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


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## DISCLOSURES

### STEVEN V. EDELMAN, MD

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

### TRICIA SANTOS CAVAIOLA, MD

- Consultant: Dexcom, Eversense
- Speaker's Bureau: 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

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- Unpredictable glycemic variability (GV), decreased 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

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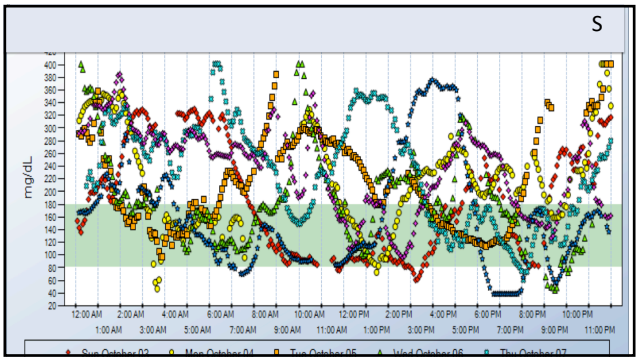


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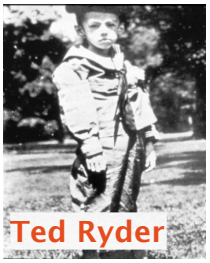
BANTING AND BEST
UNIVERSITY OF TORONTO 1921

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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

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

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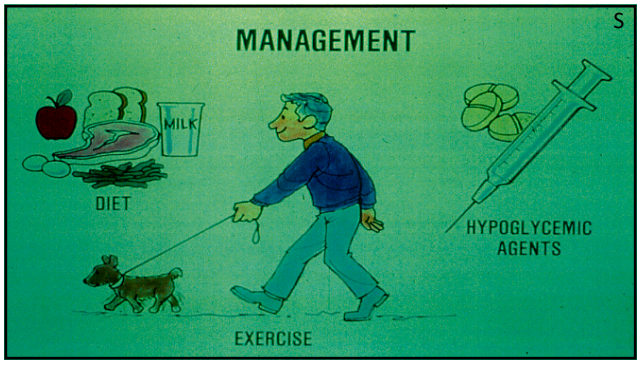
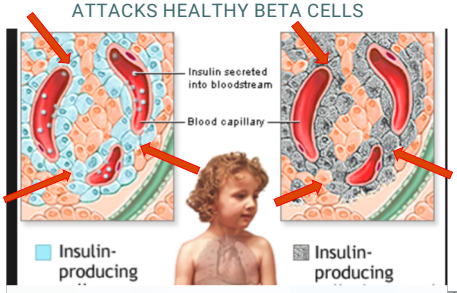


## PREVALENCE OF T1D INCREASING IN US

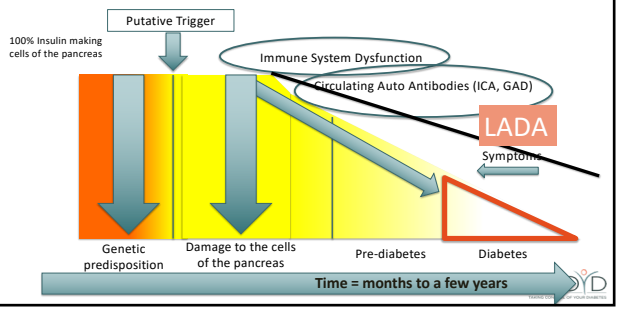
- 1.3 million people in U.S. currently have T1D[1]
  - 1 million adults ≥ 20 years
- 21% increase in prevalence of T1D in people < 20 years between 2001-2009[2]
- 40,000 people diagnosed each year in U.S.[2]
- 5 million people in U.S. expected to have T1D by 2050[2]

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




Natural Progression is months to a few years

## NATURAL HISTORY AND CAUSE OF TYPE 1 DIABETES

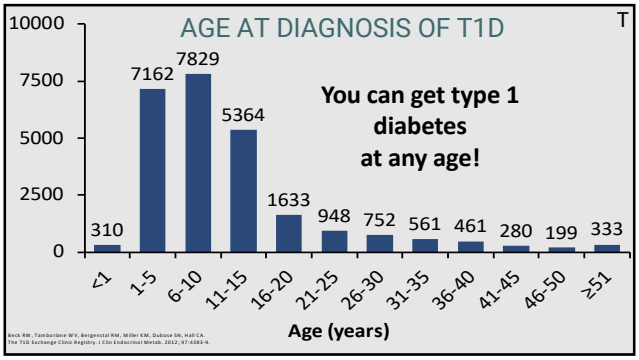


## LATENT AUTOIMMUNE DIABETES IN ADULTS (LADA)

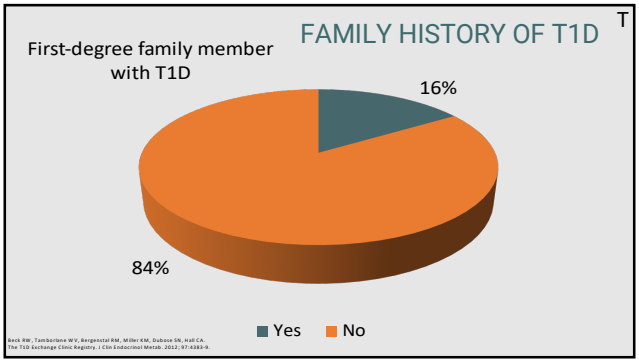
- The most missed diagnosis in diabetes
- Type 1 diabetes can occur at any age
- Slower beta-cell destruction (may respond briefly to oral agents)
- Typically does not have features of the Metabolic Syndrome
- Blood test positive for type 1 diabetes (GAD auto antibodies)

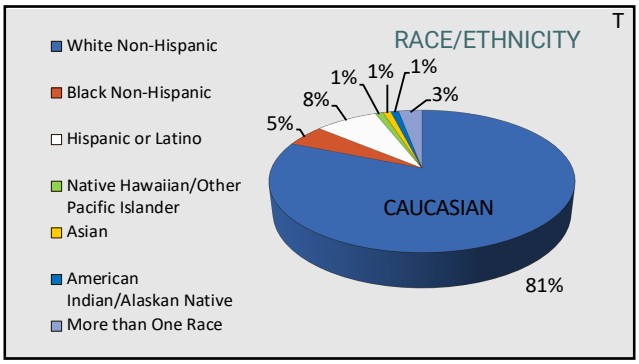
Gary Hall Jr.
Olympic Gold Medalist
World Record Holder

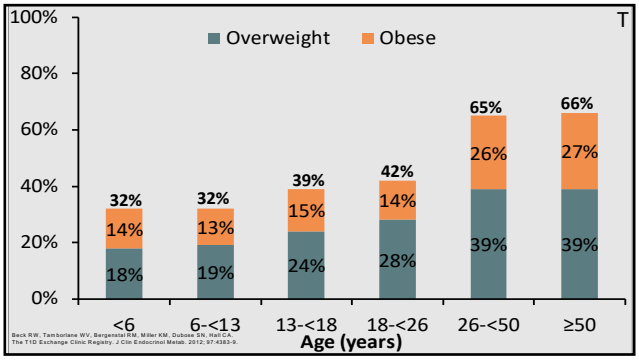
## AGE AT DIAGNOSIS OF T1D




## FAMILY HISTORY OF T1D



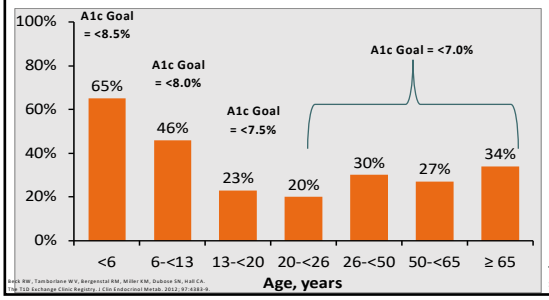



## CONSEQUENCES OF WEIGHT GAIN

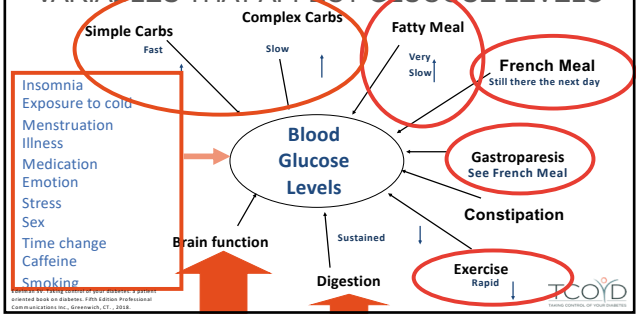
- Excess weight gain associated with risk factors for cardiovascular disease, including increased
  - Lipid levels
  - Blood pressure levels
  - Waist circumference
  - Metabolic syndrome

## ONLY ~30% OF TYPE 1S REACH ADA GOAL OF AN A1C LESS THAN 7%




Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012;97:4383-9.

