

**TYPE 1 DIABETES:  
NEW AND EMERGING  
THERAPEUTIC  
STRATEGIES TO  
ADDRESS UNMET NEEDS**

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501(c)3 Not-for-Profit Organization

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Institute, Los Angeles, CA

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**DISCLOSURES**

**STEVEN V. EDELMAN, MD**

- Board Member: Senseonics, TeamType1
- Medical Advisory Board: AstraZeneca, BrightSight, InPen, Lexicon, Lilly USA, LLC, MannKind Corporation, Merck, Novo Nordisk, Sanofi-aventis U.S. Inc.
- Speaker's Bureau: AstraZeneca, Lilly USA, LLC, MannKind Corporation, Merck, Sanofi-aventis U.S. Inc.

**JUAN P. FRIAS, MD**

- Consultant: Eli Lilly, Merck, Sanofi-aventis U.S. Inc.
- Medical Advisory Board: Eli Lilly, Gilead, Sanofi-aventis U.S., Inc.
- Research Support: AbbVie, Akcea, Allergan, AstraZeneca, Boehringer Ingelheim, BMS, Carius, CymaBay, Elcelyx, Eli Lilly, Enanta, Genentech, IONIS, Intercept, Janssen, Johnson and Johnson, Lexicon, Ligand, Madrigal, Merck, Mylan, NGM, Novartis, Novo Nordisk, Pfizer, Sanofi-aventis U.S., Inc., Theracos
- Honoraria: Merck, Sanofi-aventis, U.S., Inc.
- Speaker's Bureau: Merck, Sanofi-aventis, U.S., Inc.




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**TOPICS  
TO BE  
DISCUSSED**

- Unmet needs in type 1 diabetes
- Historical perspective of type 1 diabetes
- State of type 1 diabetes care in 2019
- Continuous glucose monitoring (CGM)
- Pumps verses multiple daily injections
- Modern basal and ultra- fast acting insulins
- Other adjunctive therapies for type 1 diabetes
- What does the future hold?




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## UNMET NEEDS IN TYPE 1 DIABETES

- Unpredictable glycemic variability (GV), increased time in range (TIR)
- Reaching A1c goal without hypoglycemia
- Controlling blood pressure
- Preventing and controlling weight gain
- Emotional burden of living with type 1 diabetes for the individual and his/her family

TCOYD

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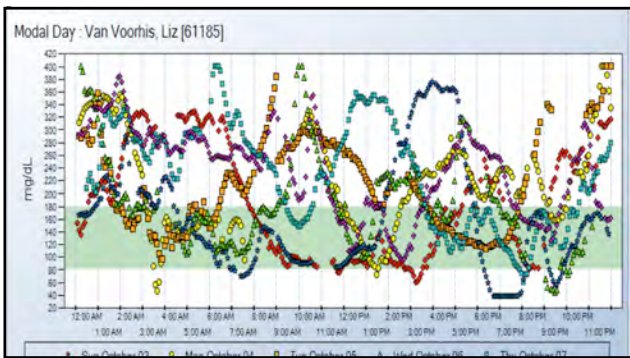
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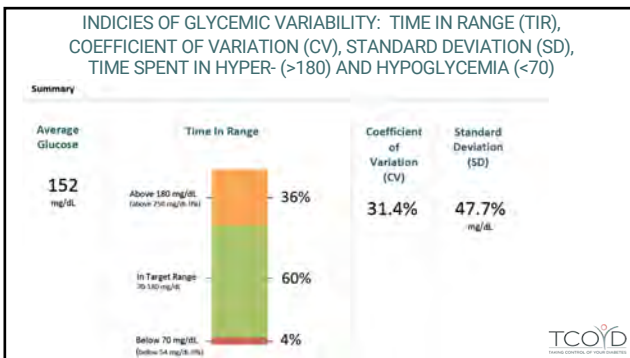
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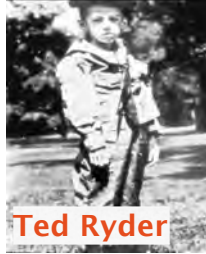
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BANTING AND BEST  
UNIVERSITY OF TORONTO 1921

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Ted Ryder



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**Ted Ryder**  
5 months  
after  
starting  
insulin



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FAST FORWARD TO T1D CARE IN 1970

- NPH and regular insulins used only once or twice a day.
- Urine testing only
- No A1c test
- No pumps or pens
- No insulin analogs
- No CGM
- No Apps



Adapted from: Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT, 2014.



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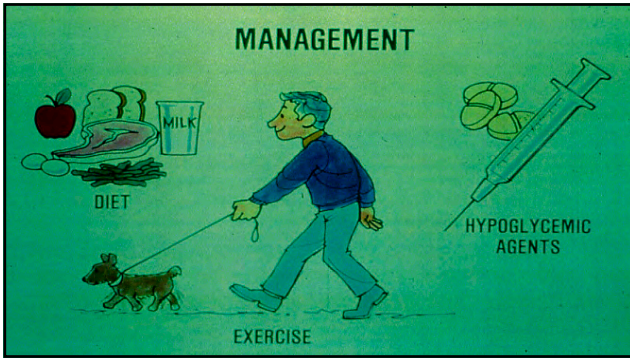
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**PREVALENCE OF T1D INCREASING IN US**

- 1.3 million adults currently have T1D<sup>1</sup>
  - 1 million adults ≥ 20 years
- 21% increase in prevalence of T1D in people < 20 years between 2001-2009<sup>2</sup>
- 40,000 people diagnosed each year in U.S.<sup>2</sup>
- 5 million people in U.S. expected to have T1D by 2050<sup>2</sup>

TCOYD

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**TYPE 1 IS AN AUTOIMMUNE DISEASE: THE IMMUNE SYSTEM ATTACKS HEALTHY BETA CELLS**

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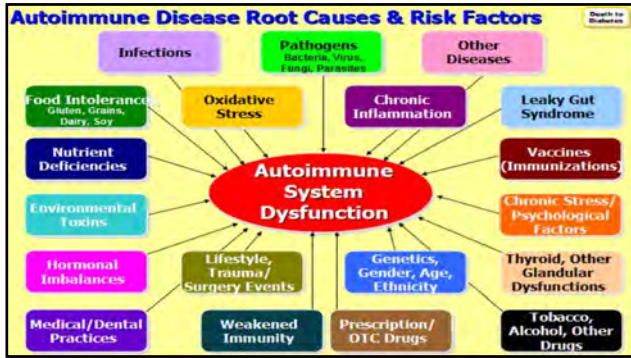
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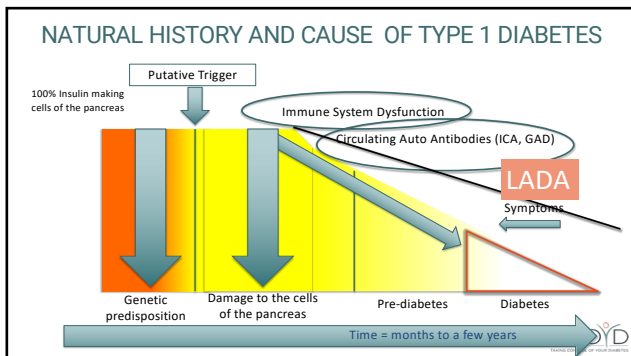
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### LATENT AUTOIMMUNE DIABETES IN ADULTS (LADA)

- o The most missed diagnosis in diabetes
- o Type 1 diabetes can occur at any age
- o Slower beta-cell destruction (may respond briefly to oral agents)
- o Typically does not have features of the Metabolic Syndrome
- o Blood test positive for type 1 diabetes (GAD auto antibodies)

Gary Hall Jr.  
Olympic Gold Medalist  
World Record Holder

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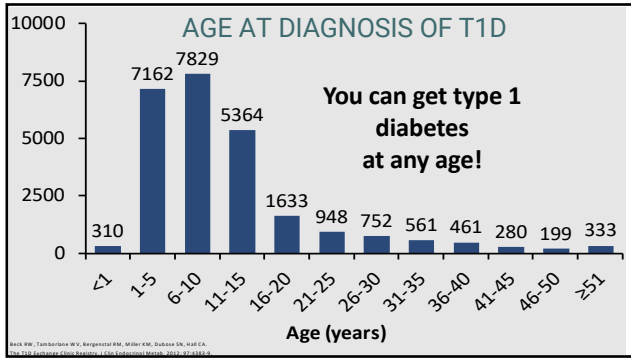
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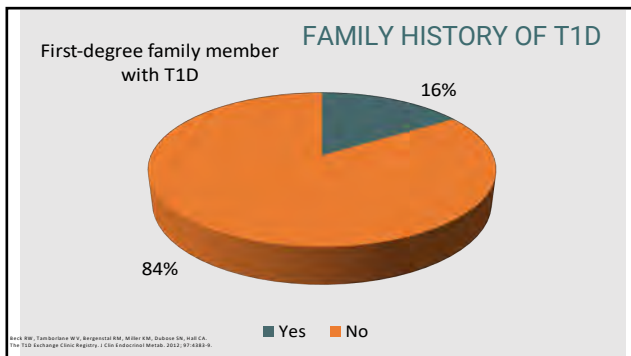
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### RISK OF DEVELOPING TYPE 1 VS TYPE 2

General Population	0.3%	8-11%
If you have a sibling with T1D	4%	~30%
If your mother has T1D	2-3%	~30%
If your father has T1D	6-8%	~30%
If you have an identical twin with T1D	~50%	100%

Adapted from: Taking control of your diabetes: a patient-centred text on diabetes. With advice from Professional Consultants Diabetes UK, Greenwich, CT. Last page, 2017.

