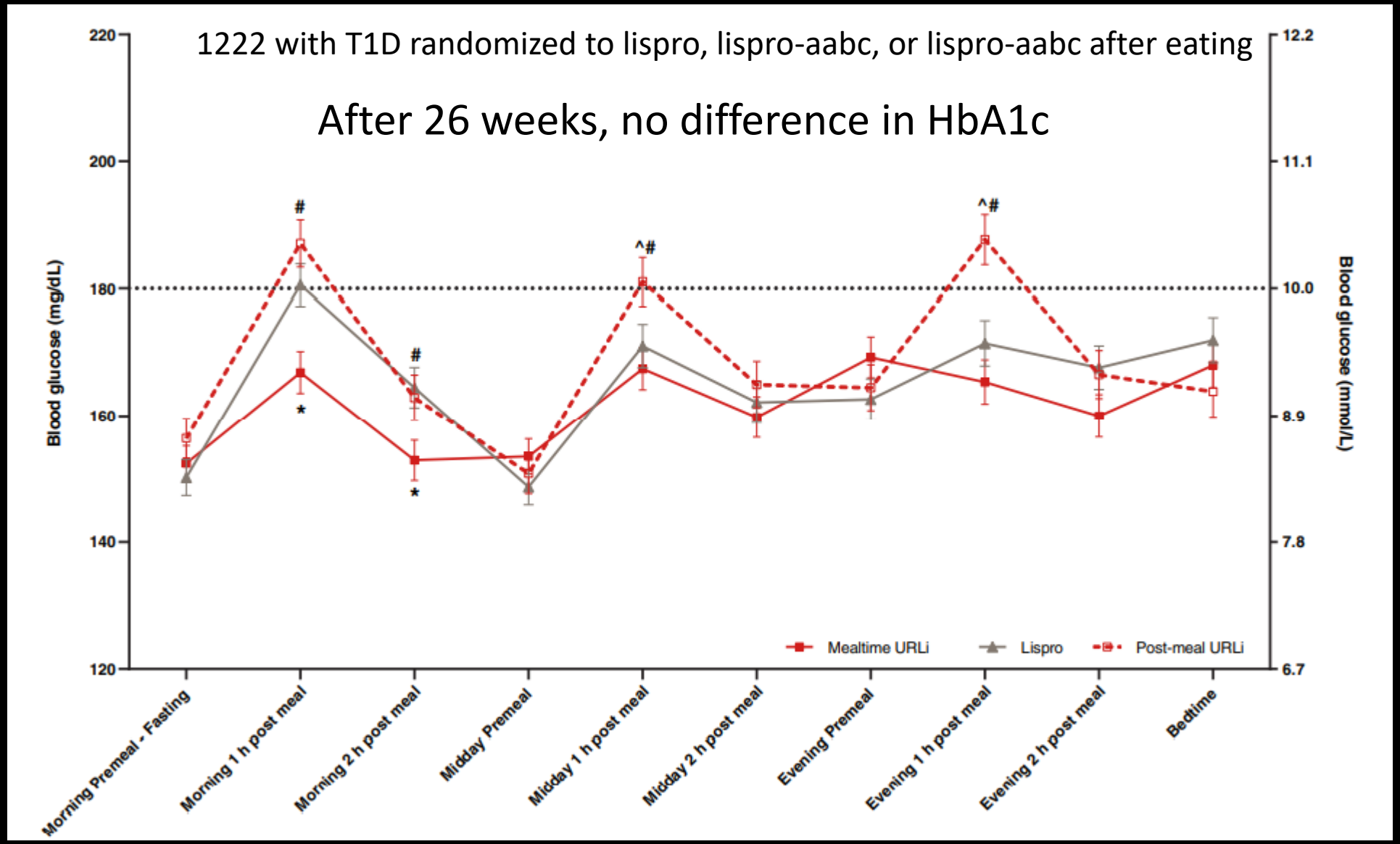
Mader JK, et al. Diabetes Care. 2013;36:780-785.