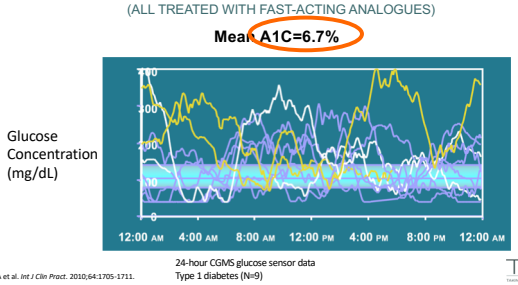
## VARIABLES THAT AFFECT GLUCOSE LEVELS




Pickup LH. Taking control of your diabetes: a patient-oriented book on diabetes. Fifth Edition ProVisional Communications Inc., Greenwich, CT., 2018.

## THE A1C REPRESENTS ONLY THE AVERAGE BLOOD GLUCOSE OVER TIME

(ALL TREATED WITH FAST-ACTING ANALOGUES)




Ceriello A et al. *Int J Clin Pract.* 2010;64:1705-1711.

24-hour CGMS glucose sensor data
Type 1 diabetes (N=9)

## DESPITE FOLLOWING ALL OF THE RULES

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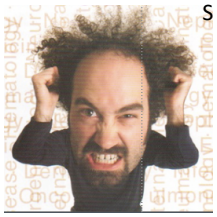

1. Unexpected highs
2. Unexpected lows
3. Carb:Insulin ratio not working consistently
4. Correction Factor not working consistently
5. Not responding to insulin and exercise consistently

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

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

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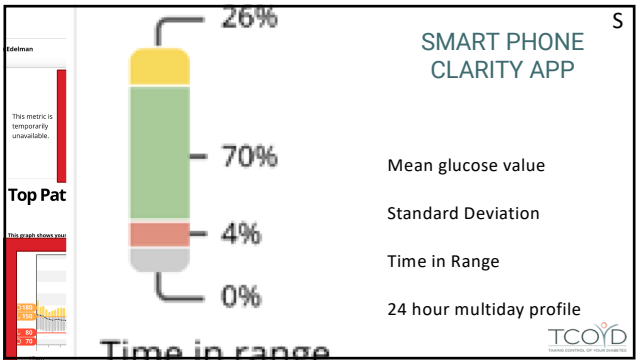
1. 1st priority is getting a CGM and educate your patients to respond to the trend arrows.
2. Bolus calculations are more than just the carbohydrates and static glucose readings
3. In addition to getting the A1c below 7%, try to reduce the daily glucose fluctuations in your patients (hyper- and hypoglycemia)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

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




## SMART PHONE CLARITY APP

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Mean glucose value

Standard Deviation

Time in Range

24 hour multiday profile

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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 vibe alerts

Gentle, daily adhesive patch


**Mobile App**

No extra device to carry

iOS and Android platform

Alarm settings & reports

## EVERSENSE IMPLANTABLE CGM

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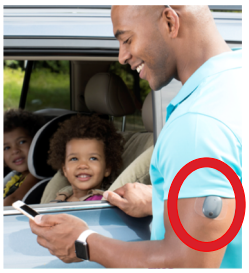


## GUARDIAN CONNECT

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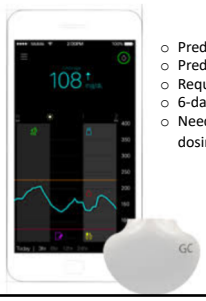


- Predictive high alerts
- Predictive low alerts
- Requires calibration
- 6-day wear
- Need to confirm with fingerstick when dosing

https://www.medtronic-diabetes.co.uk/minimed-system/minimed-640g-system; accessed April 2017

## FREESTYLE LIBRE FLASH IS OR INTERMITTENT SENSING

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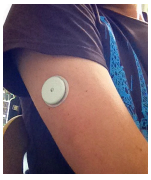
- 2 hour warm-up time
- Lasts 2 weeks
- Swipe to get a number
- Trend arrows

- No calibration
- No alerts or alarms
- No sharing features



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

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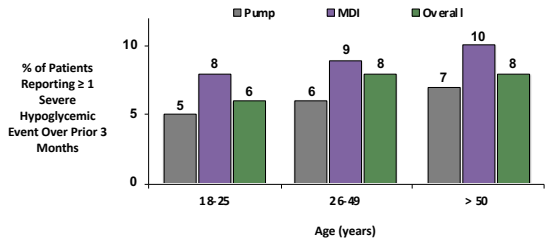


Miller KM, et al. *Diabetes Care*. 2015

## Severe Hypoglycemia and A1C: DCCT[15] (1993), JDRF[2] (2008), and STAR 3[16] (2010) Studies

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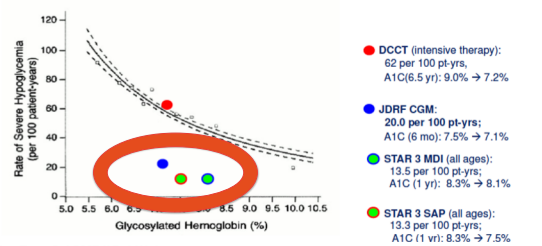


- **DCCT** (intensive therapy): 62 per 100 pt-yrs, A1C(6.5 yr): 9.0% → 7.2%
- **JDRF CGM**: 20.0 per 100 pt-yrs; A1C (6 mo): 7.5% → 7.1%
- **STAR 3 MDI** (all ages): 13.5 per 100 pt-yrs; A1C (1 yr): 8.3% → 8.1%
- **STAR 3 SAP** (all ages): 13.3 per 100 pt-yrs; A1C (1 yr): 8.3% → 7.5%

15. Adapted from Figure 5B of: DCCT. *N Engl J Med*. 1993;329:977-986.
2. JDRF data from: JDRF CGM Study Group. *N Engl J Med*. 2008;359:1465-1476.
16. Bergenstal RM, Tamborlane WV, Ahmann A, et al. [published online ahead of print June 29, 2010]. *N Engl J Med*. doi: 10.1056/NEJMoa1002853.

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

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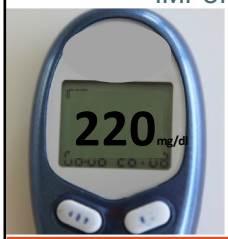


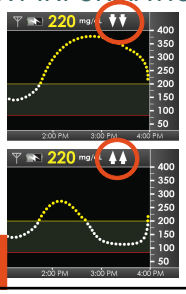


No insulin
Watch and maybe get some carbs

Take a larger than usual dose

Pump and meter software suggests the same either way

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

| | |
|---|---|
| → | **Constant:** Your glucose is steady (not increasing/decreasing more than 1 mg/dL each minute) |
| ↗ | **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 |
| ↘ | **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 |
| no arrow | **No Rate of Change Information:** The Receiver cannot always calculate how fast your glucose is rising or falling |

Heinemann K, Frias JP, Edelman SV, I
undergoing continuous subcutaneous insulin infusion therapy. *Postgraduate Medicine*. 122(1), 2013.