TCO1D  
THE COLLEGE OF TYPE 1 DIABETES

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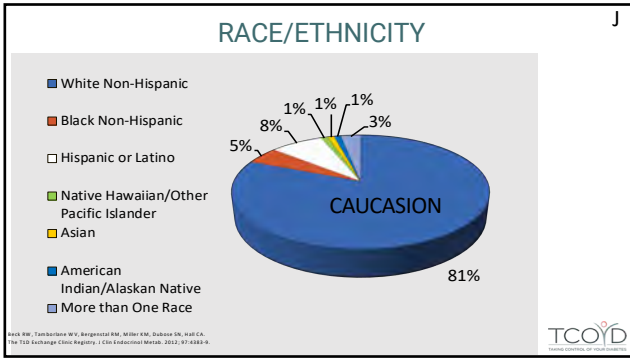
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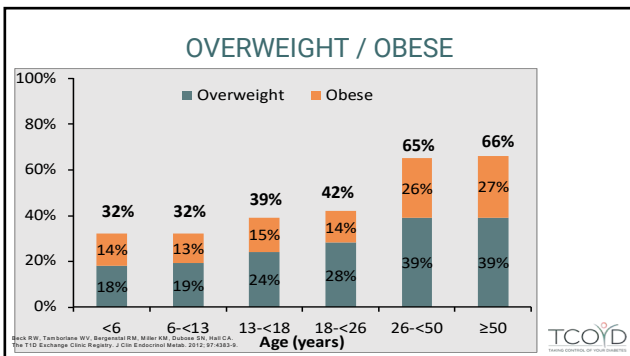
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### CONSEQUENCES OF WEIGHT GAIN

- Excess weight gain associated with risk factors for cardiovascular disease, including increased
  - Lipid levels
  - Blood pressure levels
  - Waist circumference
  - Metabolic syndrome

**TCO1D**  
THE CENTER FOR TYPE 1 DIABETES

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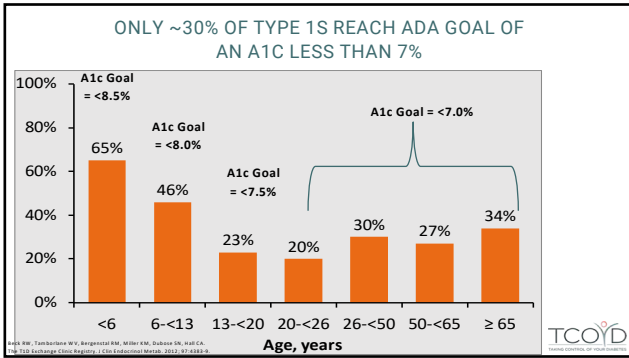
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**CASE 1: PHIL**

- ▶ 46 year old male with the diagnosis of type 1 diabetes at age 6 (Classic presentation of DKA)
- ▶ He has been on an insulin pump for many years
- ▶ Over the last 8 years he has developed central obesity and his insulin requirements doubled
- ▶ He also developed high blood pressure and dyslipidemia (triglycerides went up and his HDL when down).
- ▶ Family history is that his father and both paternal uncles have type 2 diabetes.

**TCOYD**  
Texas Children's Hospital

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**WHAT IS THE MOST LIKELY EXPLANATION OF WHY PHIL'S INSULIN REQUIREMENTS DOUBLED LATER IN LIFE?**

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<b>A</b>	He developed central obesity
<b>B</b>	He has both type 1 and type 2 diabetes
<b>C</b>	His A1c kept rising
<b>D</b>	He has high triglycerides

**TCOYD**  
Texas Children's Hospital

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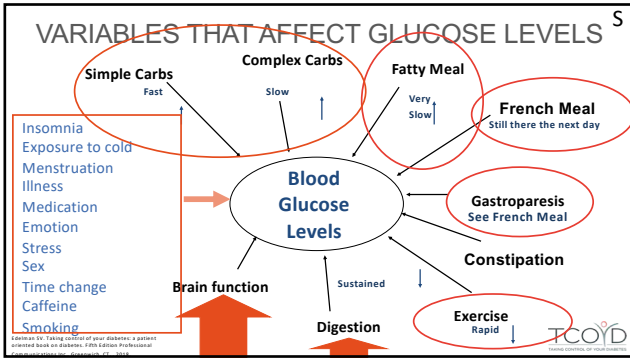
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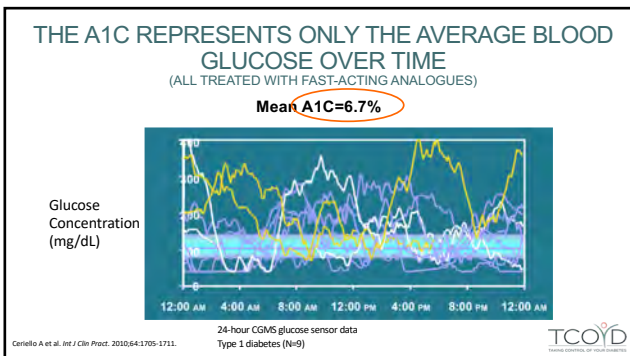
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- ### DESPITE FOLLOWING ALL OF THE RULES
1. Unexpected highs
  2. Unexpected lows
  3. Carb:Insulin ratio not working consistently
  4. Correction Factor not working consistently
  5. Not responding to insulin and exercise consistently
- 
- Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT, 2016.

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IT IS ALL ABOUT “**TIME IN RANGE**”  
KEEPING THE GLUCOSE LEVELS BETWEEN 70  
AND 180 MG/DL

1. 1<sup>st</sup> priority is getting a CGM and educate your patients to respond to the trend arrows.
2. Bolus calculations are more than just the carbohydrates and static glucose readings
3. In addition to getting the A1c below 7%, try to reduce the daily glucose fluctuations in your patients (hyper- and hypoglycemia)
4. The insulin regimen should mimic what happens in a non-diabetic state

Goldman TV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT, 2018

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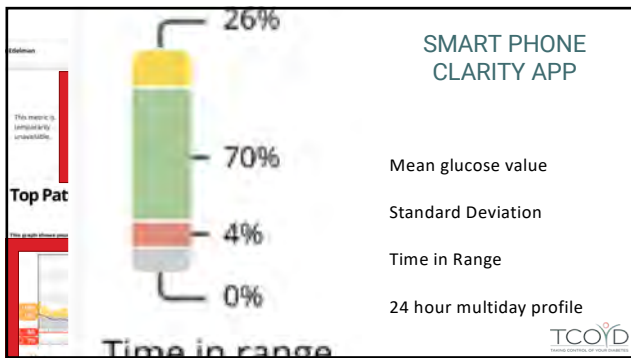
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## G6



- No calibration required
- 10 day sensor life
- Predictive low alerts
- No interference with acetaminophen
- Auto inserter
- Medicare Approved




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## EVERSENSE


Implantable Continuous Glucose Monitor



**Sensor**  
Sensor lasts up to 90 days  
No weekly sensor insertion  
No open wound



**Smart Transmitter**  
Removable and rechargeable  
On-body vibrate alerts  
Gentle, daily adhesive patch



**Mobile App**  
No extra device to carry  
iOS and Android platform  
Alarm settings & reports

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## EVERSENSE IMPLANTABLE CGM







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### GUARDIAN CONNECT



- Predictive high alerts
- Predictive low alerts
- Requires calibration
- 6-day wear
- Need to confirm with fingerstick when dosing

https://www.medtronic-diabetes.co.uk/Innovated-system/mini-med-640g-system; accessed April 2015

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### FREESTYLE LIBRE FLASH IS OR INTERMITTENT SENSING

- 12 hour warm-up time
  - Lasts 10 days (approved for 2hr/12day)
  - Swipe to get a number
  - Trend arrows
- No calibration
  - No alerts or alarms
  - No sharing features



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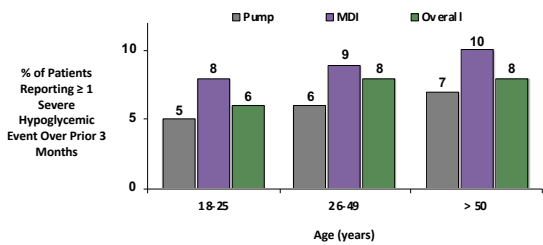
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### SEVERE HYPOGLYCEMIA – SERIOUS AE IN T1D DUE TO TOO MUCH INSULIN



Miller KM, et al. Diabetes Care. 2015

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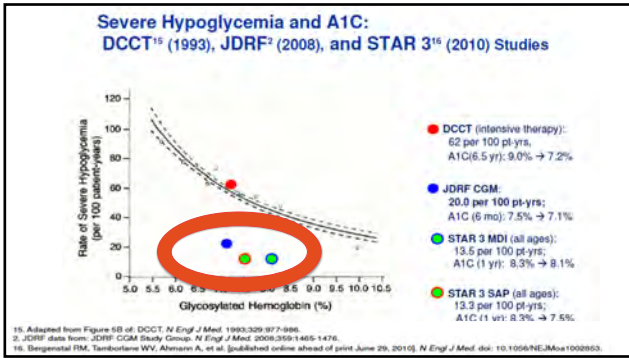
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### A SINGLE BG AT ONE POINT IN TIME LACKS IMPORTANT INFORMATION

No insulin  
Watch and  
maybe get some  
carbs

Take a larger  
than usual dose

Pump and meter software suggests the same either way

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### HOW CGM AND TRENDING INFORMATION CAN AFFECT OUR DECISIONS (CF/I:CHO)

→	<b>Constant:</b> Your glucose is steady (not increasing/decreasing more than 1 mg/dL each minute)
↗	<b>Slowly rising:</b> Your glucose is rising 1-2 mg/dL each minute
↑	<b>Rising:</b> Your glucose is rising 2-3 mg/dL each minute
↑↑	<b>Rapidly rising:</b> Your glucose is rising more than 3 mg/dL each minute
↘	<b>Slowly falling:</b> Your glucose is falling 1-2 mg/dL each minute
↓	<b>Falling:</b> Your glucose is falling 2-3 mg/dL each minute
↓↓	<b>Rapidly falling:</b> Your glucose is falling more than 3 mg/dL each minute
no arrow	<b>No Rate of Change Information:</b> This Receiver cannot always calculate how fast your glucose is rising or falling