PK URLi, lispro, aspart, fast-acting aspart

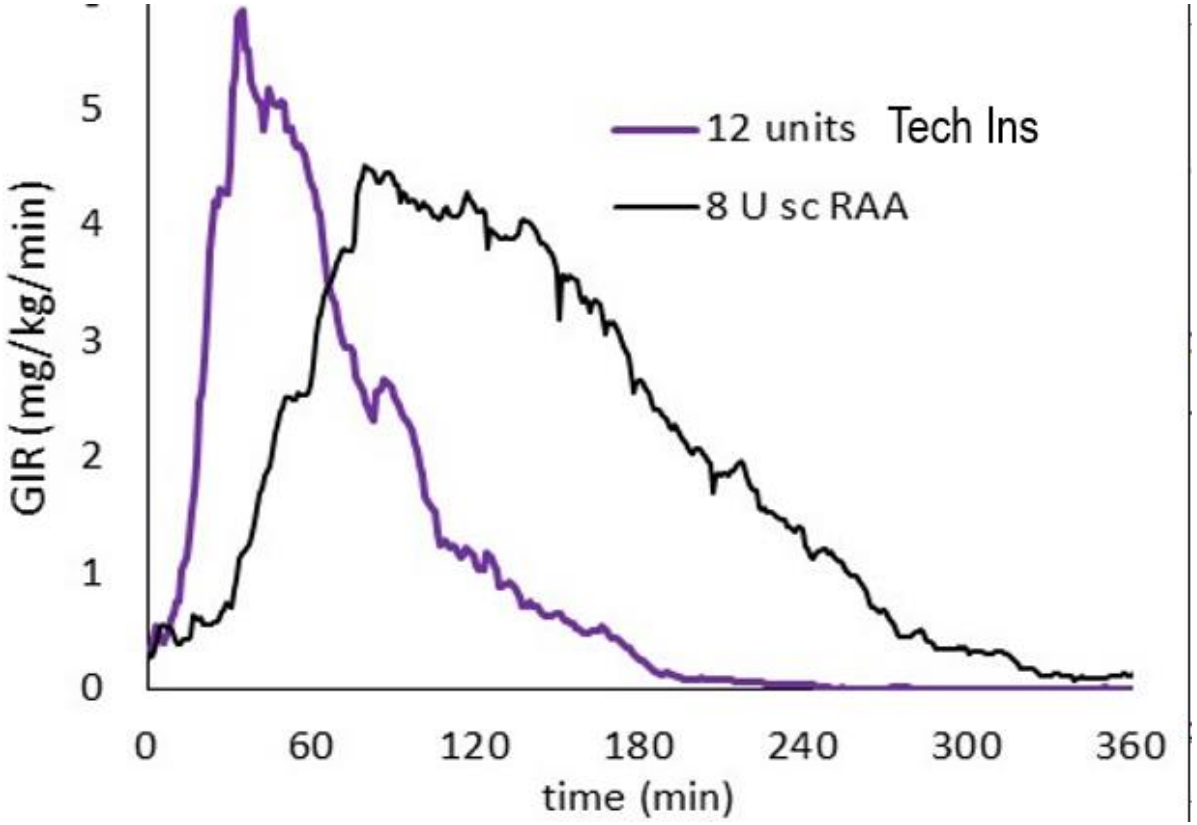
Diabetes Obes Metab. 2020;22:1789–1798

Lispro-aabc



Diabetes Obes Metab. 2020;22:1799–1807.

Why Patients Like Afrezza



Pearls for Reducing After-Meal Glucose Spike

- TIME
  - With CGM, up arrows will often need to wait 20-30 min but general rule of them: wait for the trend arrow to flatten; without CGM: wait minimum 10-15 minutes
- Correction dose insulin
  - A specific “insulin sensitivity factor” should be arranged. For most with type 1 we generally start at ~50, but many need more insulin
  - Many prefer not to use much correction insulin and only use time when possible
  - Warning: using correction with much added time often leads to hypoglycemia
    - The good news: by watching the CGM this can be avoided

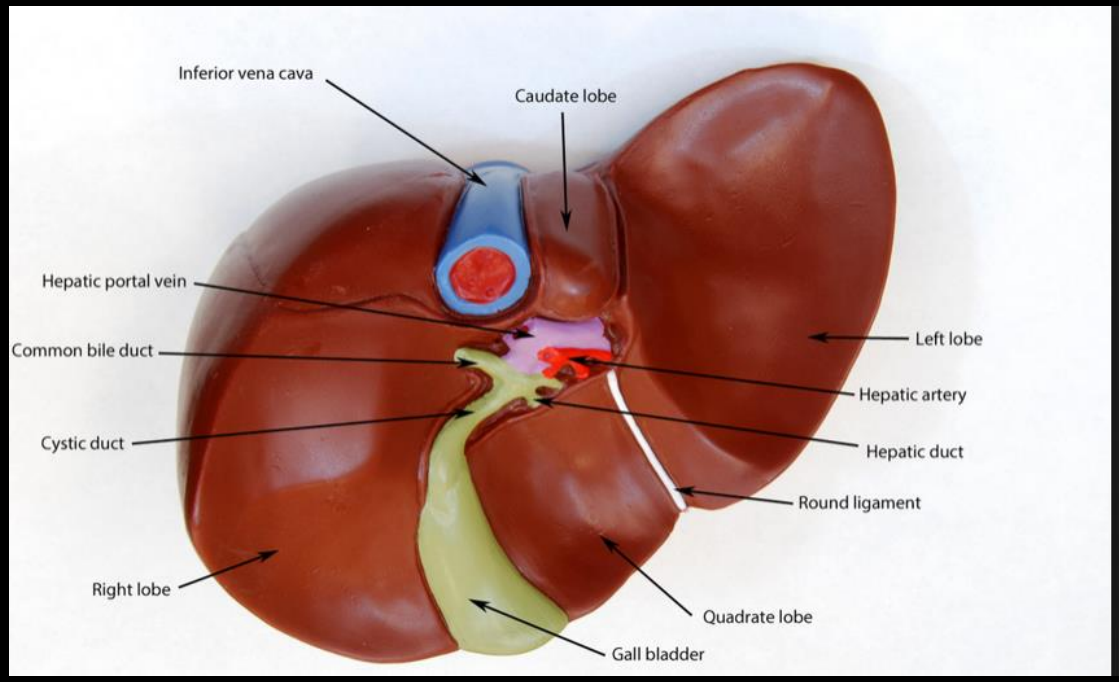
What is the Third Tool to Reduce the After-Meal Spike?

- Post-meal exercise: reduces after-meal spike
- Pre-meal exercise: reduces BOTH pre-meal and post-meal glucose levels

Last Pearl: What's the Most Important Tool to Reduce After-Meal Glucoe Spikes?

Basal Insulin

- Insulin inhibits hepatic glucose production increasing glucose uptake and conversion/storage to glycogen. Insulin also activates glycolysis and FA synthesis
- By inhibiting lipolysis and glucagon secretion, insulin can further reduce hepatic liver glucose output.



Basal Insulin

- The primary role of endogenous basal insulin secretion is to fine tune lipolysis and hepatic glucose production in the fasting state, especially overnight, while maintaining sufficient glucose for brain function
- Goal of exogenous insulin with severe insulin deficiency
  - Attempts to recreate constant, low levels of insulin overnight and between meals which with the correct dose will maintain euglycemia for 24 hours in the fasting state

What is the Correct Dose of Basal Insulin?