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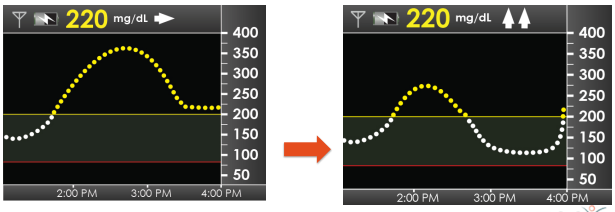
## MEAN CHANGE IN INSULIN DOSE BASEDON 2 ARROWS UP: SURVEY OF 300 CGM USERS

**3.0 units** → **6.8 units**




J. Pettus, D.A. Price, K.J. Hill, S. Edelman (2014), Diabetes Technology & Therapeutics. February 2014, 16(S1): A-76 page 198

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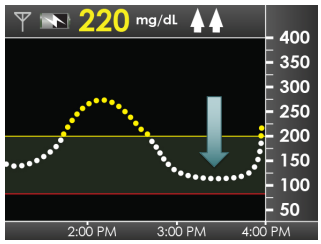
## HOW CGM AND TRENDING INFORMATION CAN AFFECT DOSING DECISIONS

| | | |
|---|---|---|
| → | **Constant:** Your glucose is steady (not increasing/decreasing more than 1 mg/dL each minute) **3.0 units** | 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 **6.8 units** | 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 **1.5 units** | 48% Mean Decrease |
| no arrow | **No Rate of Change Information:** The Receiver cannot always | |

## CASE: 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)



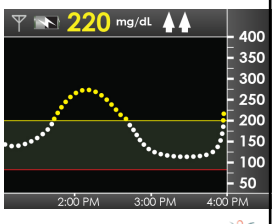

## CASE: JEREMY (CONTINUED)

- 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

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

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



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

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| | Adjusted Glucose Value for Dosing |
|---|---|
| → | No Adjustment. **Dose for current glucose value.** |
| ↗ | Adjust UP -- **current value plus 25-50 mg/dl.** Dose for adjusted value. |
| ↑ | Adjust UP -- **current value plus 50-75 mg/dl.** Dose for adjusted value. |
| ↑↑ | Adjust UP -- **current value plus 75-100 mg/dl.** Dose for adjusted value. |
| ↘ | Adjust DOWN -- **current value minus 25-50 mg/dl.** Dose for adjusted value. |
| ↓ | Adjust DOWN -- **current value minus 50-75 mg/dl.** Dose for adjusted value. |
| ↓↓ | Adjust DOWN -- **current value minus 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

## BLOOD GLUCOSE AFTER A MEAL WHEN BOLUS GIVEN 20 MINUTES BEFORE, AT START, OR 20 MIN AFTER THE MEAL

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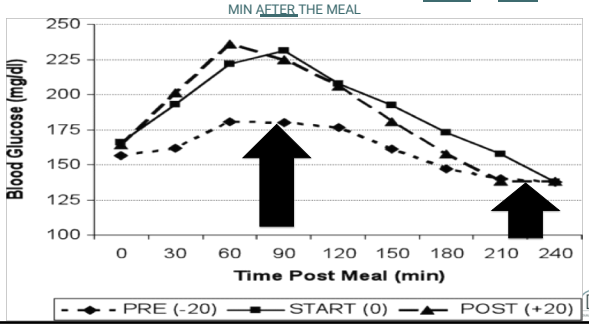


## BOTH DIETARY FAT AND PROTEIN INCREASE POST MEAL GLUCOSE CONCENTRATIONS

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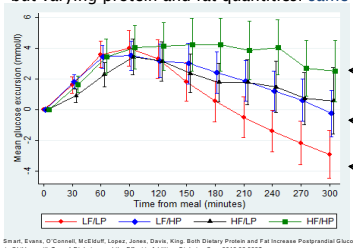
Four test breakfasts with identical carbohydrate content, but varying protein and fat quantities: same insulin dose




High fat/high protein

High fat/low protein
Low fat/high protein

Low fat/low protein

Smart, Evans, O'Connell, McElduff, Lopez, Jones, Davis, King. Both Dietary Protein and Fat Increase Postprandial Glucose Excursions in Children with Type 1 Diabetes, and the Effect is Additive. Diabetes Care 2013;36:3897

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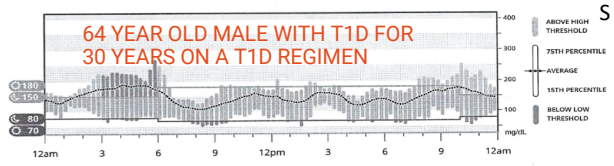
## 64 YEAR OLD MALE WITH T1D FOR 30 YEARS ON A T1D REGIMEN




What is/are the possible causes of this patients 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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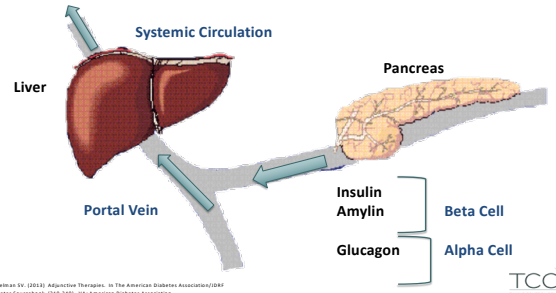
## PHYSIOLOGIC INSULIN, GLUCAGON AND AMYLIN SECRETION




Pettus J, Edelman SV. (2013) Adjunctive Therapies. In The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook (319-360). VA: American Diabetes Association

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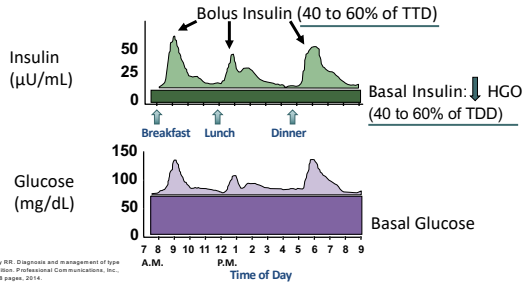
## PHYSIOLOGIC INSULIN SECRETION AND GLUCOSE LEVELS IN HEALTHY SUBJECTS

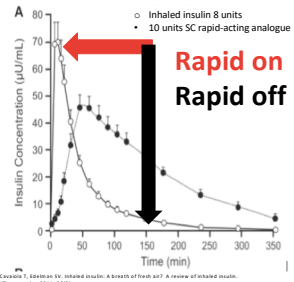



Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

## GENERIC AND TRADE NAMES: INSULIN

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

## INHALED INSULIN

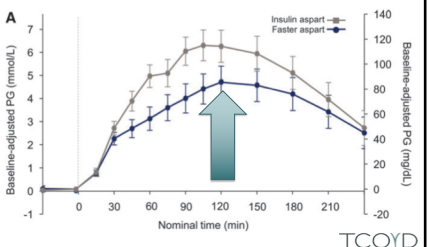



- Better post meal glucose values
- Less delayed hypoglycemia

Santos Cavaiola T, Edelman SV. Inhaled insulin: A breath of fresh air? A review of inhaled insulin. Clinical Therapeutics. 2014. 36(8).

