



**CONCENTRATED insulin update:**  
Is U500 insulin becoming a



???

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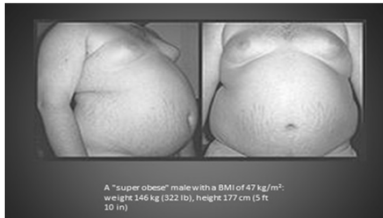
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**Obesity is the driver of insulin resistance**



A "super obese" male with a BMI of 47 kg/m<sup>2</sup>, weight 146 kg (322 lb), height 177 cm (5 ft 10 in).

**US obesity rate was 30.4% in 2015**

<http://www.cdc.gov/obesity/data/adult.html>

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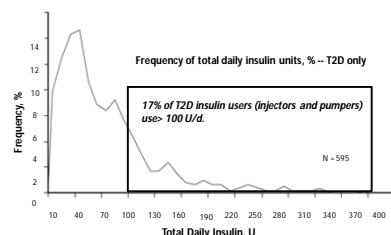
### Insulin Doses Are Increasing

- Obesity-induced insulin resistance has led to **high insulin requirements** in a sizable percentage of people with T2D
- Approximately **35%** of subjects with T2D require a basal insulin maintenance dose of **60U** or more<sup>[1]</sup>
- In a treat-to-target basal insulin trial involving insulin-naive patients with T2D, **21% of patients required > 80 U of basal insulin** at the end of the trial<sup>[2]</sup>

1. Rodbard HW, et al. *Endocr Pract.* 2014;20:285-292  
2. Gough SCJ, et al. *Diabetes Care.* 2013;36:2536-2542.

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### 17% of T2DM Patients Use > 100 U/d



2011 US Roper Diabetes Patient Market Study provided by GfK Custom Research LLC.

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### Why do we need a concentrated basal insulin?

- In a basal/bolus regimen, **the largest daily injection for continuous background glucose control is the basal injection** (usually 50% TDD and 2-3 times average bolus dose)
- Current U100 insulin syringes deliver a **maximum of 100 U** of insulin, and all but 1 current (purely basal) pen device delivers a **maximum dose of 80 U**

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### Why do we need a concentrated basal insulin? (cont)

- Insulin-resistant patients requiring > 100 U of basal insulin will need **> 1 injection (1 mL)** of insulin by syringe, and may require **> 1 pen injection** in patients requiring > 80 U/d
- There is some evidence that **large insulin volumes are poorly and inconsistently absorbed**, leading to suboptimal glycemic control<sup>[3]</sup>

3. Binder C, et al. *Diabetes Care.* 1984;7:188-199.

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### Do we need a concentrated prandial insulin?

#### MDI: PROBABLY

- keeps the injection volume **comfortable** for patients injecting large (>35 units) doses of mealtime insulin
- improve **absorption**
- makes the injection pen **last longer**

#### CSII: DEFINITELY

- facilitates **adequate insulin absorption** of high basal and bolus infusion rates
- allows **adequate insulin pump operability**

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### Potential advantages of concentrated insulin use in patients with severe IR

- Improved insulin absorption from smaller volume injection leads to **more predictable insulin action and improved glycemic control**
- Fewer injections and lower volume injections **enhance patient comfort and adherence**

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### Potential advantages of concentrated insulin use in patients with severe IR

- Concentration of the insulin can **prolong insulin action**, depending on the method of protraction<sup>[4]</sup> (U500R insulin and U300 glargine)
- Protracted PD profile of U300 glargine results in **less hypoglycemia** than U100 glargine
- **Cost savings** when used in CSII (fewer cartridge and battery changes)

4. Sindelka G, et al. *Diabetologia*. 1994;37:377-380.

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### Most common potential candidates for concentrated insulin

- Obese T2D with **severe insulin resistance**<sup>[4]</sup>
  - Multiple daily injections
  - CSII\*
- T2D requiring **high-dose insulin**<sup>[4,5]</sup>
  - Postoperatively or posttransplant
  - On high-dose glucocorticoid therapy
  - Severe systemic infection

\*Off-label use.