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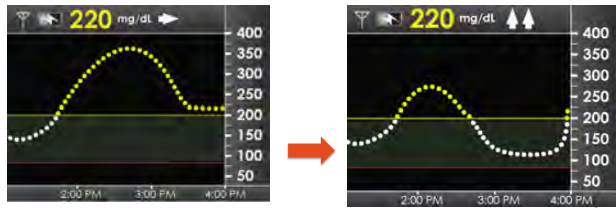
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MEAN CHANGE IN INSULIN DOSE BASED ON  
2 ARROWS UP: SURVEY OF 300 CGM USERS

**3.0 units**

**6.8 units**



J. Pettus, D.A. Price, K.J. Hill, S. Edelman (2014). Diabetes Technology & Therapeutics, February 2014, 16(2): A-76 page 198

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HOW CGM AND TRENDING INFORMATION  
CAN AFFECT DOSING DECISIONS

→	Constant: Your glucose is steady (not increasing or decreasing more than 1 mg/dL each minute)	<b>3.0 units</b>	No change in calculation
↗	Slowly rising: Your glucose is rising 1-2 mg/dL each minute		
↑	Rising: Your glucose is rising 2-3 mg/dL each minute		
↗↗	Rapidly rising: Your glucose is rising more than 3 mg/dL each minute	<b>6.8 units</b>	140% Mean Increase
↘	Slowly falling: Your glucose is falling 1-2 mg/dL each minute		
↓	Falling: Your glucose is falling 2-3 mg/dL each minute		
↘↘	Rapidly falling: Your glucose is falling more than 3 mg/dL each minute	<b>1.5 units</b>	48% Mean Decrease
↔	No Rate of Change Information: The Receiver is not receiving data		

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CASE 2: JEREMY

- 35 year old male with type 1 diabetes for 20 years
- CHO to insulin ratio 10:1
- CF 1:30 goal 120 mg/dl

Post "Snack" BS of 220mg/dL at 4:00 p.m.  
(snack at 3:30 p.m., no insulin given with snack)



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**CASE 2: JEREMY (CONTINUED)**

- Jeremy's CGM Guidelines
  - Correction factor 1:30
  - Target glucose 120 mg/dL
  - $220 - 120 / 30 = 3.3$  units

Note: A blood sugar of 220 does not lead to any symptoms




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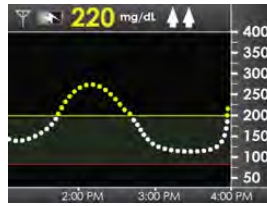
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**WHICH OPTION BELOW IS THE BEST SUGGESTION FOR JEREMY TO FOLLOW AT 4:00 PM?**

- |          |   |
|----------|---|
| <b>A</b> | Watch and wait (give no additional insulin)   |
| <b>B</b> | Walk for an hour at a brisk pace              |
| <b>C</b> | Give a correction dose of 3.3 units           |
| <b>D</b> | Give a correction dose greater than 3.3 units |




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**ADJUST INSULIN DOSE BASED ON ANTICIPATED GLUCOSE IN 30 MINUTES**

Anticipated Glucose Value for Timing	
→	No Adjustment. Dose for current glucose value.
↗	Adjust UP -- current value <b>plus</b> 25-50 mg/dL. Dose for adjusted value.
↑	Adjust UP -- current value <b>plus</b> 50-75 mg/dL. Dose for adjusted value.
↑↑	Adjust UP -- current value <b>plus</b> 75-100 mg/dL. Dose for adjusted value.
↘	Adjust DOWN -- current value <b>minus</b> 25-50 mg/dL. Dose for adjusted value.
↓	Adjust DOWN -- current value <b>minus</b> 50-75 mg/dL. Dose for adjusted value.
↓↓	Adjust DOWN -- current value <b>minus</b> 75-100 mg/dL. Dose for adjusted value.

Add 50 mg/dl

Add 75 mg/dl

Add 100 mg/dl

Wait until trend arrow becomes horizontal

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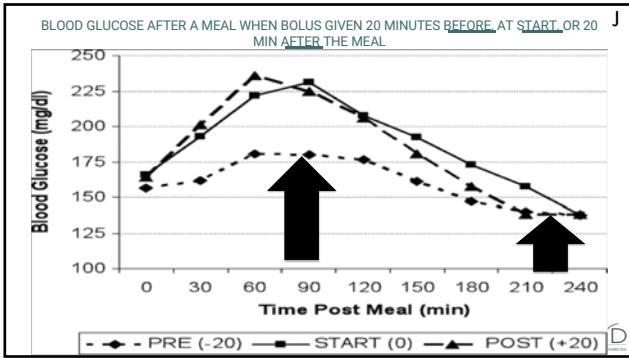
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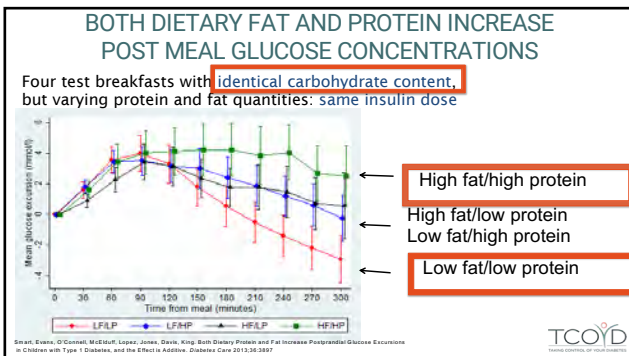
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HOW MUCH FAST ACTING INSULIN WOULD YOU RECOMMEND TO A PATIENT EATING A MEAL WITH 60 GRAMS OF CARBOHYDRATE (INSULIN TO CARB RATIO IS 1 TO 10), AN 8 OZ FILET AND A SALAD WITH OLIVES AND AVOCADO SLICES?

<b>A</b>	3 units
<b>B</b>	6 units
<b>C</b>	12 units
<b>D</b>	More than 6 units

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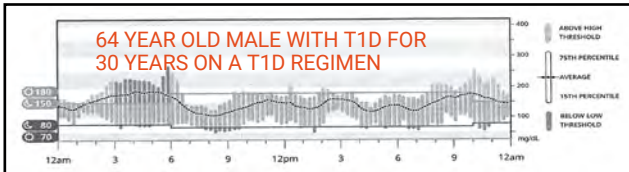
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What is/are the possible causes of this patient's glucose profiles overnight?

- |   |   |
|---|---|
| A | Needs more basal insulin                              |
| B | Needs to be more consistent in his dinner meals/times |
| C | He has gastroparesis                                  |
| D | All of the above                                      |

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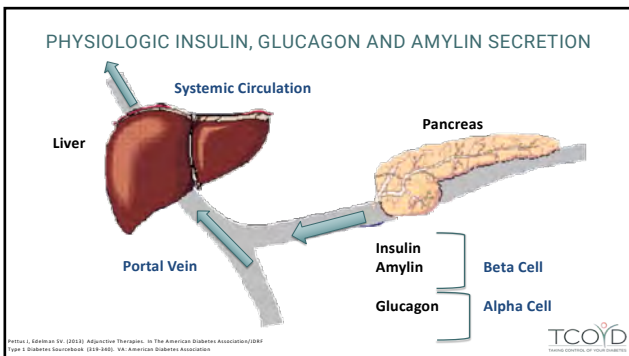
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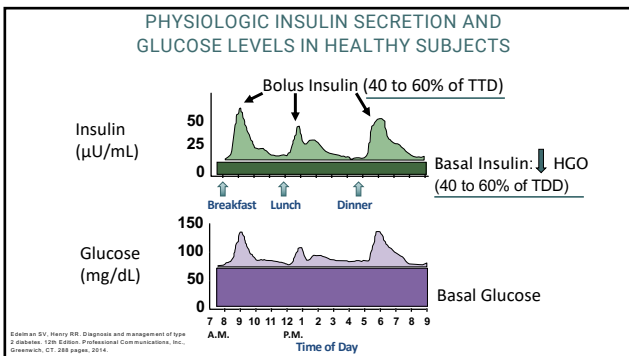
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## GENERIC AND TRADE NAMES: INSULIN <sup>S</sup>

	Generic Name	Trade Name
<b>Fast-Acting Insulin</b> 	Regular U-500 Regular Aspart Faster Acting Aspart Glulisine Lispro (U-100 and U-200) Follow on biologic lispro Inhaled Insulin	Humulin R, Novolin R Humulin R U-500 NovoLog Fiasp Apidra Humalog Admelog Afrezza
<b>Basal Insulin</b> 	Intermediate-Acting: NPH  Long-Acting: Detemir Glargine (U-100) Glargine (U-300)* Degludec (U-100/200)* Follow on biologic glargine (U-100)	Humulin N Novolin NPH  Levemir Lantus Toujeo* Tresiba* Basaglar

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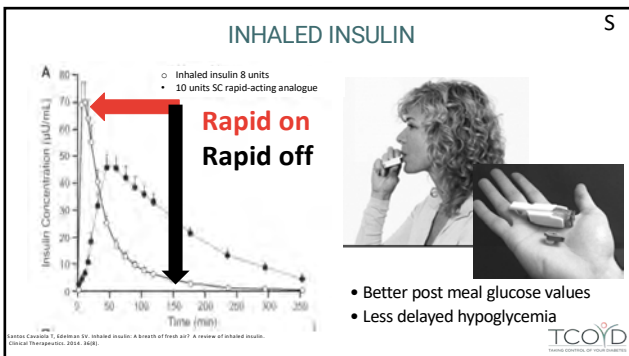
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## INHALED INSULIN <sup>S</sup>




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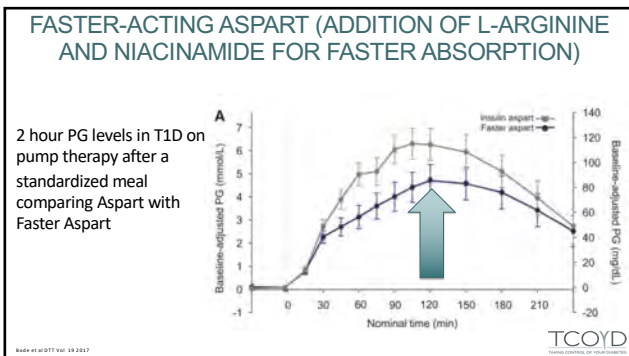
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## FASTER-ACTING ASPART (ADDITION OF L-ARGININE AND NIACINAMIDE FOR FASTER ABSORPTION)