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

2 hour PG levels in T1D on pump therapy after a standardized meal comparing Aspart with Faster Aspart




Bode et al DTT Vol 19 2017

## TWO NEW BASAL INSULINS RECENTLY ADDED TO OUR 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

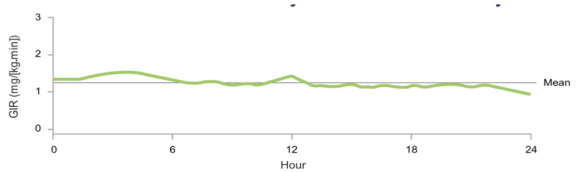
Toujeo prescribing information. Bridgewater, NJ: sanofi, US; 2015 http://products.sanofi.us/toujeo/toujeo.pdf
Tresiba prescribing information 2015. http://www.novo-pi.com/tresiba.pdf

## BENEFITS OF U-300 GLARGINE AND DEGLUDEC IN TYPE 1 DIABETES

- Less intra-subject variability
- Less hypoglycemia
- Less weight gain
- Flat, stable and prolonged action greater than 24 hours
- Tell patients it takes 4 to 5 days to reach equilibration and they may need correction doses
- 1 to 1 conversion from prior basal dose (patients switching from U-100 to U- 300 glargine may need ~15% more)
- Both insulins come in easy to use pens

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
Bolli GB *et al.* Poster presented at EASD 2014: P967; Bajaj H. Oral presentation at CDA 2014: #14; Home P *et al.* Abstract presented at EASD 2014: 0148
Bajaj H *et al.* Poster presented at CDA 2014: P112; Matsuhisa M *et al.* Poster presented at EASD2014: P975; Terauchi Y *et al.* Poster presented EASD 2014: P976

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

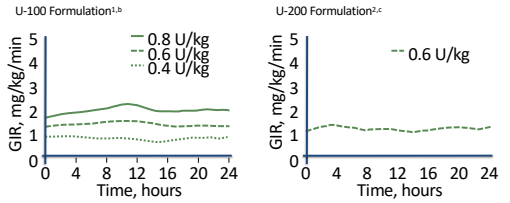



50 T1D subjects underwent two euglycemic clamp studies after six days of receiving insulin glargine U-300

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

## PHARMACODYNAMICS OF INSULIN DEGLUDEC[A] U-100 AND U-200 IN PATIENTS WITH T2DM: SAME TIME COURSE OF ACTION

T

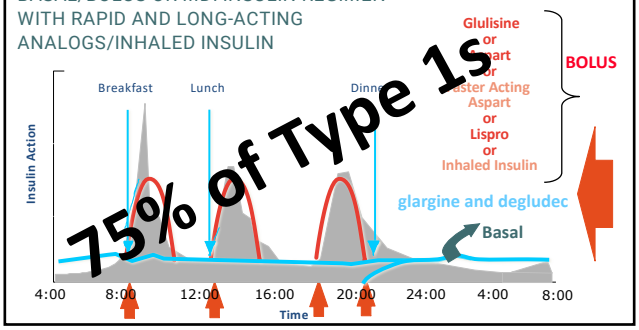



[A,B] Glucose clamp study in patients with T2DM (n = 69).
[C] Glucose clamp study in patients with T2DM (n = 16).

1. Heise T, et al. *Diabetes Obes Metab.* 2012;14:944-950.
2. Heise T, et al. *Diabetes.* 2012;61(suppl 1):A91 [abstract 349-OR].

## BASAL/BOLUS OR MDI INSULIN REGIMEN WITH RAPID AND LONG-ACTING ANALOGS/INHALED INSULIN

S




75% of Type 1s

## SOFTWARE PROGRAMS AS PUMPS

S


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

## LET YOUR PATIENTS PICK THE PUMP

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

Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fourth Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2013.

TCOYD

## INSULIN PUMPS: ADVANTAGES

- **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
- **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, Taking Control Of Your Diabetes 5th edition. 2018 and Walsh JA, Roberts R. Pumping Insulin 5th edition. 2011.

TCOYD

## PUMP VS. MULTIPLE DAILY INJECTIONS?


It comes down to personal choice!

## TESTING THE BASAL RATE IN TYPE 1

S

**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

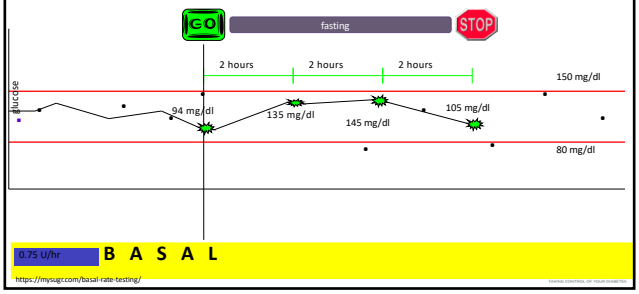
Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc. Greenwich, CT. 544 pages. 2017.

TCOYD

## TESTING A BASAL SEGMENT IN T1D:

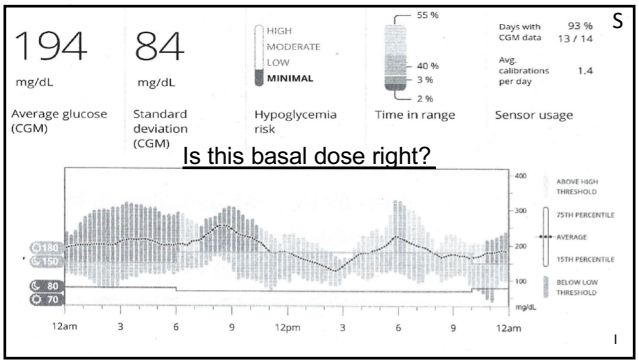
## FOUNDATION OF ANY INSULIN REGIMEN

S




https://mysugr.com/basal-rate-testing/

S



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

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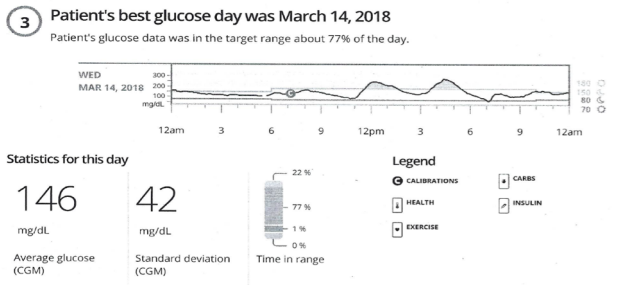
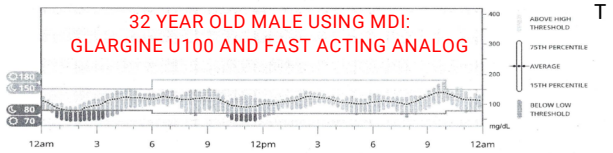



## 32 YEAR OLD MALE USING MDI: GLARGINE U100 AND FAST ACTING ANALOG

T




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 |

## ADJUNCTIVE THERAPIES FOR PEOPLE WITH TYPE 1 DIABETES

T

- 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

T

## 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

Petrie et al. Lancet DE 2017; 5:597-609
Garg et al. Endocrine Practice, 2013

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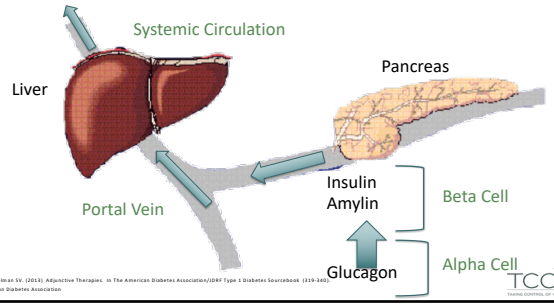
## PHYSIOLOGIC INSULIN, GLUCAGON AND AMYLIN SECRETION




Pettus J, Edelman SV. (2013). Adjunctive Therapies. In The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook (319-340). VA: American Diabetes Association

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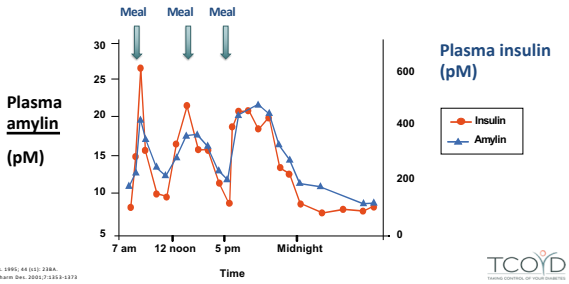
## PHYSIOLOGIC INSULIN AND AMYLIN SECRETION AFTER MEALS

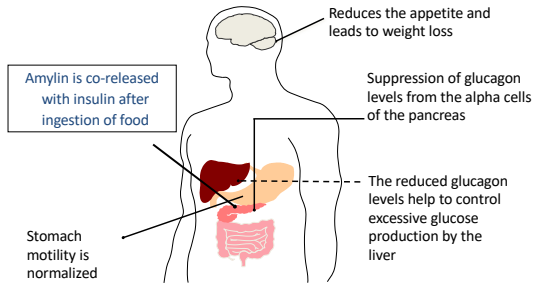



Koda et al, Diabetes. 1995; 44 (s1): 238A.
Weyer et al. Curr Pharm Des. 2001;7:1313-1373