- Traditional Teaching: 50% basal/50% prandial (T1D, isocaloric diet)

What Do We Know from HCL Data?

- Adolescents: % Basal = 46.4%
  - SG 158.5 mg/dL
- Adults: % basal = 46.8%
  - SG 148.3 mg/dL

Difficult to get < 140 mg/dL with Medtronic 670G

DT&T 2017;19(3): 155–163

What is clear: we have been over-basalizing* our patients for years, with most patients coming in from 50-70% basal both with CSII and MDI. There are times this is appropriate (pregnancy) but in general, basal dose should be closer to 45% in T1D and many are closer to 40%

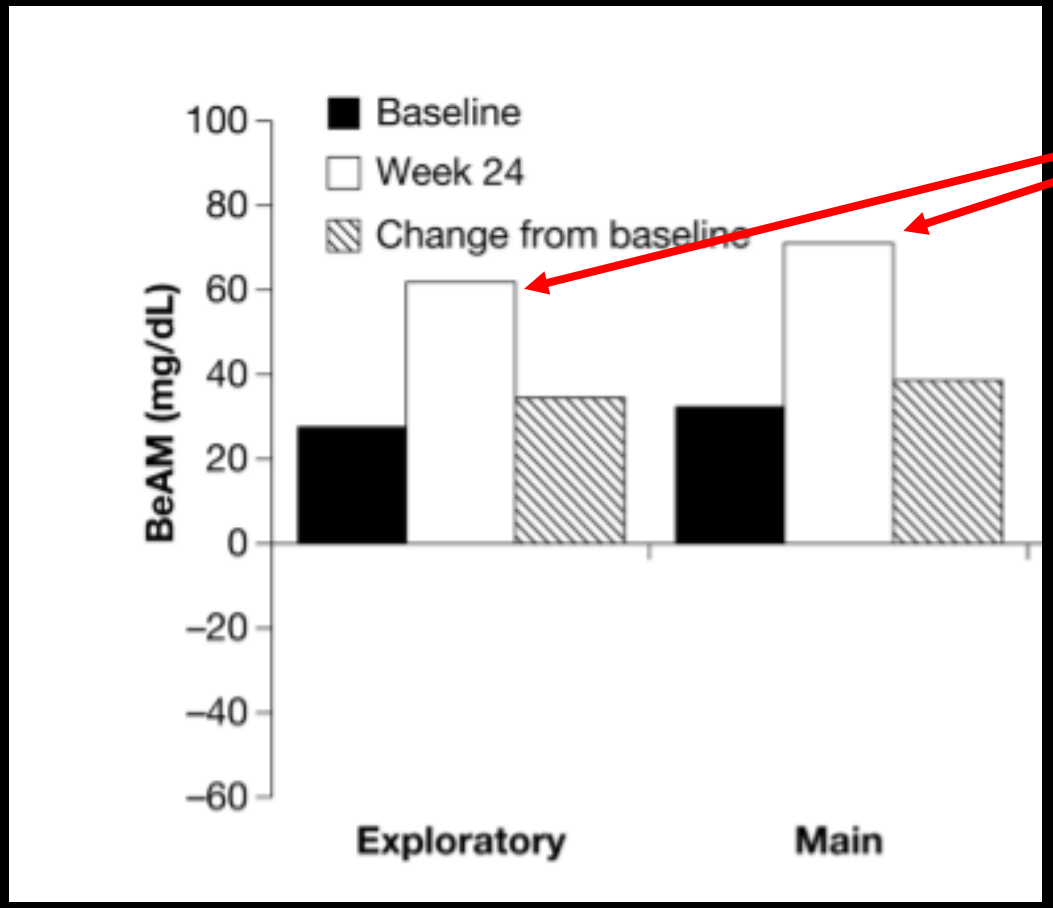
Also called “over-Lantusizing” and “over-Tresibasizeing”

How to Dose Basal Insulin?

- BeAM factor = bedtime glucose – AM glucose
- A + BeAM factor: bedtime glucose is higher than AM glucose
  - For example, mean HS BG = 200, mean FBG = 100, BeAM = 100
- A – BeAM factor: bedtime glucose is lower than AM glucose
  - For example, mean HS BG = 120, mean FBG = 180, BeAM = -60

Sidenote: BeAM in T2D

- Adding basal insulin in T2D (N = 1401 and 553)