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## SHORTCOMINGS OF BASAL INSULINS INCLUDE: <sup>J</sup>

- Hypoglycemia resulting in:
  - Insulin under-dosing
  - Insufficient glycemic control
- Weight gain
- Inconsistent insulin action...leading to inconsistent blood glucose levels
- Not enough flexibility with timing of injections
- Insufficient duration of action...therefore, requiring a minimum of 1 and, sometimes, 2 injections/day
- Large volume injections required for some patients

Expert Opin. Biol. Ther. (2014) 14(6):7909-88



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## TWO NEW BASAL INSULINS RECENTLY ADDED TO LIST OF OPTIONS

BOTH APPROVED BY THE FDA AND NOW AVAILABLE FOR PATIENTS

1. U-300 glargine a long-acting basal insulin
2. U-100 and U- 200 degludec a long-acting basal insulin

Toujeo prescribing information. Bridgewater, NJ: sanofi, US; 2015 <http://products.sanofi.us/toujeo/toujeo.pdf>  
Tresiba prescribing information 2015. <http://www.novo-pi.com/tresiba.pdf>



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## U-300 GLARGINE

- A more concentrated (300 units/ml) form of traditional glargine insulin (100 units/ml)
- Compared to U-100 glargine, U-300 glargine has less intra-subject variability, less hypoglycemia and less weight gain.
- Flat, stable and prolonged action up to 30 hours (**needs 5 days to equilibrate...tell your patients!**)
- In the clinical trials patients on U-300 glargine with type 1 and type 2 diabetes may require a dose 12 to 18% higher than previous U-100 glargine (still with less hypo and less weight gain).
- Pen holds 450 units
- New Pen holds 900 units and can give 150U at one time

Riddle MC et al. Diabetes Care. 2014;37:2755-2762; Yki-Järvinen H et al. Diabetes Care. 2014; Published ahead of print: doi: 10.2337/dc14-0990  
Boll GB et al. Poster presented at EASD 2014; P947; Bajaj H. Oral presentation at CDA 2014; #14; Horne P et al. Abstract presented at EASD 2014; 0148  
Bajaj H et al. Poster presented at CDA 2014; P112; Matsuoka H et al. Poster presented at EASD 2014; P975; Tomiyasu Y et al. Poster presented at EASD 2014; P976



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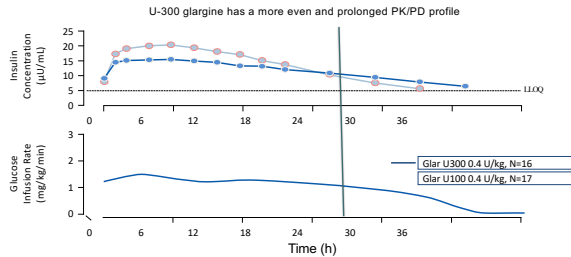
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### PK/PD PROFILE WITH GLAR U-300 VS GLAR U-100



May need 13 to 17% more than previous dose of glargine

Becker RH, et al. Diabetes Care. 2015;48:639-643.

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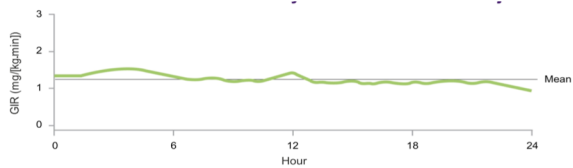
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### GLUCOSE INFUSION RATE IN SUBJECTS WITH TYPE 1 DIABETES INSULIN GLARGINE U-300



50 T1D subjects underwent two euglycemic clamp studies after six days of receiving insulin glargine U-300

Becker RHA, et al. Diabetes Obes Metab. 2015; 17(3): 261-267

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### U-100 AND U-200 INSULIN DEGLUDEC

- Available as either 100 units/ml (~detemir) or 200 units/ml
- Long duration of action up to 42 hours (needs 5 days to equilibrate...tell your patients!)
- Peakless
- Low intra-subject variability
- Less hypoglycemia and variability compared to U-100 glargine
- Disposable pens hold a maximum of 300 (U-100) and 600(units)
- 160 units can be given at one time.

Owens et al. Diabetes Metab Res Rev. 2014;30:104-119.  
Hight et al. Diabetes Care. 2014;37:1944-1950.  
Jonsson et al. Pharm Res. 2012;29:2104-2114.  
Pruessner  
U-100 and U-200 insulin degludec. Attachment:GLU0-1



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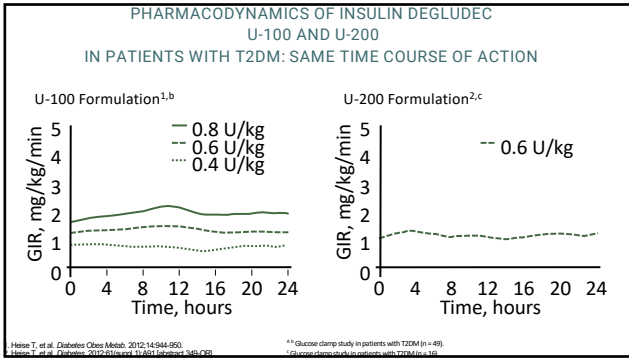
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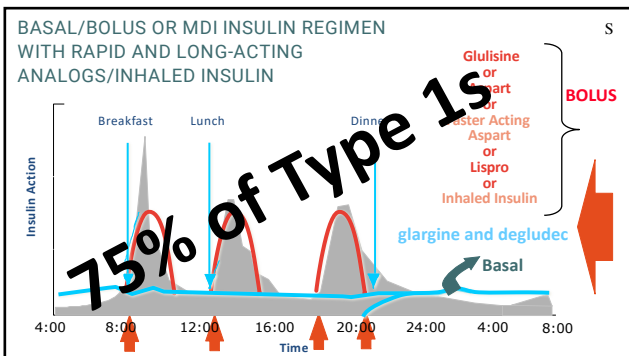
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SOFTWARE PROGRAMS AS PUMPS

- I:Carb ratio
- Correction factor
- Insulin log
- Cloud based

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## LET YOUR PATIENTS PICK THE PUMP

- o Animas Vibe G4 (Discontinued)
- o t:slim G6/X2
- o 630/670G/530G
- o OmniPod



Edelman SV. Taking control of your diabetes: a patient oriented, basic on diabetes. Fourth Edition. Professional Communications Inc., Greenwich, CT. 564 pages. 2013.




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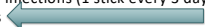
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## INSULIN PUMPS: ADVANTAGES

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- o **Improved glycemic control**
  - More precise, physiologic insulin delivery
  - Greater ability to handle dawn phenomenon, stress and other conditions that alter insulin requirements
  - "Smart features" help to estimate insulin doses and reduce errors, i.e. stacking insulin
- o **In some situations (but not all) freedom and flexibility in lifestyle**
  - Eliminate multiple daily injections (1 stick every 3 days) Very easy to respond to CGM results
  - Reduce restrictions on eating, exercise and sleeping patterns; could have the same benefits with MDI
  - Greater flexibility with sports, travel, work schedule and other activities (not with water sports)



Edelman SV. Taking Control Of Your Diabetes 5th edition. 2018 and Walsh JM, Roberts R. Pumping insulin 5th edition. 2012.




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## PUMP VS. MULTIPLE DAILY INJECTIONS?



It comes down to personal choice!

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## TESTING THE BASAL RATE IN TYPE 1

### Testing Overnight

1. Ask the patient have an early dinner, make sure the post prandial BS is between 140 and 180mg/dl (may need a correction dose) with a horizontal trend arrow
2. Fast until the next morning
3. If not on a CGM then he/she needs to test the BS every few hours

### Testing During The Day (different day than testing pm)

1. Ask the patient if he/she can skip breakfast and fast as long as possible.
2. If patient wants to eat a small breakfast then make sure the post breakfast BS is between 140-180mg/dl with a horizontal trend arrow

Edelman DV. Taking control of your diabetes: a patient oriented book on diabetes. 6th Edition. Elsevier Saunders/Elsevier Inc.; Copyright 2017. 497

**TCOYD**  
THE CENTER FOR TYPE 1 DIABETES CARE

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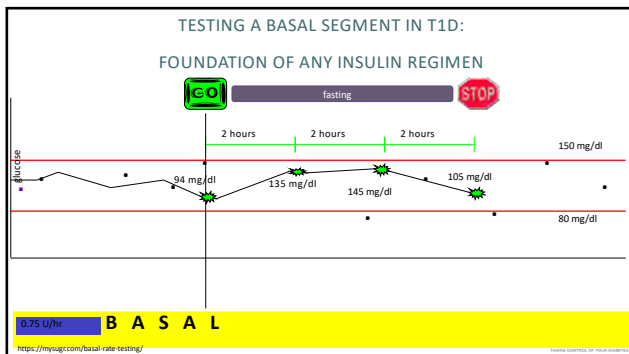
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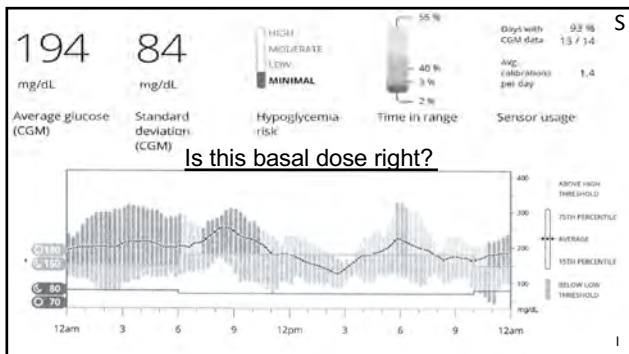
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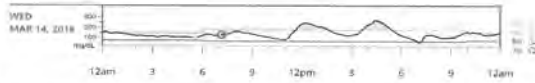
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### SAME PT. FASTING FROM 9PM UNTIL 7AM

3 Patient's best glucose day was March 14, 2018

Patient's glucose data was in the target range about 77% of the day.