TCOYD

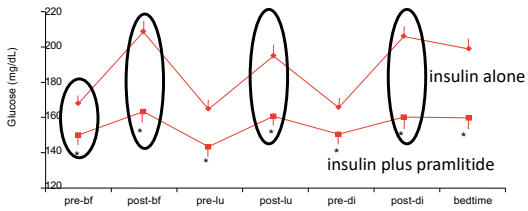
## REGULATION OF BLOOD GLUCOSE LEVELS AFTER MEALS BY AMYLIN

T




## PRAMLINTIDE REDUCES FBG, PPG AND GLUCOSE FLUCTUATIONS

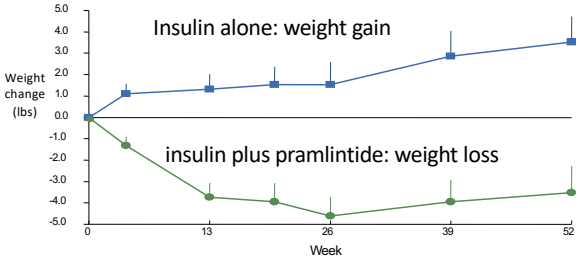
T




Clinical Practice Study, 120 µg SYMLIN
bf, breakfast; lu, lunch; di, dinner
N=166; *p-values for all data points <0.05
Data on file, Amylin Pharmaceuticals, Inc.

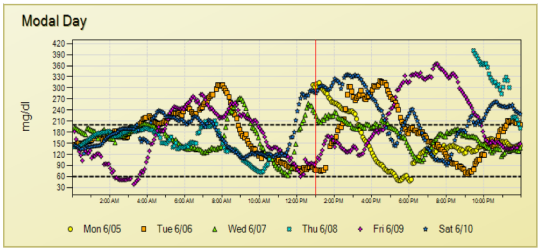
## PRAMLINTIDE + INSULIN: EFFECT ON SUSTAINED WEIGHT LOSS

T



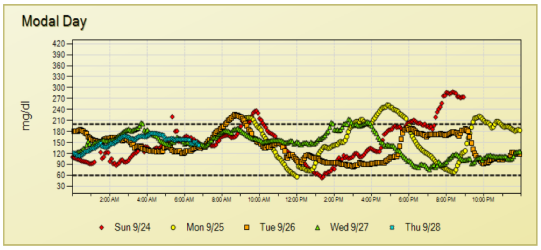
## 49YO WOMAN WITH T1D X 33 YEARS, A1C 9% AVG GLUCOSE 176.9 / S.D. 66.3

T




## AFTER 3 MONTHS ON PRAMLINTIDE, A1C 7.4%, LOST 12 LBS. AVG GLUCOSE 122.4 / S.D. 30.4

S




## GLP-1 RECEPTOR AGONIST IN T1D

S

- 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 ½ inhibitors
- No agent is actively being studied for FDA approval in type 1 diabetes

## RECAP OF KEY RESULTS OF LIRAGLUTIDE IN T1DM

S

| | ADJUNCT ONE[1] | ADJUNCT TWO[2] |
|---|---|---|
| **HbA$_{1c}$ change** (placebo-adjusted) | Mean decrease up to 0.2% | Mean decrease up to 0.35% |
| **Insulin dose change** (placebo-adjusted) | Mean decrease up to 9% | Mean decrease up to 10% |
| **Body weight loss** (placebo-adjusted) | Mean decrease up to 5 kg | Mean decrease up to 5 kg |
| **Severe hypoglycaemia** | Numerically lower in Lira vs placebo | No apparent difference |
| **Symptomatic hypoglycaemia** | Lira 1.8 mg and Lira 1.2 mg higher vs placebo | Lira 1.2 mg higher vs placebo |
| **Hyperglycaemia with ketosis** | Lira 1.8 mg higher vs placebo | Lira 1.8 mg higher vs placebo |

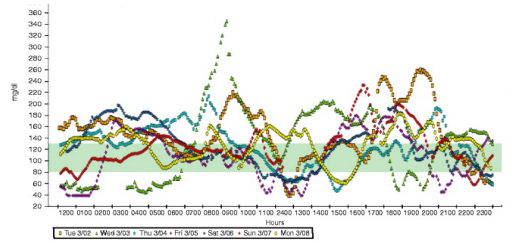
HbA$_{1c}$, glycosylated haemoglobin; Lira, liraglutide.
1. Mathieu C et al. *Diabetes Care* 2016;39:1702–1710; 2. Ahrén B et al. *Diabetes Care* 2016;39:1693–1701.

Liraglutide is not approved for the management of type 1 diabetes

TCOYD

## WEEKLY CGM RECORD FOR ONE PATIENT PRIOR TO LIRAGLUTIDE

S

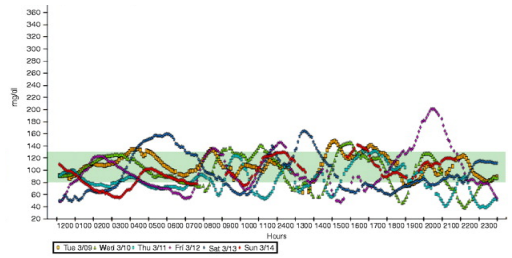



Varanasi A et al. *Eur J Endocrinol* 2011;165:77–84

TCOYD

## WEEKLY CGM RECORD FOR ONE PATIENT FOLLOWING LIRAGLUTIDE

S



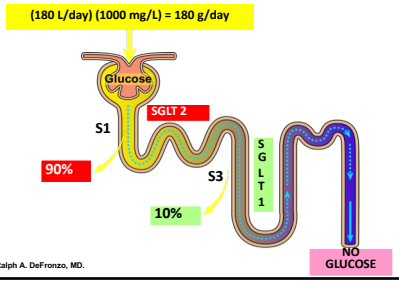

Varanasi A et al. *Eur J Endocrinol* 2011;165:77–84

TCOYD

## SGLT 1/2 INHIBITORS IN T1D

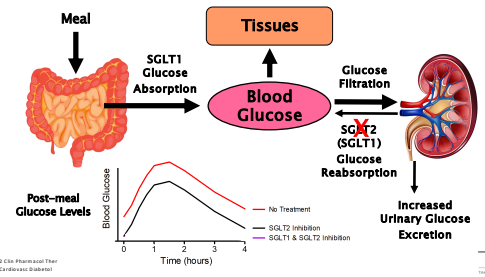
- There are 3 different drugs being studied in type 1 diabetes (empagliflozin, dapagliflozin and sotagliflozin)
- Sotagliflozin has filed with the FDA and is the furthest alone in development and will review the clinical trial data for Sotagliflozin in detail and summarize the other studies and also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

## RENAL HANDLING OF GLUCOSE

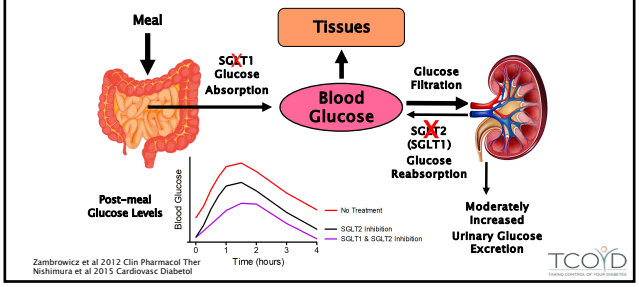



Slide courtesy of Ralph A. DeFronzo, MD.