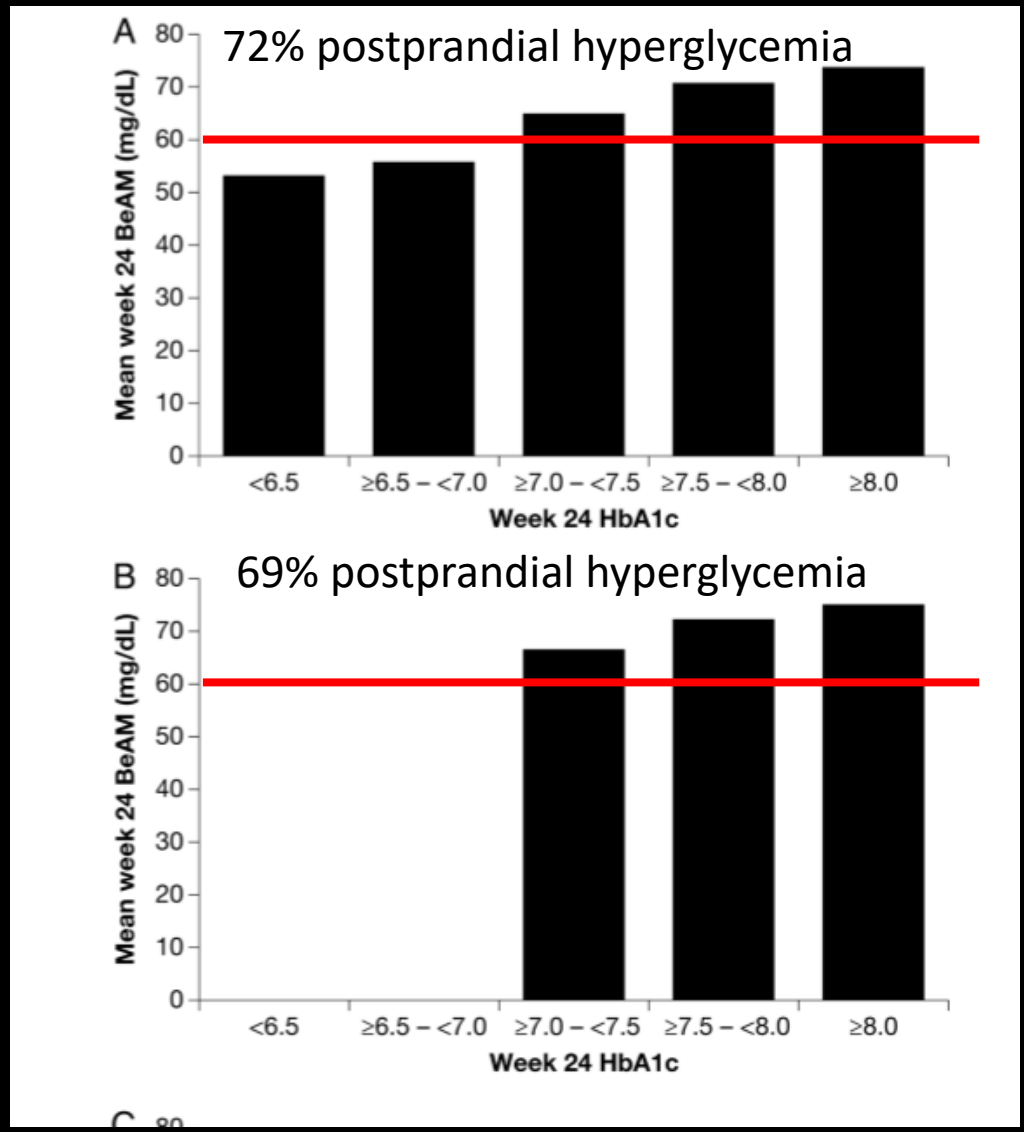
BeAM increased to 60 mg/dL due to lower FBG without change in HS BG

BMJ Open Diabetes Res Care 2016;4:1-8

BeAM in T2D: Basal Insulin Only

- The higher the BeAM, the higher
- of
- arly

In T2D with basal insulin alone, it appears a BeAM level > 60 mg/dL is associated with A1C levels > 7%. Should the goal in T2D on basal insulin be early a BeAM < 60 mg/dL?