4. Cochran E, et al. *Diabetes Care*. 2005;28:1240-1244.

5. Garg R, et al. *Diabetes Metab Res Rev*. 2007;23:265-268.

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### Currently available concentrated basal insulins

- U500 regular human insulin (Lilly) (basal and prandial; available in pen and vial)
- U300 glargine (Sanofi) (pen only)
- U200 degludec (Novo Nordisk) (pen only)

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### Currently available concentrated prandial insulin

- U200 lispro (Lilly) (pen only)

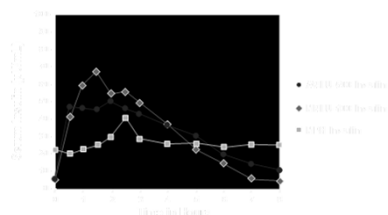
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### Pharmacokinetic (PK) and pharmacodynamic (PD) profiles of concentrated insulins

- PK: insulin levels in blood over time (reflects absorption)
- PD: insulin action over time (glucodynamics)
- Measures of bioequivalence of different concentrations of insulins

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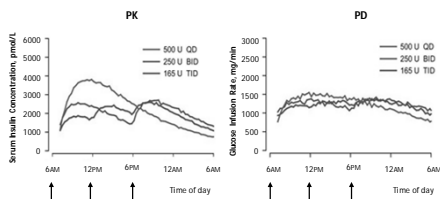
### Pharmacokinetics of Concentrated Insulin: U500 R



Adapted from Galloway JA, et al. *Diabetes Care*. 1981;4:366

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### PK/PD Modeling of U500R Doses at Steady-State During 24H of Day 5: 500 U QD, 250 U BID, 165 U TID



de la Peña A, et al. *J Diabetes Sci Technol*. 2014;8:821-829.

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### U-500 Insulin MDI: BID or TID?

- 325 patients with T2DM with mean baseline U-100 insulin dose 287.5 U/day in 5 injections/day with mean baseline HbA1c 8.7% were randomized to receive U-500 insulin BID or TID.
- Results showed both regimens had comparable HbA1c reduction at 24 weeks (BID: -1.22%; TID -1.12%;  $p < .001$  vs. baseline for each regimen), comparable increases in total daily insulin dose for each regimen, comparable weight gain (BID: 4.9 kg, TID: 5.4 kg) and comparable incidence of severe hypoglycemia for each regimen, HOWEVER:
- Incidence and rates of documented symptomatic and nocturnal hypoglycemia ( $BG \leq 70$  mg/dl) and nocturnal hypoglycemia ( $BG < 50$ ) were significantly lower for TID vs. BID.

Hood, RC, Arakaki, RF, Wysham C, et al. *Endocr Practice* 2015;21:782-793

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### Clinical Case Series Results (Literature Review 2003-2012)

Recent review and meta-analysis

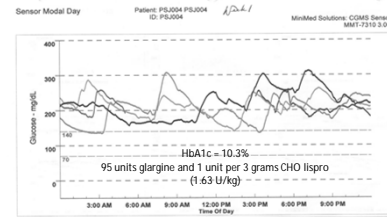
- 9 MDI series (310 patients):
  - 1.59% decrease in A1C (95% CI, 1.26-1.92)
  - 51.9 unit increase in insulin dose over 6-36 mean months of use (95% CI, 19.6-84.1)
  - 4.38 kg weight gain (95% CI, 2.35-6.41)
- 6 CSII\* series (55 patients):
  - 1.64% decrease in A1C (95% CI, 1.14-2.14)
  - 13.6 unit decrease in insulin dose over 3 to 30 mean months of use (95% CI, -42.4 to 15.2; NS)
  - 2.99 kg weight gain (95% CI, -1.83-7.81; NS)

U-500 = 500 units/mL, A1C, glycated hemoglobin; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; NS, nonsignificant.

\*U-500 regular insulin is not approved for use by CSII. Reutrakul S, et al. *J Diabetes Sci Technol*. 2012;6(2):412-420.