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

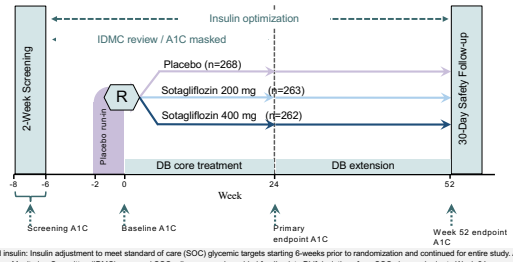


## GLUCOSE ABSORPTION/REABSORPTION IN PATIENTS TREATED WITH A DUAL SGLT1& SGLT2 INHIBITOR (SOTAGLIFLOZIN): INHIBITS SGLT1 LOCALLY IN THE GI TRACT AND SGLT2 SYSTEMICALLY IN THE KIDNEY




Zambrowicz et al 2012 Clin Pharmacol Ther
Nishimura et al 2015 Cardiovasc Diabetol

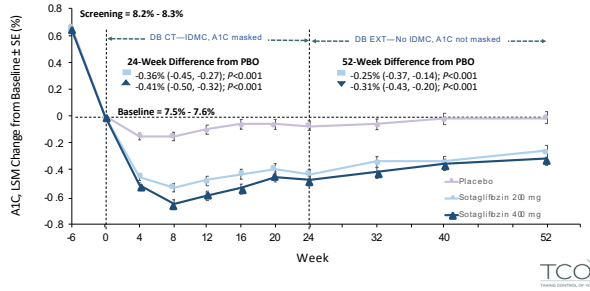
## INTANDEM STUDY DESIGN



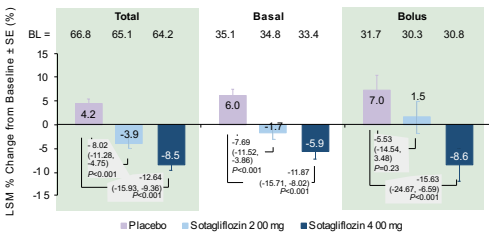

Optimized insulin: Insulin adjustment to meet standard of care (SOC) glycemic targets starting 6-weeks prior to randomization and continued for entire study. An independent Insulin Dose-Monitoring Committee (IDMC) assessed SOC adherence and provided feedback to PI if deviations from SOC observed prior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

DB, double-blind; R, randomized.

## INTANDEM1: A1C



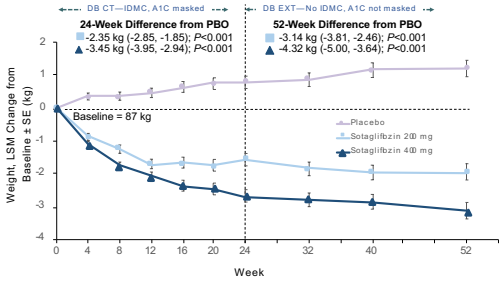
## INTANDEM1: INSULIN DOSE




LSM, least squares mean.
Data presented as the mean change from baseline in insulin dose (95% CI), *P*-value.

T

## INTANDEM1: WEIGHT

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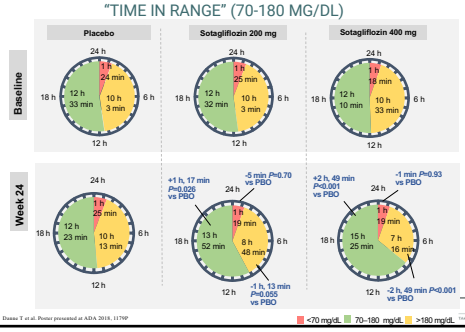
## INTANDEM 1&2 (POOLED): CONTINUOUS GLUCOSE MONITORING "TIME IN RANGE" (70-180 MG/DL)




Dunne T et al. Poster presented at ADA 2018, 1179P

T

## 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

## RISK MITIGATION OF DKA WITH SGLT INHIBITORS

- Hold the SGLT inhibitor
  - when NPO is required, viral illness, surgery, colonoscopy, etc.
- Avoid the keto diets and and excess alcohol
- 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.

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

Wallet Card - front

**S**

**T** **STop** SGLT inhibitor

**I** inject bolus **Insulin**

**C** consume 30 g **Carbohydrates**

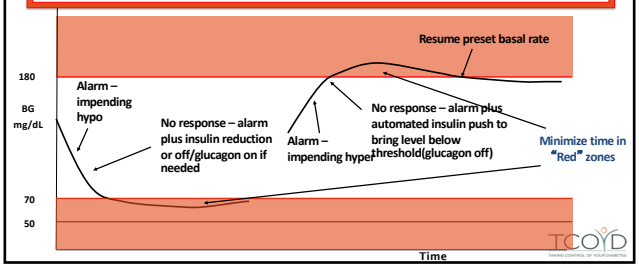
**H** **Hydrate** (drink water)

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

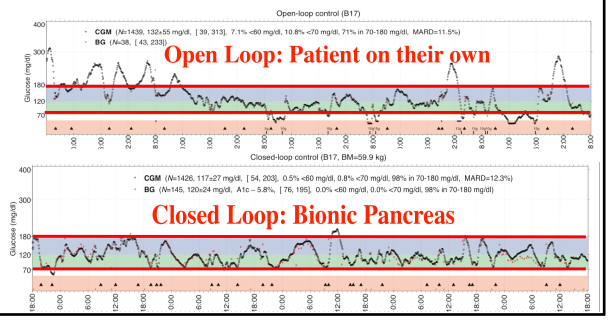
Garg S, et al. *Diab Tech Ther* 2018; epub.

## AN ARTIFICIAL PANCREAS IS COMING FASTER THAN WE THOUGHT POSSIBLE

iLet • BigFoot • Tandem • Insulet • Lilly • Medtronic




## CGM READINGS ON AND OFF THE BIONIC PANCREAS




## 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

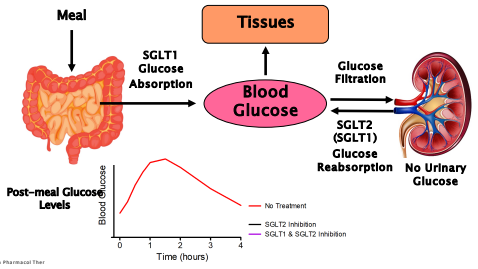
# SUPPLEMENTAL DATA SLIDES

## 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

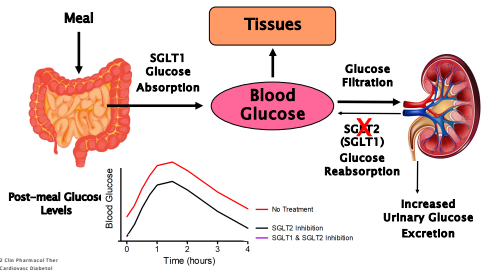


## INTESTINAL SGLT1-MEDIATED GLUCOSE ABSORPTION
## RENAL SGLT2 (SGLT1) MEDIATED GLUCOSE REABSORPTION



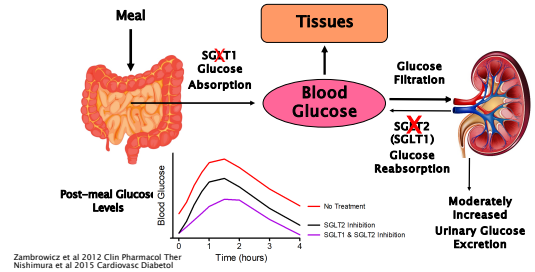

Zambrowicz et al 2012 Clin Pharmacol Ther

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



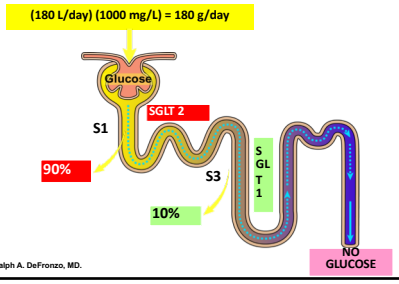

Zambrowicz et al 2012 Clin Pharmacol Ther
Nishimura et al 2015 Cardiovasc Diabetol

## 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




Zambrowicz et al 2012 Clin Pharmacol Ther
Nishimura et al 2015 Cardiovasc Diabetol

## RENAL HANDLING OF GLUCOSE



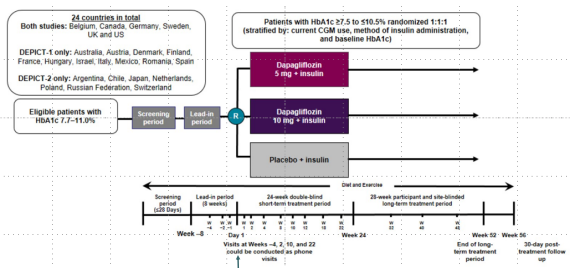

Slide courtesy of Ralph A. DeFronzo, MD.