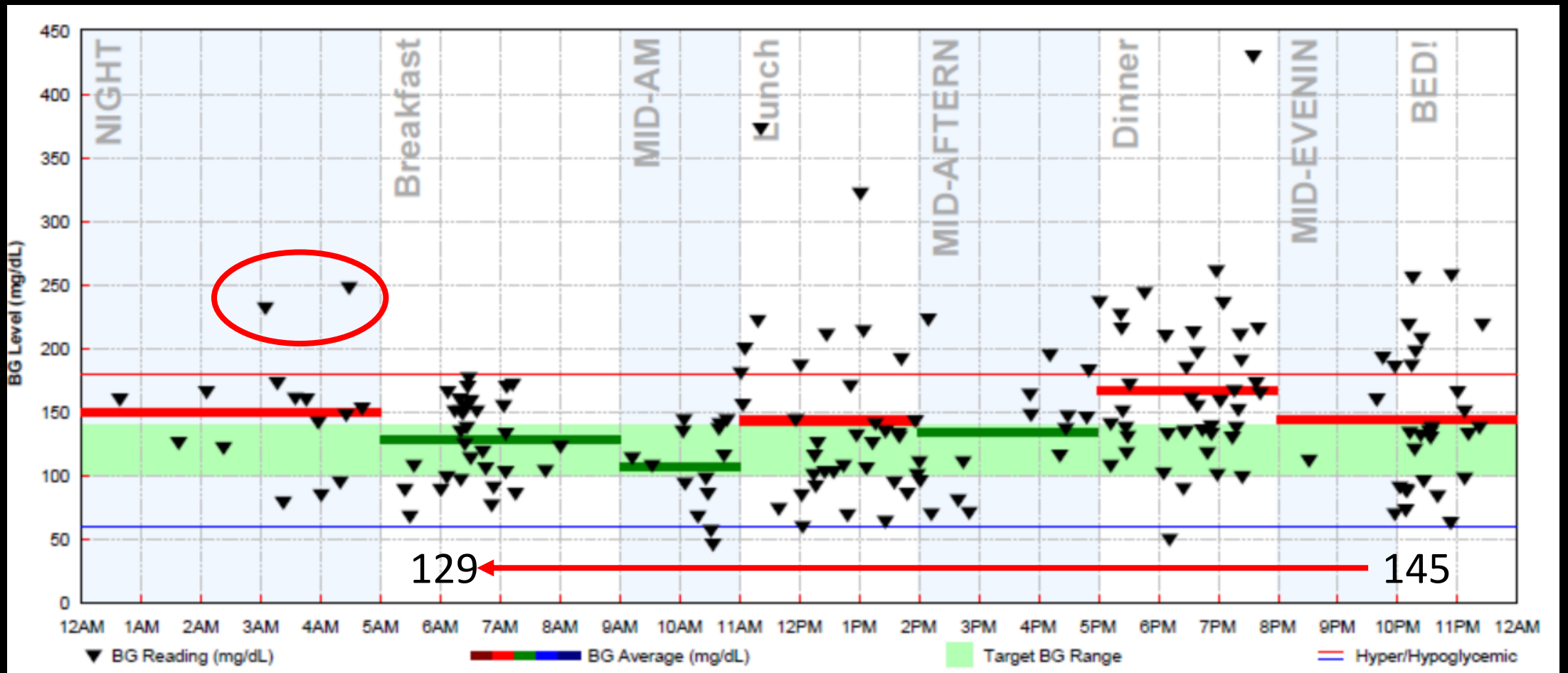


BMJ Open Diabetes Res Care 2016;4:1-8

What About the BeAM Score in T1D?

- No studies but the overall goal for anyone on MDI or CSII should be ideally a BeAM score of 0
- What I do in my clinic: I look to ensure BeAM between -30 and + 30
- What is most typical (especially with MDI patients)-BeAM scores are +50

Example: 55 y/o man with T1D, MDI, BID Glargine

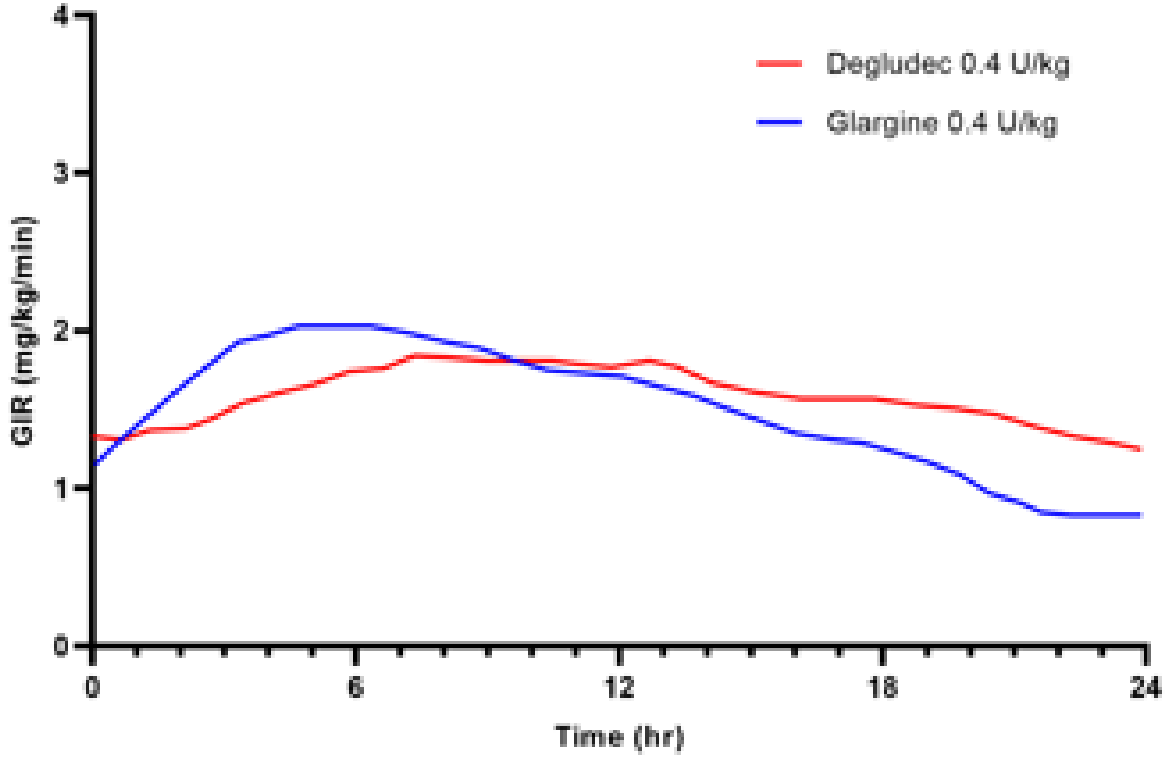


		NIGHT 12:00 AM		Breakfast 5:00 AM		MID-AM 9:00 AM		Lunch 11:00 AM		MID-AFTERN 2:00 PM		Dinner 5:00 PM		MID-EVENIN 8:00 PM		BED! 10:00 PM		Aggregate 12:00 AM	
# of Readings		8%	15	17%	32	8%	14	19%	35	8%	15	23%	42	3%	5	14%	26	100%	184
Readings Per Day																		6.13	
Maximum	mg/dL	249		178		145		374		224		431		194		259		431	
Minimum	mg/dL	80		69		47		61		71		51		71		64		47	
Mean	mg/dL	151		129		107		144		134		168		145		145		144	
Std Dev	mg/dL	45.58		31.39		31.77		66.93		44.09		62.26		46.73		54.10		55.40	