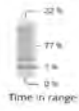
Statistics for this day

146

mg/dL  
Average glucose (CGM)

42

mg/dL  
Standard deviation (CGM)



Legend

- CALIBRATIONS
- HEALTH
- EXERCISE
- CARBS
- INSULIN

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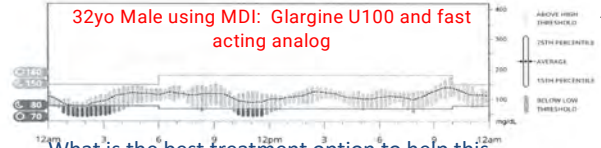
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32yo Male using MDI: Glargine U100 and fast acting analog



What is the best treatment option to help this patient with his overnight values?

- |   |  |
|---|--|
| A | Decrease the basal insulin                               |
| B | Switch the U-100 glargine for U-300 glargine or degludec |
| C | Have a larger bedtime snack                              |
| D | Do not exercise after 7pm                                |

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### ADJUNCTIVE THERAPIES FOR PEOPLE WITH TYPE 1 DIABETES

- Amylin Analog (Pramlintide)
- Incretins (GLP-1 RA) \*
- SGLT-2 Inhibitors\*
- DPP4 Inhibitors\*
- Metformin\*

\*Medications FDA approved only in type 2 diabetes at the current time




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### DPP-4 INHIBITORS IN T1D

- No statistically significant differences compared to placebo

### METFORMIN IN T1D

- No statistically significant differences compared to placebo in A1c, hypoglycemia and DKA
- Slight reduction in weight and insulin dose

Patel et al. Lancet Diab Met 2017; 15:687-699  
Yang et al. Endocrine Practice 2013




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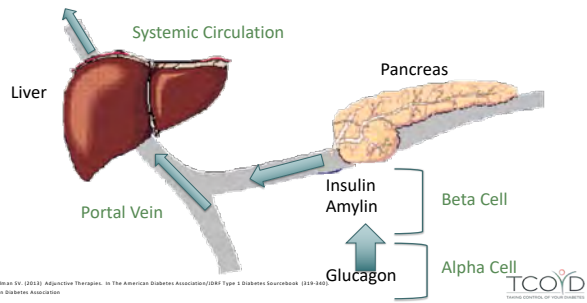
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### PHYSIOLOGIC INSULIN, GLUCAGON AND AMYLIN SECRETION




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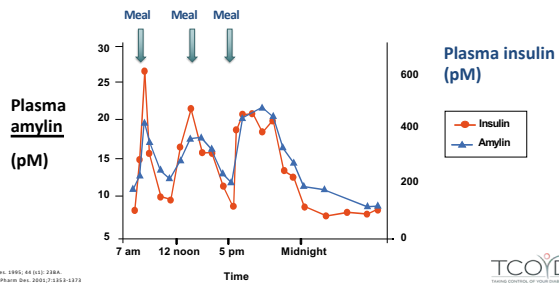
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### PHYSIOLOGIC INSULIN AND AMYLIN SECRETION AFTER MEALS




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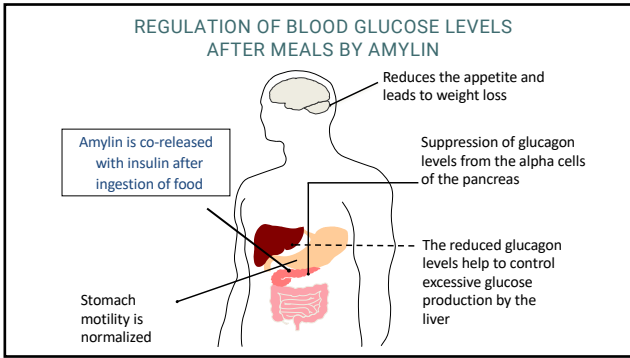
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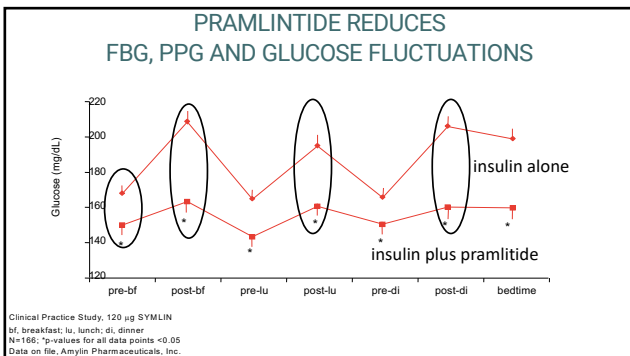
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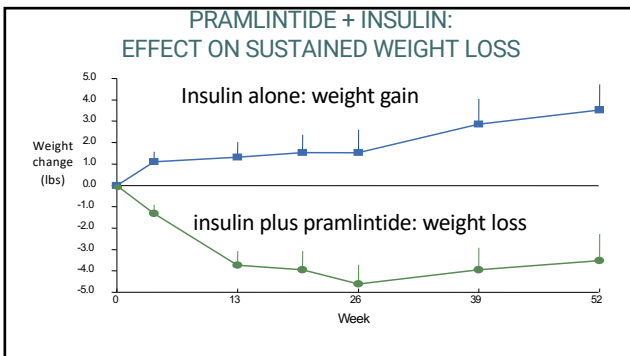
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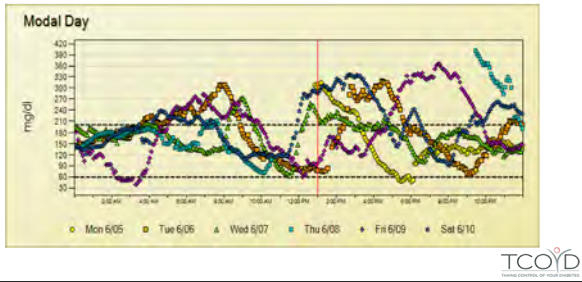
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49YO WOMAN WITH T1D X 33 YEARS, A1C 9%  
AVG GLUCOSE 176.9 / S.D. 66.3




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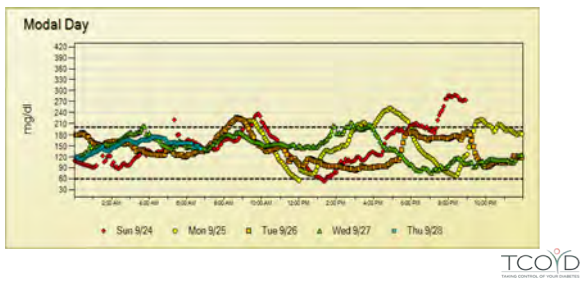
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AFTER 3 MONTHS ON PRAMLINTIDE, A1C 7.4%, LOST 125  
LBS. AVG GLUCOSE 122.4 / S.D. 30.4




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GLP-1 RECEPTOR AGONIST IN T1D

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- There were small very early studies with exenatide
- One large well controlled study looking at liraglutide
- Many of the clinical effects in type 1 are similar to what is seen with SGLT 1/2 inhibitors
- No agent is actively being studied for FDA approval in type 1 diabetes




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## RECAP OF KEY RESULTS OF LIRAGLUTIDE IN T1DM

	ADJUNCT ONE <sup>1</sup>	ADJUNCT TWO <sup>2</sup>
<b>HbA<sub>1c</sub> change</b> (placebo-adjusted)	Mean decrease up to 0.2%	Mean decrease up to 0.35%
<b>Insulin dose change</b> (placebo-adjusted)	Mean decrease up to 9%	Mean decrease up to 10%
<b>Body weight loss</b> (placebo-adjusted)	Mean decrease up to 5 kg	Mean decrease up to 5 kg
<b>Severe hypoglycaemia</b>	Numerically lower in Lira vs placebo	No apparent difference
<b>Symptomatic hypoglycaemia</b>	Lira 1.8 mg and Lira 1.2 mg higher vs placebo	Lira 1.2 mg higher vs placebo
<b>Hyperglycaemia with ketosis</b>	Lira 1.8 mg higher vs placebo	Lira 1.8 mg higher vs placebo

1. Holm G, et al. *Diabetes Care* 2014;37:1242-1248  
2. Madsen LR, et al. *Diabetes Care* 2014;37:1249-1255

Copyright © not approved for the management of Type 1 Diabetes




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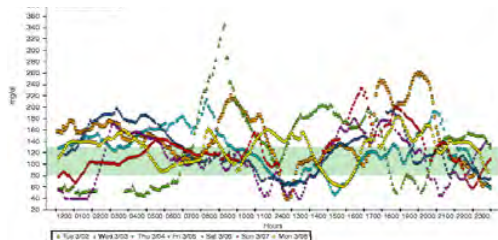
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## WEEKLY CGM RECORD FOR ONE PATIENT PRIOR TO LIRAGLUTIDE



Yarmanli B, et al. *Eur J Endocrinol* 2011;165:113-120




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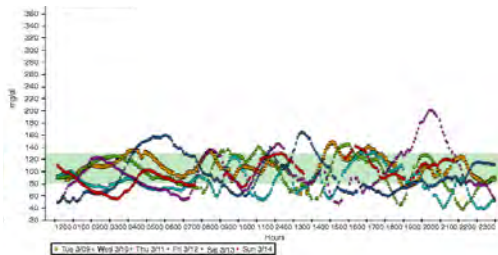
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## WEEKLY CGM RECORD FOR ONE PATIENT FOLLOWING LIRAGLUTIDE



Yarmanli B, et al. *Eur J Endocrinol* 2011;165:113-120




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## SGLT 1/2 INHIBITORS IN T1D

- There are 3 different drugs being studied in type 1 diabetes (empagliflozin, dapagliflozin and sotagliflozin)
- Sotagliflozin has filed with the FDA and is the furthest alone in development and will review the clinical trial data for Sotagliflozin in detail and summarize the other studies and also shown in the supplemental slide PDF
- If any are approved it would be the first oral agent for type 1 diabetes