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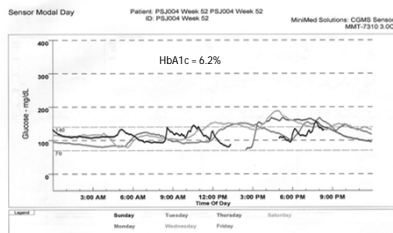
### High dose U100 MDI converted to U500 by CSII\*: Baseline CGM



\*Off-Label Use

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### CGM on U500 by CSII\* at 52 weeks



\* Denotes off-label use

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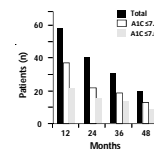
### U-500 Regular Insulin: Use by CSII

#### DESIGN

- Retrospective study of patients with insulin-resistant T2DM and high insulin requirements (N = 59) treated with U-500 regular insulin by CSII for 1 to 9.5 years

#### RESULTS

- Mean decrease in A1C of 1.0% from baseline of 8.3% ( $P = .003$ ) within 3 months
- 60% of the patients achieved a sustained A1C < 7.5%, while 31% achieved A1C < 7.0%
- No statistically significant weight gain at any time point
- No significant change in TDD from baseline to any time point up to 114 months after initiation of U-500 insulin
- Rate of severe hypoglycemia was 0.1 per patient per year



U-500 = 500 units/mL, A1C, glycated hemoglobin; CSII, continuous subcutaneous insulin infusion; TDD, total daily insulin dose; U-500 regular insulin is not approved for use by CSII.

Lane WS, et al. *Endocr Pract*. 2012;27:1-18.

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### U-500 R Insulin: Limitations

- Long duration of action, with potential for “stacking” of doses
- In CSII (off-label use), must do **mathematical conversions for pump settings** (as current pumps can only be programmed for U100 insulin)
- In CSII, meal boluses must be taken **30-60 minutes ahead of meal** to control postprandial BG (inconvenient)
- **Does not act rapidly enough to use for correction doses**, leading some clinicians to prescribe a rapid-acting analogue to use for correction dosing

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Beware of stacking:  
if you stack, you snack....!

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### U500R insulin: good news and bad news

The good news: U500 has both prandial and basal activity

The bad news: U500 has both prandial and basal activity

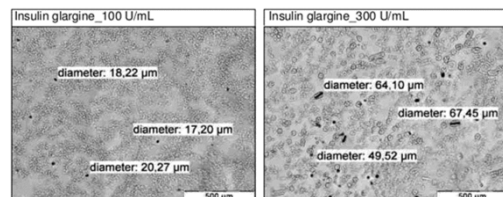
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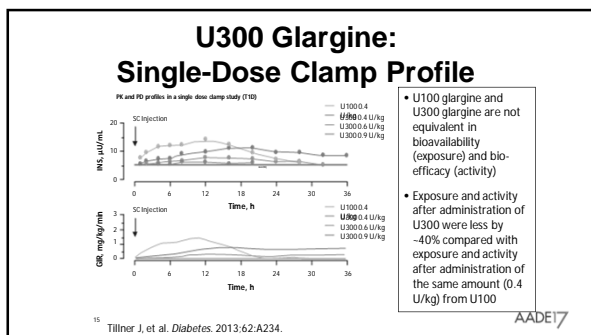
So, if we don't want to use U500 insulin in a high dose (>200 units/d) insulin patient, what are our other options?

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### U300 Glargine



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### U-300 Glargine: clinical efficacy and potential benefits

- Reduced rate of confirmed (< 70 mg/dl) or severe (requiring assistance) hypoglycemia in phase 3 trials in T2DM (RR: 0.86 to 0.96) with 16 to 38% less nocturnal hypoglycemia in T2 trials<sup>1</sup>
- Longer duration of action than U100 glargine (up to 36 vs. < 24 hours)<sup>1</sup>
- Slightly more flexible dosing window (24 +/- 3 hours) possible compared to U100 glargine without loss of glycemic control<sup>2</sup>