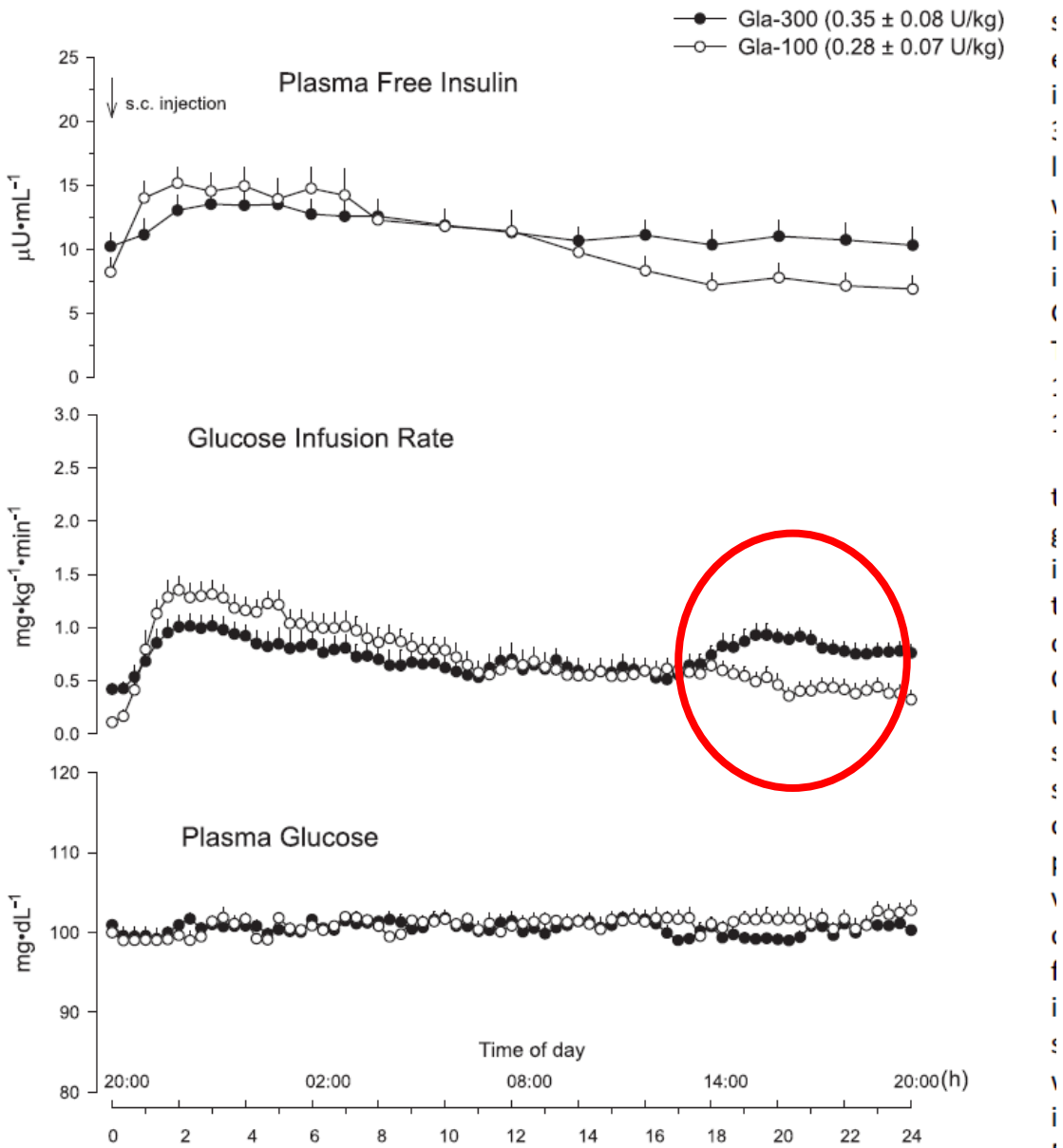
Basal Insulins

- Not all the same!
- NPH-occasionally used for severe dawn phenomenon, morning steroids
- Glargine (Lantus, Basaglar, Semglee): most common used basal insulin
- U-300 glargine (Toujeo)
- Degludec (Tresiba)

Insulin Action Curves: Degludec vs. Glargine



What About U100 Glargine vs. U300 Glargine?



U300 lasts longer than U100 BUT requires about 15% more in the dose

Glargine: One or Two Shots for T1D?

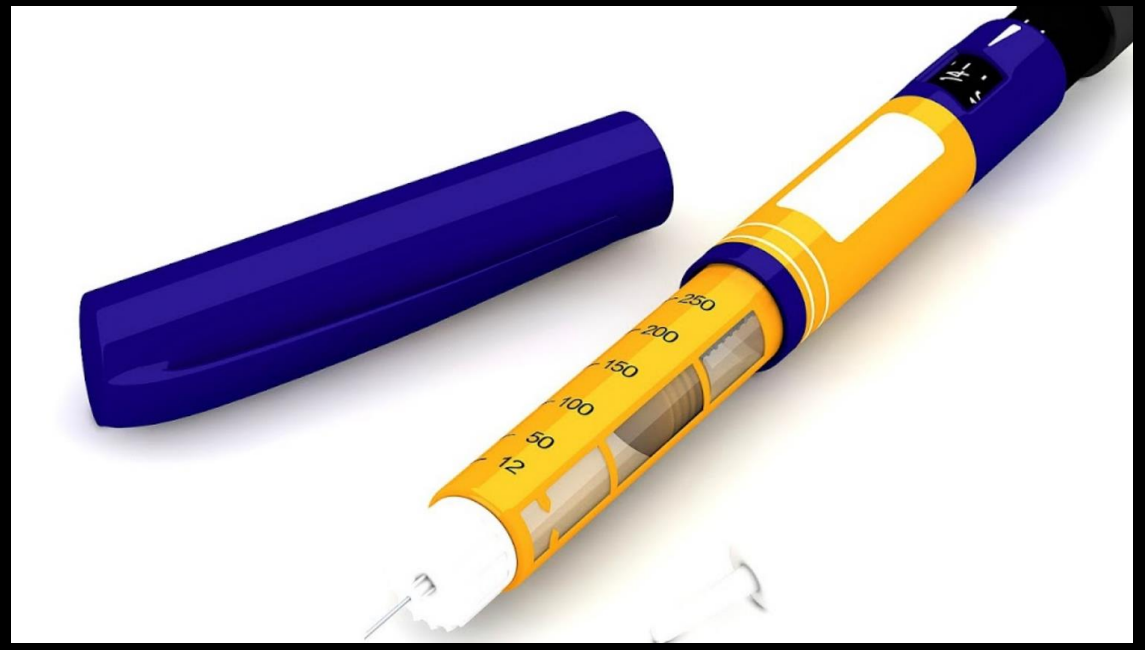
- Many with T1D do fine with once daily, especially if taking dinner-time insulin regularly
- For *most* who make no insulin, twice daily works better and give more flexibility (illness, sedentary, exercise)