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

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

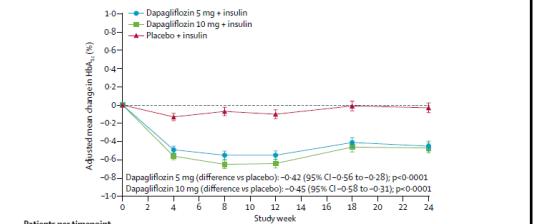

1. Dandona P, et al. Lancet Diabetes Endocrinol. 2017;5:864-876.
2. Matthaei C, et al. Diabetes Care. 2018;41:1938-1946.
3. Garg SK, et al. N Engl J Med. 2017;377:2337-2348.
4. Buse JB, et al. Diabetes Care. 2018;41:1970-1980.
5. Danne T, et al. Diabetes Care. 2018;41:1981-1990.
6. Rosenstock J, et al. Diabetes Care. 2018 Oct 4. pii: dc181749. doi: 10.2337/dc18-1749. [Epub ahead of print]

## DEPICT STUDIES (DAPAGLIFLOZIN): DESIGN




Insulin dose reduced 20% at randomi

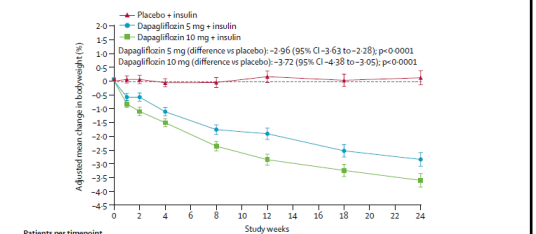
## DEPICT1 – A1C




| Patients per timepoint | | | | | | |
|---|---|---|---|---|---|---|
| Dapagliflozin 5 mg + insulin | 254 | 252 | 246 | 238 | 233 | 230 |
| Dapagliflozin 10 mg + insulin | 254 | 249 | 251 | 247 | 241 | 229 |
| Placebo + insulin | 257 | 256 | 248 | 237 | 233 | 227 |

Dapagliflozin 5 mg: mean baseline HbA1c was 8·52% (SD 0·72) and mean week 24 HbA1c was 8·04% (SD 0·90); adjusted mean change, −0·45% (SE 0·05).
Dapagliflozin 10 mg: mean baseline HbA1c was 8·50% (SD 0·62) and mean week 24 HbA1c was 8·04% (SD 0·83); adjusted mean change, −0·47% (SE 0·05).
Placebo: mean baseline HbA1c was 8·50% (SD 0·67) and mean week 24 HbA1c was 8·43% (SD 0·92); adjusted mean change, −0·03% (SE 0·05).

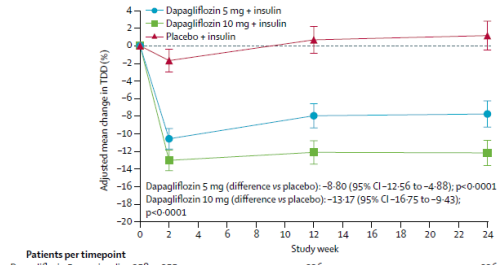
## DEPICT1 - WEIGHT




| Patients per timepoint | | | | | | |
|---|---|---|---|---|---|---|
| Dapagliflozin 5 mg + insulin | 259 | 259 | 255 | 250 | 249 | 243 | 236 | 231 |
| Dapagliflozin 10 mg + insulin | 258 | 257 | 246 | 254 | 251 | 249 | 240 | 236 |
| Placebo + insulin | 260 | 260 | 251 | 256 | 251 | 240 | 235 | 230 |

Dapagliflozin 5 mg: mean baseline bodyweight was 81·67 kg (SD 18·40) and mean week 24 bodyweight was 79·38 kg (SD 18·15); adjusted mean change, −2·84% (SE 0·25).
Dapagliflozin 10 mg: mean baseline bodyweight was 81·70 kg (SD 16·40) and mean week 24 bodyweight was 78·72 kg (SD 15·91); adjusted mean change, −3·60% (SE 0·25).
Placebo: mean baseline bodyweight was 84·36 kg (SD 18·45) and mean week 24 bodyweight was 84·50 kg (SD 18·75); adjusted mean change, 0·12% (SE 0·26).

## DEPICT1 – TOTAL DAILY DOSE (TDD) INSULIN

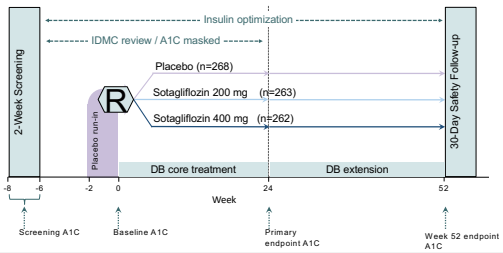



| Patients per timepoint | | | | |
|---|---|---|---|---|
| Dapagliflozin 5 mg + insulin | 258 | 255 | 236 | 226 |
| Dapagliflozin 10 mg + insulin | 254 | 253 | 238 | 225 |
| Placebo + insulin | 258 | 254 | 229 | 217 |

## 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

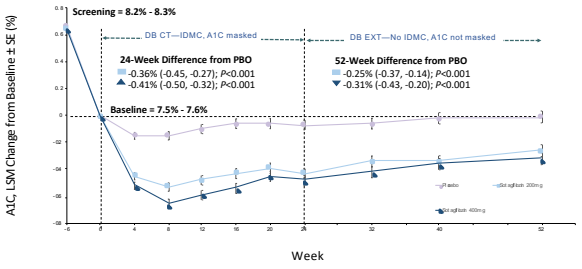
## INTANDEM STUDY DESIGN




Optimized insulin: Insulin adjustment to meet standard of care (SOC) glycemic 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.

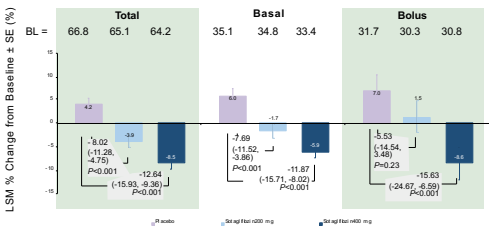
DB, double-blind; R, randomized.

## INTANDEM1: A1C



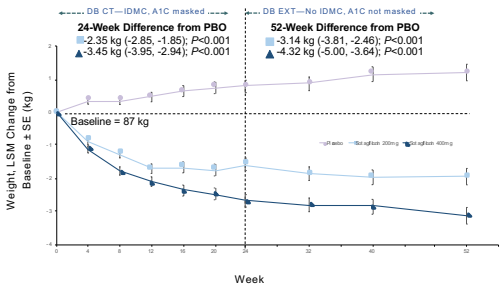

13

## INTANDEM1: INSULIN DOSE

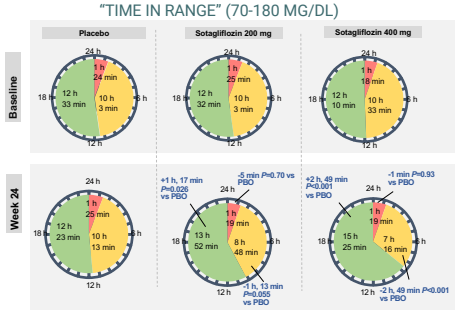



LSM, least squares mean.
Data presented as the mean change from baseline in insulin dose (95% CI), *P*-value.