TCOYD

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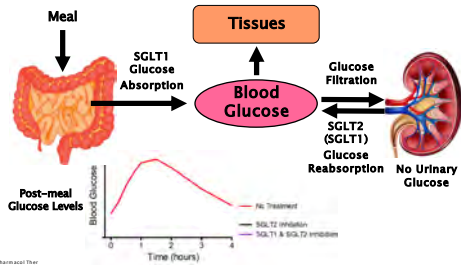
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### INTESTINAL SGLT1-MEDIATED GLUCOSE ABSORPTION RENAL SGLT2 (SGLT1) MEDIATED GLUCOSE REABSORPTION




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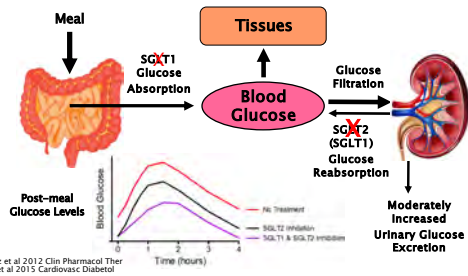
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### GLUCOSE ABSORPTION/REABSORPTION IN PATIENTS TREATED WITH A DUAL SGLT1 & SGLT2 INHIBITOR (SOTAGLIFLOZIN): INHIBITS SGLT1 LOCALLY IN THE GI TRACT AND SGLT2 SYSTEMICALLY IN THE KIDNEY




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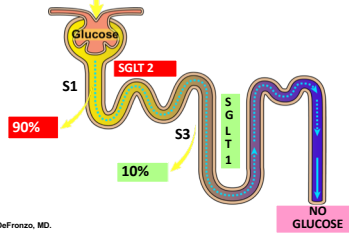
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## RENAL HANDLING OF GLUCOSE

(180 L/day) (1000 mg/L) = 180 g/day



Slide courtesy of Ralph A. DeFronzo, MD.

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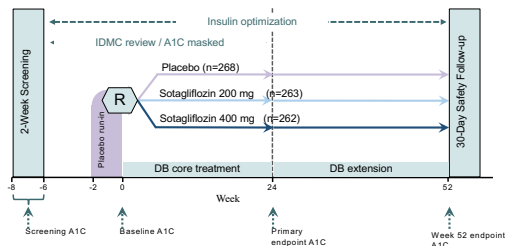
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## INTANDEM STUDY DESIGN

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Optimized insulin: Insulin adjustment to meet standard of care (SOC) glyemic targets starting 6-weeks prior to randomization and continued for entire study. An independent Insulin Dose-Monitoring Committee (IDMC) assessed SOC adherence and provided feedback to PI if deviations from SOC observed prior to Week 24.  
DB: Double-Blind, R: Randomized

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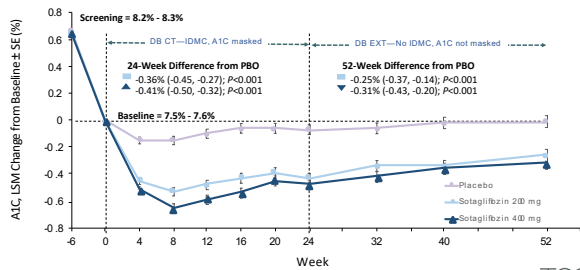
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## INTANDEM1: A1C



TCOYD  
THERAPEUTIC CONCEPTS OF OXYD

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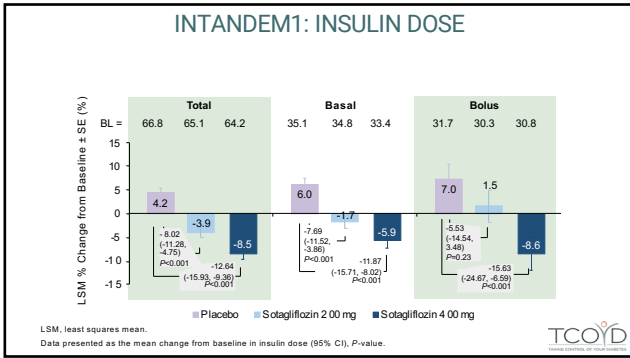
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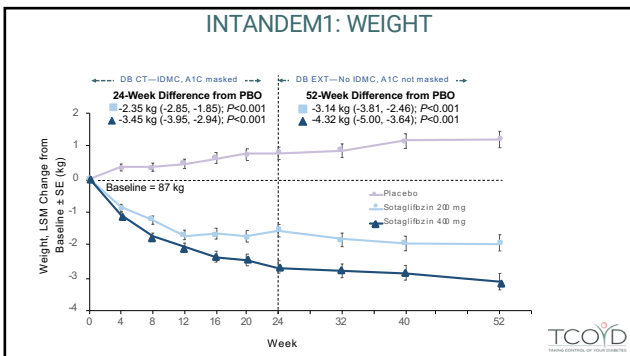
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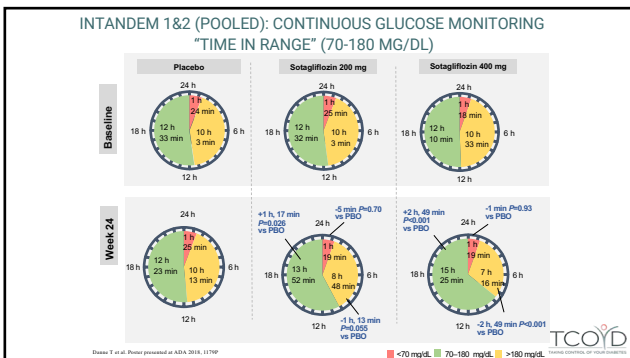
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**SUMMARIZE FINDINGS FROM ALL SGLT -1/2 INHIBITORS**  
 (DIFFICULT TO MAKE PRECISE EFFICACY COMPARISONS ACROSS TRIALS DUE TO DESIGN AND ANALYSIS DIFFERENCES)

S

Efficacy (placebo adjusted)	Highest dose*
A1C reduction	~0.4%
Time in Range (blinded CGM)	~3 hour increase
Time in Hypoglycemia (CGM)	No change or some reduction
Insulin dose	10-15% reduction
Weight	~2-3 kg reduction
Systolic blood pressure	~3-4 mm Hg reduction
Patient reported outcomes	Improved

Clinically relevant adverse events include genital mycotic infections (primarily in women 12 to 15%) and DKA (3 to 4%), sometimes euglycemic DKA

\* Lower doses retain much of the glycemic efficacy with lesser effect on weight and blood pressure




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**RISK MITIGATION OF DKA WITH SGLT INHIBITORS**

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- If unable to eat or drink, hold the SGLT inhibitor  
 - such as NPO, viral illness, surgery, colonoscopy, etc.
- If on a SGLT inhibitor, avoid the keto diets and drink adequate fluids
- Do not prescribe in poorly adherent patients and use with caution if A1c above 9% or frequent episodes of DKA
- If nauseous or sick in any way, hold the SGLT inhibitor and troubleshoot their insulin delivery and check blood or urine ketones. If ketones are positive, take insulin per protocol along with carbs and fluids (your glucose may be normal!)
- If unable to drink and eat, go to the ER for fluids and further management.




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**APPROACH TO REDUCE DKA RISK WITH SGLTIS: STICH PROTOCOL**

Wallet Card - front



Please carry this card if you are using a SGLT inhibitor with insulin to treat diabetes

Garg S, et al. *Diab Tech Ther* 2018; epub.




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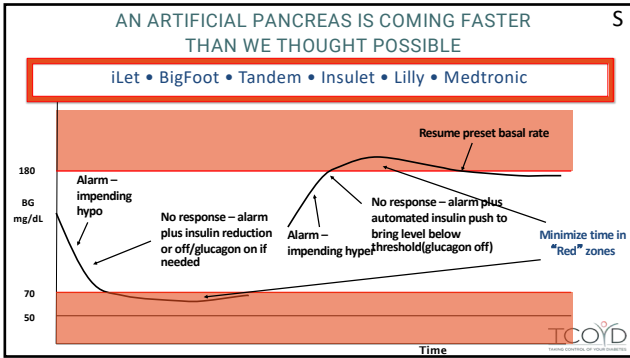
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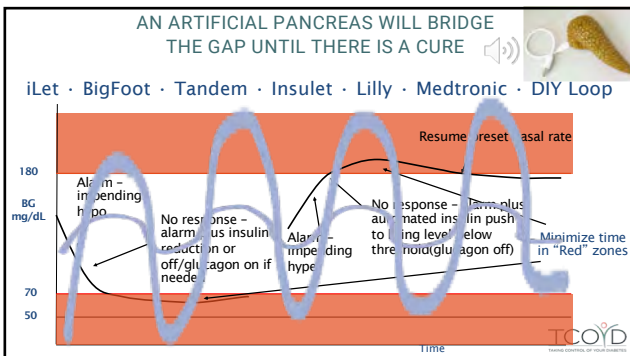
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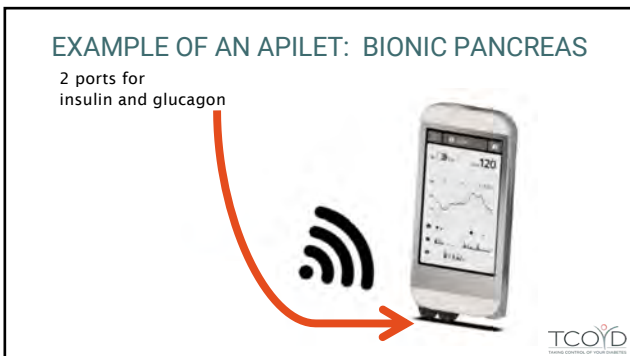
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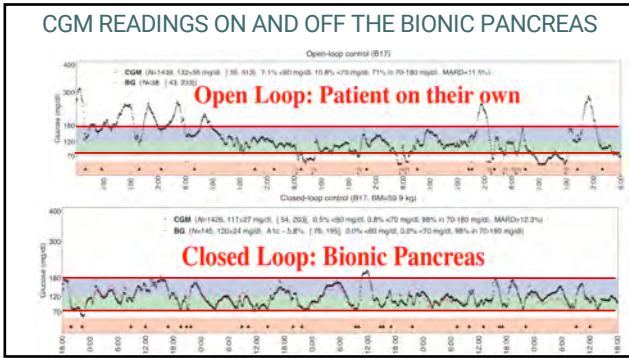
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## CGM READINGS ON AND OFF THE BIONIC PANCREAS