U-100 Glargine vs. Degludec/U-300 Glargine

- Degludec: consistently less hypoglycemia
- U300 glargine: some but not all studies with less hypoglycemia
- Bottom line: Degludec and U300 glargine are better basal insulins than U100 glargine; as a rule of thumb if you can get them, you should for T1D

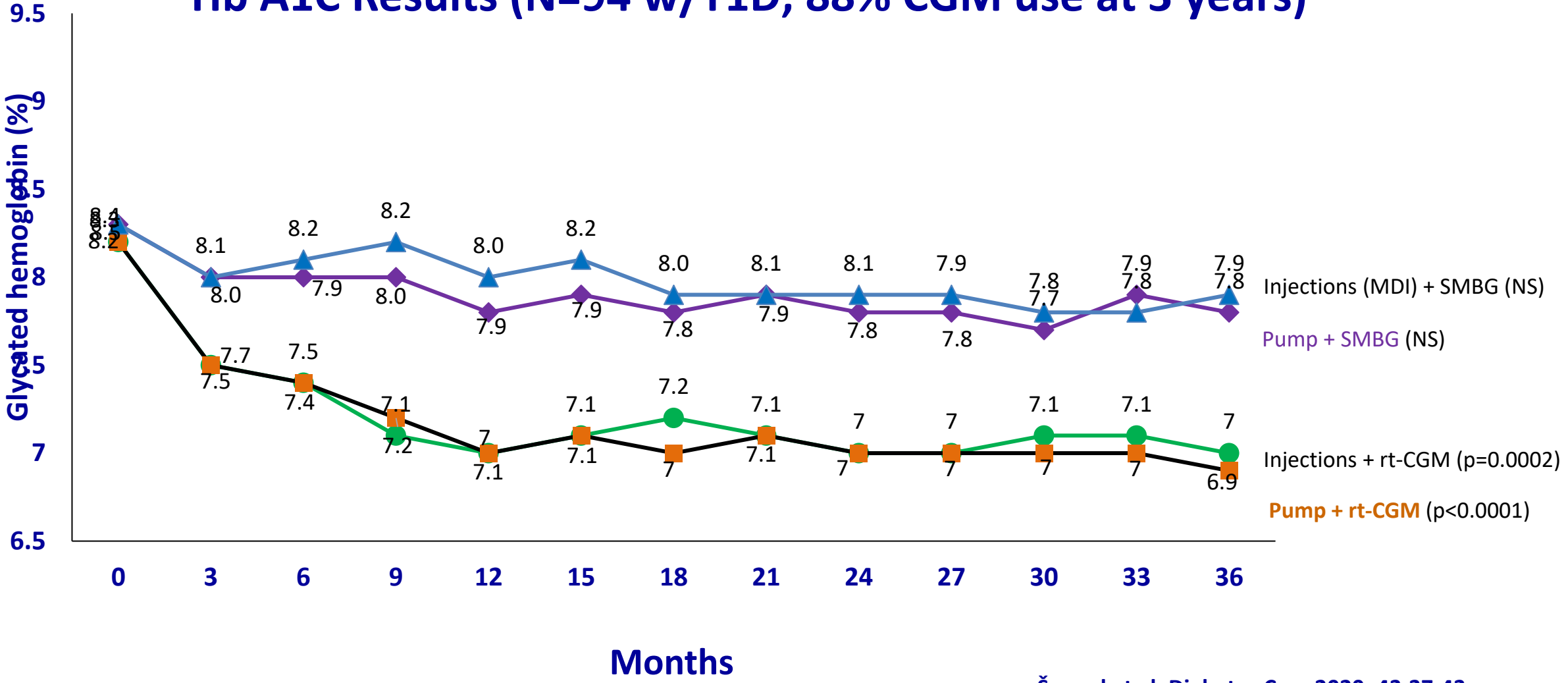
What You Should Take Away

- MDI is not an inferior way to get insulin!



“Dude-it’s not how I get my insulin-it’s all about my CGM!”

Hb A1C Results (N=94 w/T1D; 88% CGM use at 3 years)