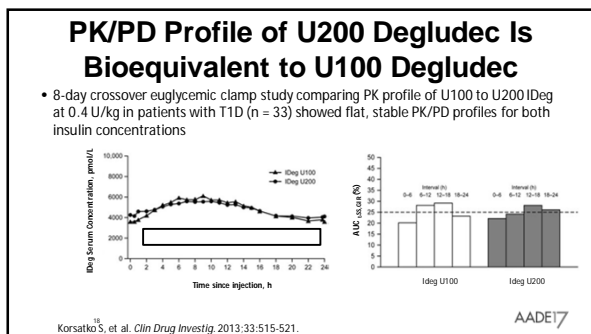
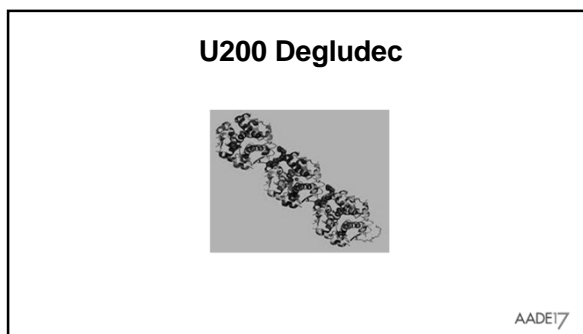
1. Rosselli JL, et al. *J Pharmacy Technol*. DOI: 10.1177/8755122515584193pharmatech.sagepub.com: 11/7/2015  
 2. Riddle MC, et al. *Diabetes Technol and Therapeutics* 2016; 18(4): 252-257

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### U-300 Glargine: limitations

- Lower bioavailability with **need to up-titrate dose** vs. U-100 glargine (11 to 17% higher dose of U300 glargine vs. U100 glargine needed across phase 3 clinical trials)<sup>1</sup>
- Hypoglycemia reduction only seen in T2DM trials, not in T1DM trials, and was inconsistent across T2DM trials.<sup>1</sup>
- U300 glargine pen cannot deliver more than 80 units with one injection.**
- U300 glargine pen only contains 450 units of insulin (vs. 600 units for U200 insulin pens and 1500 units per U500 insulin pen), so prescription (for 3 pens) only gives 1350 units of insulin (vs. 1800 to 3000 units for other concentrated insulin products) per copay.

1. Rosselli JL, et al. *J Pharmacy Technol*. DOI: 10.1177/8755122515584193pharmatech.sagepub.com: 11/7/2015. AADE17



### U200 Degludec: clinical efficacy and potential benefits

- Longest duration of action** of all basal insulins (>42 hours)<sup>1</sup>
- Pen can inject **up to 160 units with single injection**, eliminating need for 2 daily basal insulin injections for those patients requiring over 80 to 100 units of basal insulin per day.
- Bioequivalence of U100 and U200 formulations means **no dose titration** when changing from one formulation to the other
- Bioequivalence of U100 and U200 formulations suggests therapeutic benefits of U100 degludec would also apply to U200 formulation (ie, consistent hypoglycemia reduction vs. U100 basal insulins, flexible dosing window of 8 to 40 hours)

1. Rosselli JL, et al. *J Pharmacy Technol* DOI:10.1177/8755122515584193pharmatech.sagepub.com/11/7/2015  
 2. Landsiedel-Hellmich. *Curr Med Res Opin* 2015; Aug 31(8):1487-93

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### U200 Degludec: clinical efficacy and potential benefits

- **Slightly lower dose requirement** (approximately 10% lower basal insulin dose for U100 or U200 formulation) vs. other basal insulins<sup>1</sup>
- Pen contains **600 units of insulin**, so prescription for 3 pens yields 1800 units per copay (vs. 1500 units for U100 insulin pens and 1350 units for U300 glargine pens)

1. Landstedt-Hallin L. *Curr Med Res Opin* 2015; Aug;31(8):1487-93

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### U200 degludec in high dose patients with type 2 DM (BEGIN: HIGH DOSE\* study)

- 32 week study crossover study comparing U200 degludec to U100 glargine in 144 patients with type 2 DM on oral agents plus >81 units of basal insulin qd.
- At the end of the study, A1c reduction was similar in both arms with lower FPG's, lower incidence of confirmed hypoglycemia (RR 0.59), lower injection frequency and greater patient satisfaction (using the TRIM-DD questionnaire) with U200 degludec than with U100 glargine.