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## SUMMARY

- The important unmet needs in T1D include improved glycemic variability (GV), increased time in range (TIR)
- Reaching A1c goal without hypoglycemia
- Controlling blood pressure and weight gain
- Addressing the emotional burden of living
- CGM and the newer ultra rapid and basal insulins can help improve TIR
- Adjunctive therapies can address some of the unmet needs




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# SUPPLEMENTAL DATA SLIDES

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## SGLT 1/2 INHIBITORS IN T1D

- There are 3 different drugs being studied in type 1 diabetes (empagliflozin, dapagliflozin and sotagliflozin)
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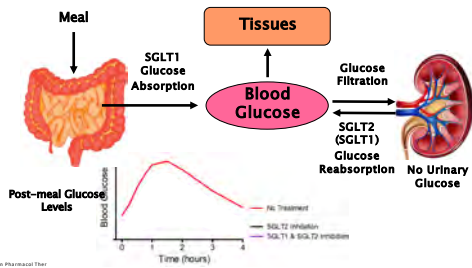
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### INTESTINAL SGLT1-MEDIATED GLUCOSE ABSORPTION RENAL SGLT2 (SGLT1) MEDIATED GLUCOSE REABSORPTION



Zemke et al. 2012. Clin Pharmacol Ther.

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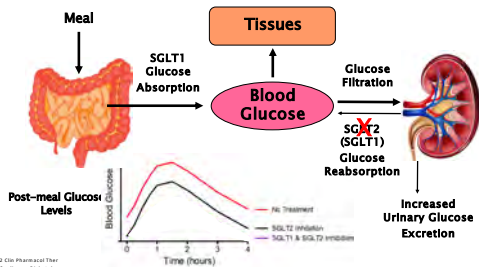
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### GLUCOSE ABSORPTION AND REABSORPTION IN PATIENTS WITH DIABETES TREATED WITH A SELECTIVE SGLT2 INHIBITOR: CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN, ERTUGLIFLOZIN



Zemke et al. 2012. Clin Pharmacol Ther.

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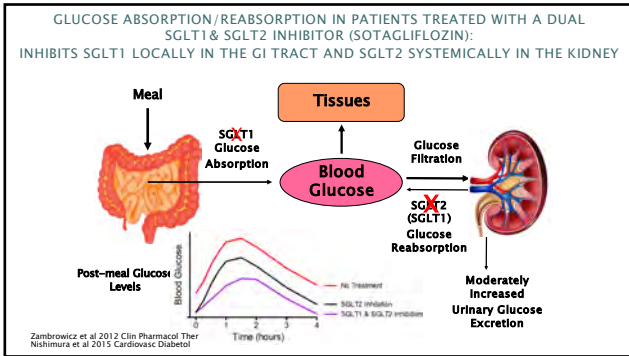
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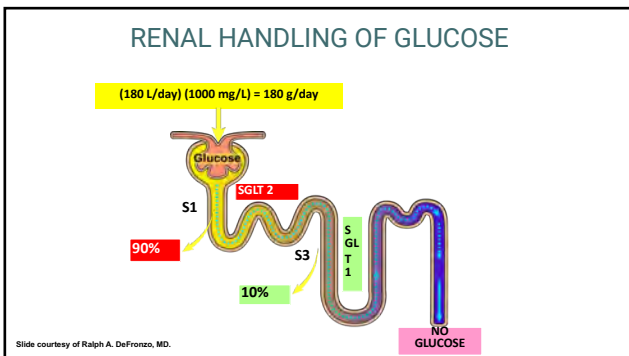
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THREE SGLT DEVELOPMENT PROGRAMS HAVE COMPLETED PHASE III: DEPICT, INTANDEM, EASE

Study	DEPICT <sup>1,2</sup>	inTandem <sup>3-5</sup>	EASE <sup>6</sup>
Drug, dose	Dapagliflozin • 5 mg • 10 mg • Placebo	Sotagliflozin • 200 mg • 400 mg • Placebo	Empagliflozin • 2.5 mg • 10 mg • 25 mg • Placebo

1. Dandona P et al. Lancet Diabetes Endocrinol. 2017;5:664-676.  
2. Wadwa M, et al. Diabetes Care. 2016;39:1388-1394.  
3. Gang SA, et al. N Engl J Med. 2017;377:2337-2346.  
4. Gang SA, et al. Diabetes Care. 2016;39:1379-1385.  
5. Dandona P, et al. Diabetes Care. 2015;38:1585-1590.  
6. Zambrowicz K, et al. Diabetes Care. 2016;39:6. doi: 10.2337/1618-1749. [Epub ahead of print].

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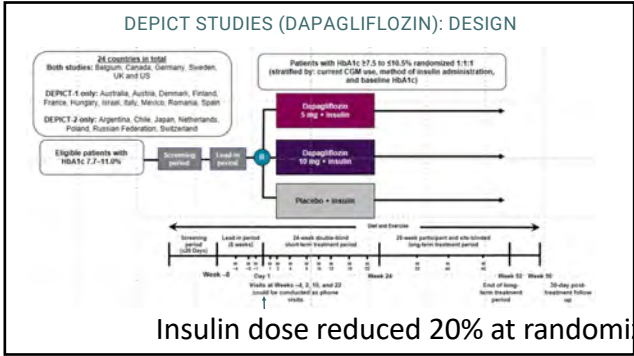
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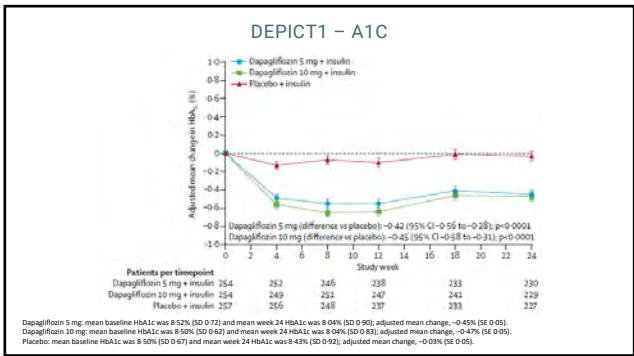
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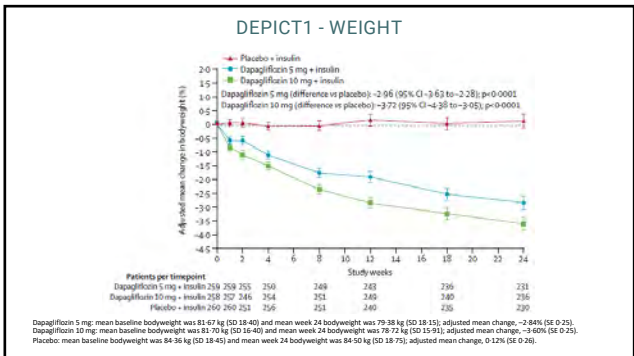
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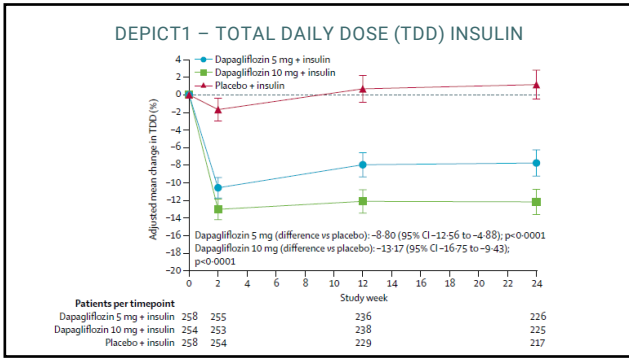
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- ### DEPICT1 – CONTINUOUS GLUCOSE MONITORING “TIME IN RANGE” (70-180 MG/DL)
- Dapagliflozin 5 mg: Increased from 43.2% (SD 12.4) at baseline to 52.3% (SD 14.8) at week 24.
    - An absolute increase of 9.1% (SD 13.5): 2.2 hours per day
  - Dapagliflozin 10 mg: Increased from 44.6% (SD 12.4) to 54.6% (SD 13.1) at week 24.
    - An absolute increase of 10.1% (SD14.2): 2.4 hours per day
  - Placebo group: essentially unchanged
    - An absolute decrease of 0.6%: -0.14 hours a day