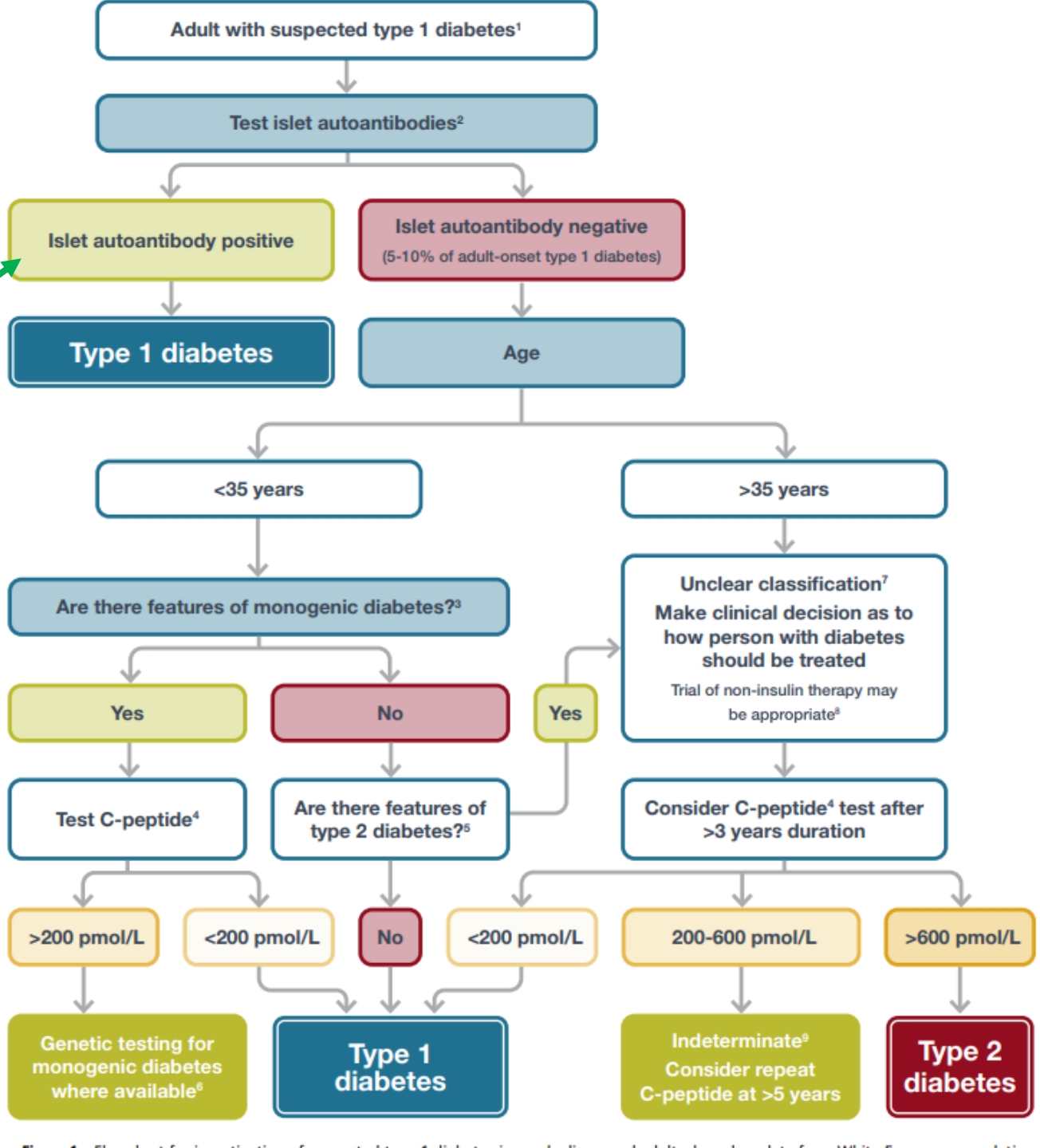
Šoupal et al. Diabetes Care 2020; 43:37-43

Case

- A 42 y/o man presents with fatigue and polyuria, a 5-pound weight loss in the past month.
- PMH unremarkable, mother with Graves disease
- PE unremarkable
- Random glucose 255 mg/dL, HbA1c 9.5%, no ketonuria
- What to do next?

Unclear Diabetes Type: Based on White European Populations

Our patient had strongly + GAD65 and TPO Ab



Diabetes Care 2021 Sep; dci210043
On-line Sept 29, 2021

Starting Insulin in New-Onset Adult T1D

- 50% of all new T1D above the age of 18
- 23% will be making some insulin 40 years later
- Initial insulin doses can be low, especially if no ketonuria at beginning (e.g., 0.3 u/kg/day) in a basal-bolus regimen
- In c-peptide negative T1D, using glargine BID works best. With new-onset in an adult, qd is fine
- It is fine to start at a 50/50 ratio of basal to bolus at first

Our Patient

- Weight is 80 kg
- Starting TDD is 80 X 0.3 = 24 units/day
- 12 units glargine
- In T1D, carb counting is a generally a better strategy but with newly diagnosed T1D that is not possible. Use meal estimates of small/medium/large doses for each meal
- Medium meal would be 4 units (12/3). Large 5 units, small 3 units
- ISF 50 over 150 (over 200 @HS)

Our Patient After 1 Week

Breakfast	Lunch	Dinner	HS	0300
88. 4 lispro+0	213. 4+2	145. 5 + 0	195 12 G + 0	
105 5+0	241 3+2	118 5+0	266 12G + 2	
145 3+0	276 5+3	156 5+1	210 12G +1	64
188 4+1	310 4+4	125 4+0	235 12G+1	

- Conclusions:
  - BeAM > 30 consistently. Needs less basal insulin (not correction dose)
  - Not enough breakfast or dinner insulin-need to increase and ideally learn carb counting
  - Correction doses looks fine
  - Be careful-insulin requirements may come down after a few weeks

Our Patient After 1 Year

- Now taking 18 units glargine q HS
- Carb counting: 1:12 with ISF 40 >150 with breakfast, 1:15 with ISF 50 lunch and dinner, ISF 50 > 200 q HS
- HbA1c 7.1%

Breakfast	Lunch	Dinner	HS	0300
132 8 +0	111. 4+0	197. 6 + 2	191 18 G + 0	
185 7+2	133 4+0	No dinner	266 18G + 2	
125 4+0	98 3+0	144	189 18G +0	
175 5+1	167 4+1	135 4+0	235 18G+1	

Conclusions:

1. BeAM is low, glargine dose overnight is fine
2. Good mealtime insulin replacement-both ICR and ISF
3. High BGs at bedtime due to lack of basal insulin, NOT prandial problem at dinner best seen on day #2

Hope This Was Helpful-Thank You