Warren M. et al., *Clinical Diabetes* 2017; 35(2):90-95

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### U200 Degludec: limitations

- **May need to down-titrate dose** from previous basal insulin (prescriber should be aware)
- Patients need to be aware that it takes **2 to 3 days to build to a steady state**
- **Cost/Formulary restrictions** (access improving in 2017)

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### PK Bioequivalence: Lispro U-200 versus Lispro U-100<sup>1</sup>

IL U-100 = Insulin lispro 100 U/mL; IL U-200 = Insulin lispro 200 U/mL

1. EMA/CHMP/HTTP://WWW.EMA.EUROPA.EU/DOCS/EN\_CB/DOCUMENT\_LIBRARY/EPAR/\_Assessment\_Report/\_Variation/human/000088/WC500176434.pdf

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### U200 Lispro: Benefits

- **In MDI:** can give larger prandial insulin dose in smaller (50%) volume
- Pen holds 600 units of insulin; **lasts twice as long as U100 pen** (1800 units per copay vs. 1500 units for U100 lispro)

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### U200 Lispro has potential benefits in CSII\*

- Ability to deliver basal and bolus insulin doses in **half the volume**, allowing for patients requiring up to 200 units of insulin per day to change insulin pump cartridges every 3 days
- Theoretical **improvement in postprandial glucose control** over U500R\* insulin (since it is a rapid-acting analogue)
- Ability to bolus insulin within 15 minutes of meals (instead of 30 to 60 minutes ahead)

\*Off-label use

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### U200 Lispro\* vs. U500R\* in CSII: a pilot study

- 11 subjects (1 with T1DM and 10 with T2DM) on U500R in CSII\* with stable pump settings for >12 months (mean TDID 217 U/d)
- Mean baseline A1c: 8.0 +/- 1.0 %
- Changed to equivalent U200 lispro insulin delivery rates for basal and bolus insulin and correction doses for 1 week run in and 4 week trial period
- Insulin-on-board time changed from 6 hours for U500R to 3 hours for U200 lispro
- Time of meal boluses changed from 30 to 60 minutes before meals to 0 to 15 minutes before meals
- Primary endpoint: peak (2 hour) postprandial BG by CGM
- Secondary endpoints: percent time in euglycemia, hypoglycemia and hyperglycemia by CGM; total daily insulin dose, HbA1c

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AADE 25th annual meeting, Poster 1308, 5/28/2016

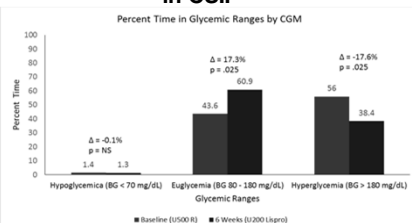
### U200 lispro improved postprandial glucose compared to U500R in CSII\*



\*Off-label use

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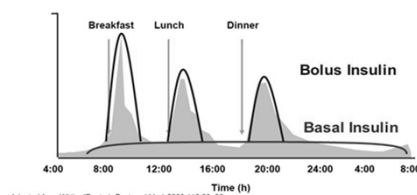
### U200 lispro improved time spent in euglycemia (BG 80 to 180 mg/dl) by CGM compared to U500R in CSII\*



\*Off-label use

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### Ideal Insulin Replacement Strategy



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### What do we need for a PHYSIOLOGIC high dose insulin regimen?

1. In MDI: a CONCENTRATED rapid (or ultra-rapid) acting insulin analogue plus a CONCENTRATED basal insulin analogue
2. In CSII: a CONCENTRATED rapid (or ultra-rapid) acting analogue
3. Physiologic PD profiles that mimic normal insulin action
4. Bioequivalence to the same analogues at lower (U100) concentrations (for safest dose conversion)

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### Physiologic concentrated insulin analogues for high dose MDI regimens

- U200 degludec
- U200 lispro

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### Insulin-sparing adjunct therapies

- Metformin
- SGLT2/SGLT1,2\* inhibitors
- GLP-1 RA's

\* Not yet approved

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### Benefits of adding adjunct agents to high-dose insulin therapy

- Lower insulin requirement; smaller injections and possibly fewer injections
- Limit insulin associated weight gain; may help patient lose weight
- Lower glycemic variability than with insulin alone
- Possible CV benefits (empagliflozin, canagliflozin, liraglutide, semaglutide\*, ?others)