## INTANDEM1: WEIGHT

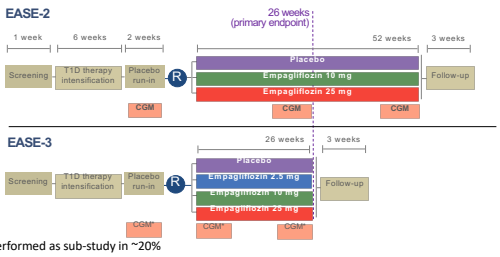


## INTANDEM 1&2 (POOLED): CONTINUOUS GLUCOSE MONITORING "TIME IN RANGE" (70-180 MG/DL)



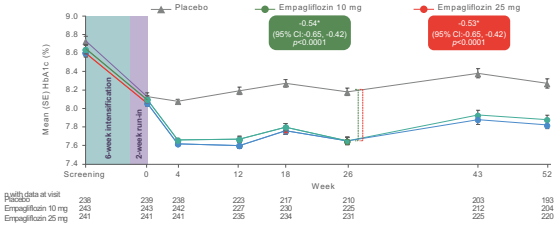

Dunne T et al. Poster presented at ADA 2018, 1179P

## EASE-2 AND EASE-3 (EMPAGLIFLOZIN): TRIAL DESIGN



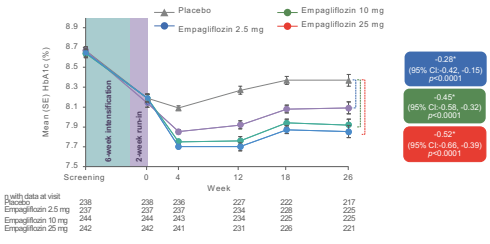

*CGM performed as sub-study in ~20% patients; R, randomisation

## EASE-2: A1C




*Adjusted mean change from baseline vs placebo; Screening and week 0: descriptive data in full analysis set. Week 4–52: adjusted data based on mixed model repeated measures in full analysis set (observed cases); SE, standard error

## EASE-3: A1C

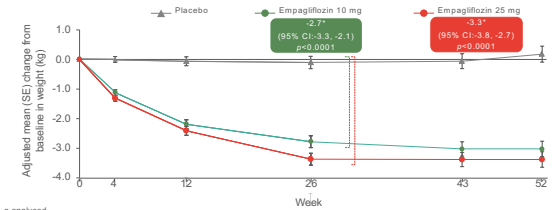



n with data at visit

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 238 | 238 | 236 | 227 | 222 | 217 |
| Empagliflozin 2.5 mg | 237 | 237 | 237 | 234 | 228 | 225 |
| Empagliflozin 10 mg | 244 | 244 | 243 | 234 | 225 | 225 |
| Empagliflozin 25 mg | 242 | 242 | 241 | 231 | 226 | 221 |

*Adjusted mean change from baseline vs placebo; Screening and week 0: descriptive data in full analysis set. Week 4–26: adjusted data based on mixed model repeated measures in full analysis set (observed cases).

## EASE-3: WEIGHT

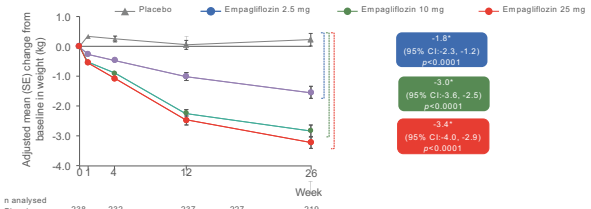



n analysed

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 238 | 238 | 224 | 211 | 200 | 194 |
| Empa 10 mg | 243 | 242 | 237 | 228 | 211 | 203 |
| Empa 25 mg | 240 | 240 | 239 | 232 | 226 | 218 |

*Adjusted mean change from baseline vs placebo. Screening and week 0: descriptive data in full analysis set. Week 4–52: adjusted data based on mixed model repeated measures in full analysis set (observed cases).

## EASE-3: WEIGHT

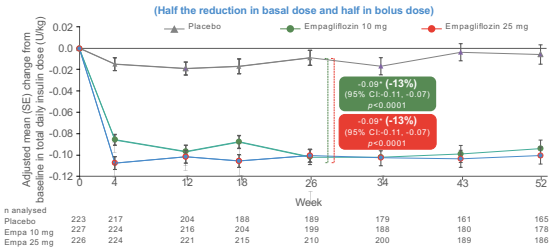



n analysed

| | | | | | |
|---|---|---|---|---|---|
| Placebo | 238 | 232 | 237 | 227 | 219 |
| Empa 2.5 mg | 237 | 234 | 236 | 233 | 223 |
| Empa 10 mg | 243 | 239 | 242 | 233 | 225 |
| Empa 25 mg | 240 | 239 | 237 | 231 | 223 |

*Adjusted mean change from baseline vs placebo; Screening and week 0: descriptive data in full analysis set. Week 4–26: adjusted data based on mixed model repeated measures in full analysis set (observed cases).

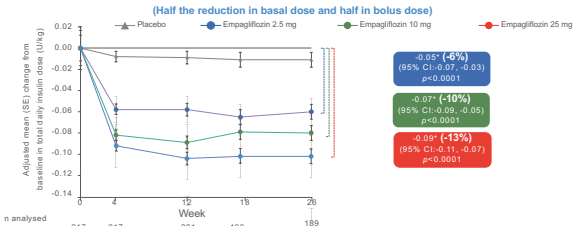
## EASE-2: TOTAL DAILY INSULIN DOSE REDUCTION OVER TIME




| n analysed | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 223 | 217 | 204 | 188 | 189 | 179 | 161 | 165 |
| Empa 10 mg | 227 | 224 | 216 | 204 | 199 | 188 | 180 | 178 |
| Empa 25 mg | 226 | 224 | 221 | 215 | 210 | 200 | 189 | 186 |

*Adjusted mean change from baseline vs placebo. Screening and week 0: descriptive data in full analysis set. Week 4–52: adjusted data based on mixed model repeated measures in full analysis set (observed cases).

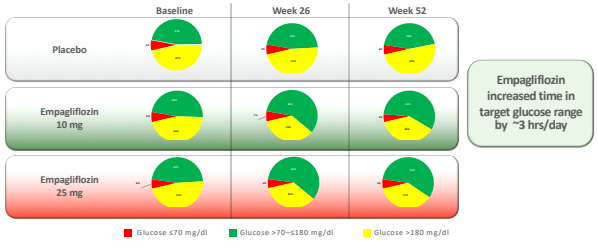
## EASE-3: TOTAL DAILY INSULIN DOSE REDUCTION OVER TIME




| n analysed | | | | | |
|---|---|---|---|---|---|
| Placebo | 217 | 217 | 201 | 196 | 189 |
| Empa 2.5 mg | 223 | 222 | 208 | 202 | 189 |
| Empa 10 mg | 217 | 215 | 195 | 187 | 177 |
| Empa 25 mg | 220 | 218 | 206 | 195 | 187 |

Adjusted mean change from baseline vs placebo. Screening and week 0: descriptive data in full analysis set. Week 4–26: adjusted data based on mixed model repeated measures in full analysis set (observed cases).

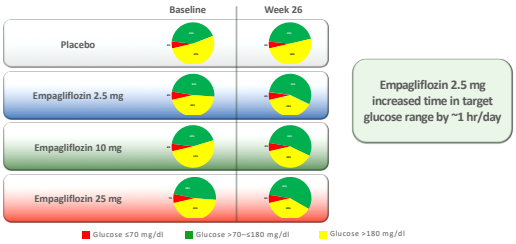
## EASE-2: CGM RESULTS




Empagliflozin increased time in target glucose range by ~3 hrs/day

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

## EASE-3: SUBANALYSIS CGM RESULTS




Empagliflozin 2.5 mg increased time in target glucose range by ~1 hr/day

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

## 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

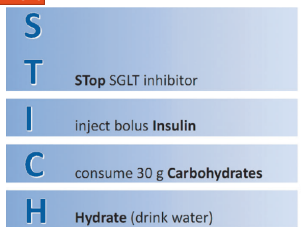
* Lower doses retain much of the glycemic efficacy with lesser effect on weight and blood pressure

## 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.

## 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.