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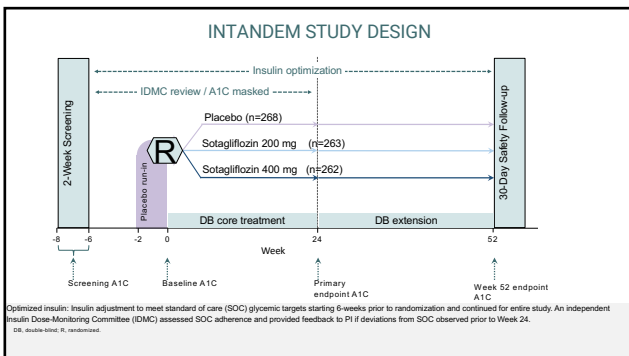
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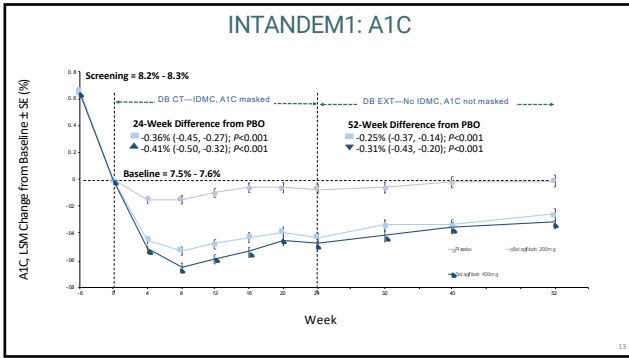
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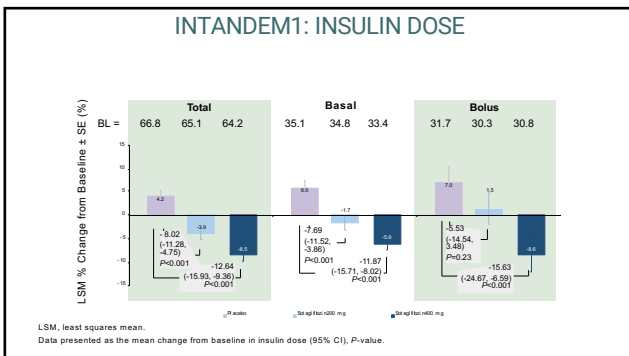
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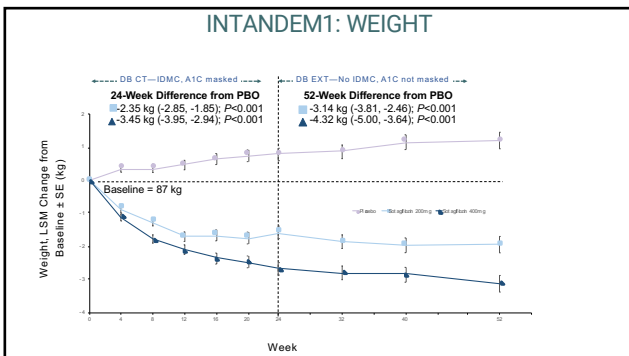
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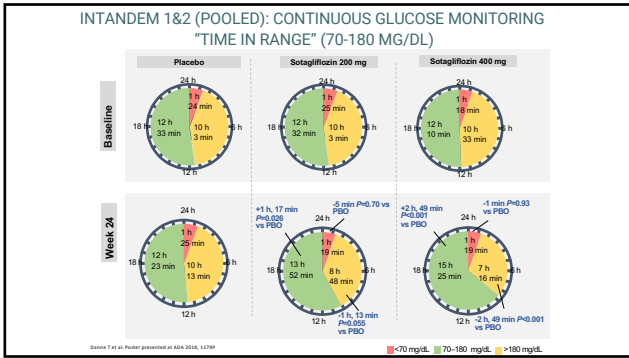
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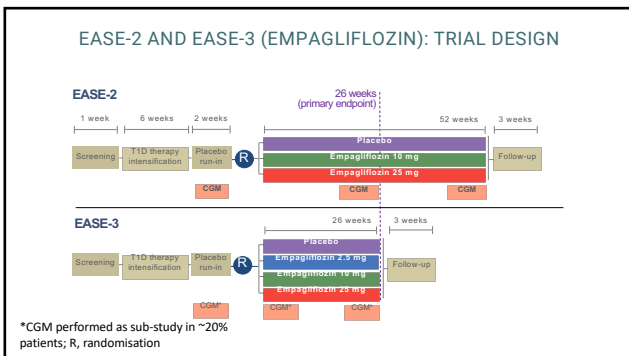
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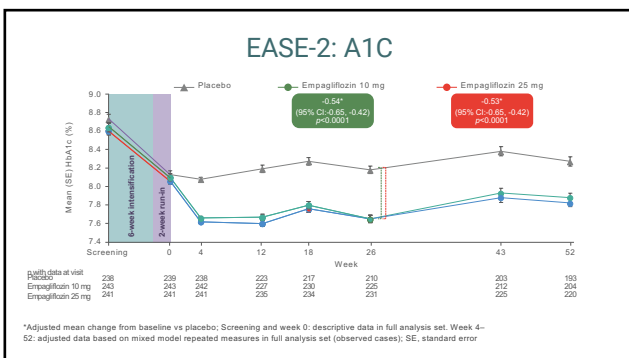
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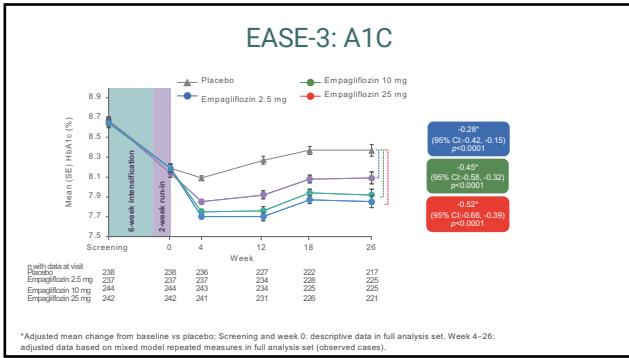
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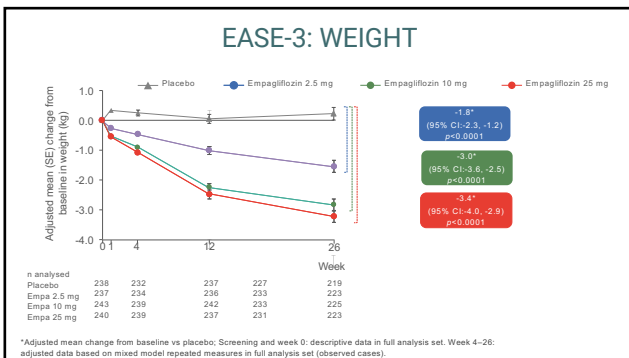
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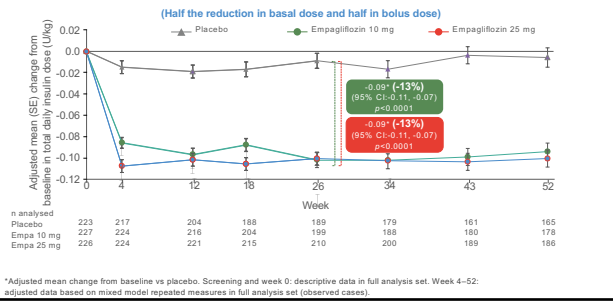
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### EASE-2: TOTAL DAILY INSULIN DOSE REDUCTION OVER TIME




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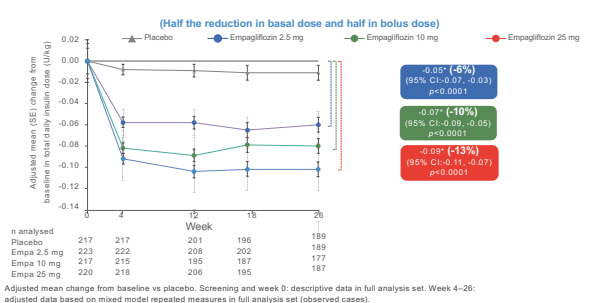
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### EASE-3: TOTAL DAILY INSULIN DOSE REDUCTION OVER TIME




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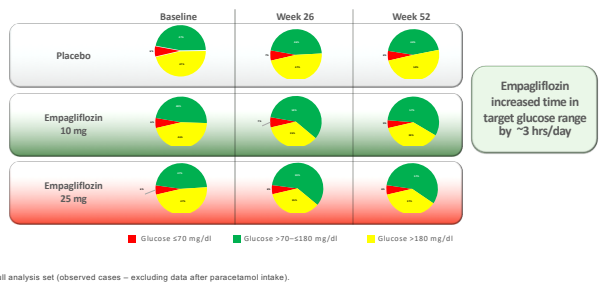
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### EASE-2: CGM RESULTS




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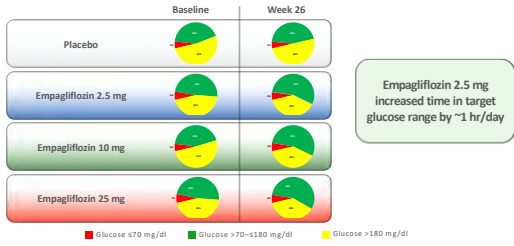
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### EASE-3: SUBANALYSIS CGM RESULTS



Full analysis set (observed cases – excluding data after paracetamol intake)

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### SUMMARIZE FINDINGS FROM ALL SGLT -1/2 INHIBITORS (DIFFICULT TO MAKE PRECISE EFFICACY COMPARISONS ACROSS TRIALS DUE TO DESIGN AND ANALYSIS DIFFERENCES)

Efficacy (placebo adjusted)	Highest dose*
A1C reduction	~0.4%
Time in Range (blinded CGM)	~3 hour increase
Time in Hypoglycemia (CGM)	No change or some reduction
Insulin dose	10-15% reduction
Weight	~2-3 kg reduction
Systolic blood pressure	~3-4 mm Hg reduction
Patient reported outcomes	Improved

Clinically relevant adverse events include genital mycotic infections (primarily in women 12 to 15%) and DKA (3 to 4%), sometimes euglycemic DKA

\* Lower doses retain much of the glycemic efficacy with lesser effect on weight and blood pressure

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### RISK MITIGATION OF DKA WITH SGLT INHIBITORS

- If unable to eat or drink, hold the SGLT inhibitor  
- such as NPO, viral illness, surgery, colonoscopy, etc
- If on a SGLT inhibitor, avoid the keto diets and drink adequate fluids
- Do not prescribe in poorly adherent patients and use with caution if A1c above 9% or frequent episodes of DKA
- If nauseous or sick in any way, hold the SGLT inhibitor and troubleshoot their insulin delivery and check blood or urine ketones. If ketones are positive, take insulin per protocol along with carbs and fluids.
- If unable to drink and eat, go to the ER for fluids and further management.

WWW.TCDDP.ORG

Taking Control Of Your Diabetes, 01/2019 is not for profit educational organization.

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## APPROACH TO REDUCE DKA RISK WITH SGLTIS: STICH PROTOCOL

Wallet Card - front

<b>S</b>	
<b>T</b>	Stop SGLT inhibitor
<b>I</b>	inject bolus Insulin
<b>C</b>	consume 30 g Carbohydrates
<b>H</b>	Hydrate (drink water)

Please carry this card if you are using a SGLT inhibitor with insulin to treat diabetes.

Garg S, et al. *Diab Tech Ther* 2018; epub.

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