\*Not yet approved

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### CONCENTRATED insulin case studies

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### Case 1: Greg

Greg is a 60 year old white male who was diagnosed with HIV infection at the age of 30. He then developed type 1 DM at the age of 31. He has been treated with protease inhibitors for the past 25 years. Greg states that he has "always had a high insulin requirement". For the past 5 years, he has used U500 insulin by CSII\* with basal U500 infusion rates of 0.8 to 1.6 "pump units" (4 to 8 actual units) per hour, with a meal bolus ratio of one unit of insulin per 3 grams of carbohydrate (up to 60 units per meal). Greg also uses CGM.

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### Case study: Greg

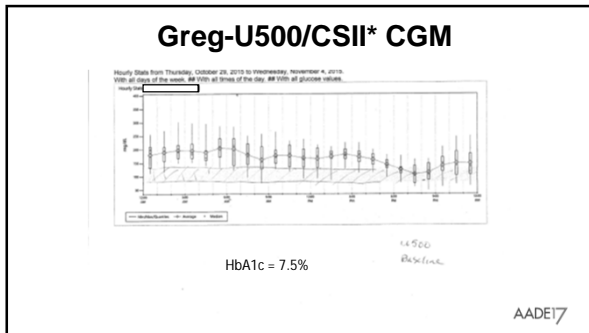
PMH: Type 1 DM with minimal BGR, HIV, Dyslipidemia  
 Meds: U500 insulin via CSII\*, losartan, pravastatin, aspirin, acyclovir, ritonavir, atazanovir, tenofovir/emtricitabine, didanosine  
 PE: Height: 74" Weight: 233 lb (106 kg) BMI: 30 BP: 126/86  
 Total Daily insulin dose: 250 to 300 U (2.4 to 2.8 U/kg)  
 HbA1c: 7.5%

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### Case study: Greg

Greg states he has a problem controlling his post-meal blood sugars, and that he must bolus more than an hour ahead of meals to control them. This has become an inconvenience, and he finds himself missing boluses. However, if he boluses too late in the evening, he will experience nocturnal hypoglycemia. Thus, he tends to run high overnight from under-bolusing for late meals and snacks.

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### Case study: Greg

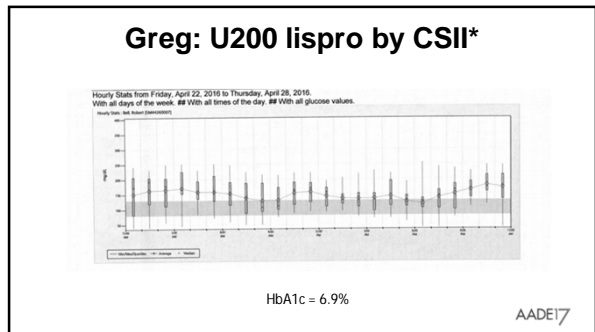
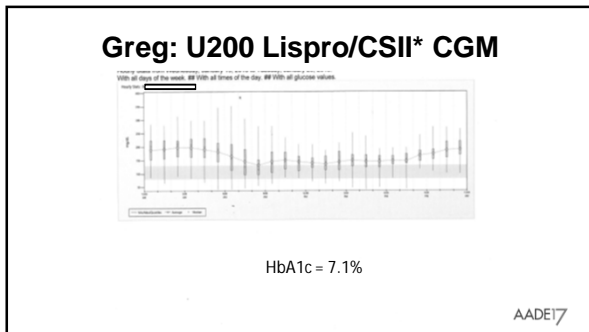
Greg would benefit from a rapid-acting insulin analog for use in his pump, but his large insulin requirement precludes the use of a U100 RAA. Therefore we elected to do a therapeutic trial of U200 lispro by CSII\*.

Initial U200 lispro pump\* basal settings: MN to 0400: 3.6 "pump units" (7.2 actual units), 0400 to 0700: 4.0 "pump units" (8 actual units), 0700 to 1200: 3.0 "pump units" (6 actual units); 1200 to MN: 2.0 "pump units" (4 actual units)

U200 lispro ICR: 1:10 (1 unit per 5 grams carb)

U200 lispro ISF: 60 (1 unit decreases BG by 30 points)

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### Case 2: Kimberly

- 46 year old WF with history of PCOS and 15 year hx T2DM; she failed oral agents and BID exenatide and was placed on intensive insulin regimen. She relates having trouble remembering her insulin injections.
- Present regimen: 90 units of insulin glargine (U100 via syringe) at hs, 35 units of lispro ac (1.6 U/kg) plus metformin ER 2000 mg/d
- HbA1c ranges from 10.5% to 12.6% for past several years; all SMBG's 200 to 400 mg/dl

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### Kimberly: exam

- PE: Height 65" Weight 264 lbs (BMI 44)
- HEENT: thinning scalp hair, facial hirsutism; heart, lungs, thyroid all normal; obese abdomen; mild pedal edema; ankle jerk reflexes and monofilament sensation is diminished
- HbA1c: 10.1%

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### Kimberly: treatment plan

- Discontinue glargine and lispro. Begin U500R insulin, 100 units BID (20 unit markings on insulin syringe). Begin liraglutide; titrate to 1.2 mg/d. Continue metformin 2000 mg/d
- 4 week follow-up: SMBG's 57 to 154 mg/dl; several (symptomatic non-severe) hypoglycemic episodes (57-66 mg/dl)
- U500R is reduced to 75 units BID; continue liraglutide
- 3 month follow-up: weight 267 lbs (3 lb increase); still having occasional BG's in 50's and 60's; range of SMBG's 54 to 240 mg/dl; HbA1c 7.8%
- Plan: increase liraglutide to 1.8 mg/d; continue U500R 75 U BID and metformin

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### Case study: Kimberly

- 6 month follow-up: HbA1c has risen to 8.3%; SMBG's range from 80 to 250 mg/dl; no further hypoglycemia but persistent excessive GV on U500R BID, liraglutide 1.8 mg/d
- Suggested she try an insulin pump (with U500R insulin); her insurance denies coverage
- Plan: U500R 50 units TID with liraglutide 1.8 mg/d
- Phone follow-up: patient experiences recurrent hypoglycemia; U500R dose is reduced to 40 units TID (with liraglutide and metformin)

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### Case study: Kimberly

- For next 2 years on U500R 40 to 60 units TID (plus liraglutide and metformin) HbA1c's range from 7.9 to 10.3% and SMBG's range from 60 to 250 mg/dl. Weight is stable at 256 lbs. She continues to show excessive GV and well as variability of HbA1c, although no severe hypoglycemia.
- Kimberly agrees to again try a basal/bolus insulin regimen with U200 degludec and U200 lispro (February 2017). HbA1c 8.6%. Plan: Begin U200 degludec, 72 units qd and U200 lispro 24 units TID ac. Discontinue liraglutide; begin dulaglutide 1.5 mg q week (to reduce injection burden); continue metformin.

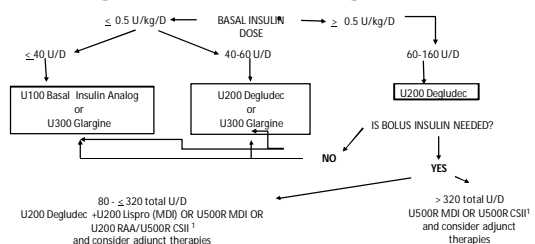
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### Kimberly: last follow up visit

HbA1c 7.5%; All SMBG's 90-175 mg/dl. No further hypoglycemia; markedly improved GV. She feels much better with stable BG's and is willing to continue the qid (basal/bolus) regimen with U200 insulin analogues.

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### High Dose Insulin Algorithm



1. Off-Label Use

Wendy Lane MD, Mountain Diabetes and Endocrine Center 2/16

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### So, is U500R a DINOSAUR??

- NO**, FOR PATIENTS REQUIRING OVER 300 UNITS OF INSULIN PER DAY (BUT FOR BEST RESULTS, USE IN CSII\*)
- YES**, FOR EVERYONE ELSE!!



\*Off-label use

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