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

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DISCLOSURES

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- 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.

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- Research Funding: Novo Nordisk

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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 2018
- 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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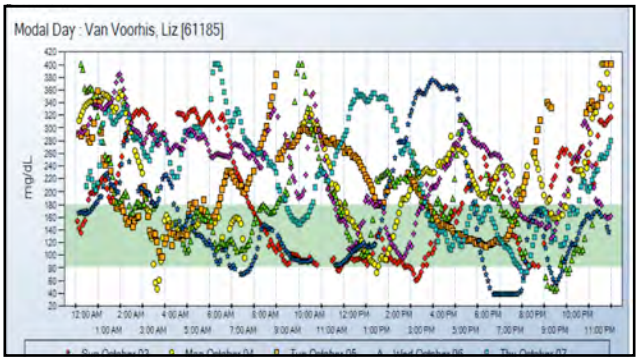
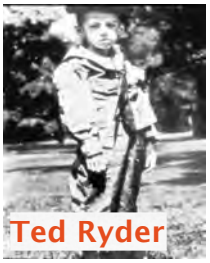
UNMET NEEDS IN TYPE 1 DIABETES

- 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



INDICIES OF GLYCEMIC VARIABILITY: TIME IN RANGE (TIR), COEFFICIENT OF VARIATION (CV), STANDARD DEVIATION (SD), TIME SPENT IN HYPER- (>180) AND HYPOGLYCEMIA (<70)

BANTING AND BEST
UNIVERSITY OF TORONTO 1921



Ted Ryder

TCOYD

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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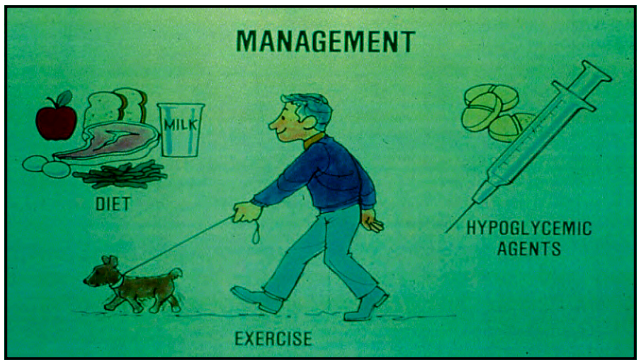

PREVALENCE OF T1D INCREASING IN US

- 1.3 million adults 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]

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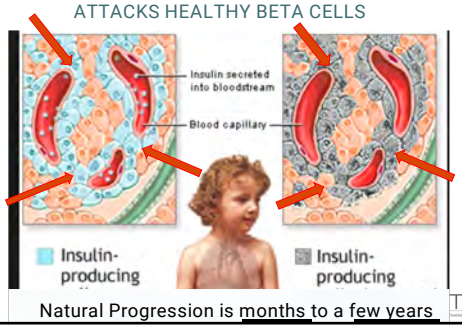
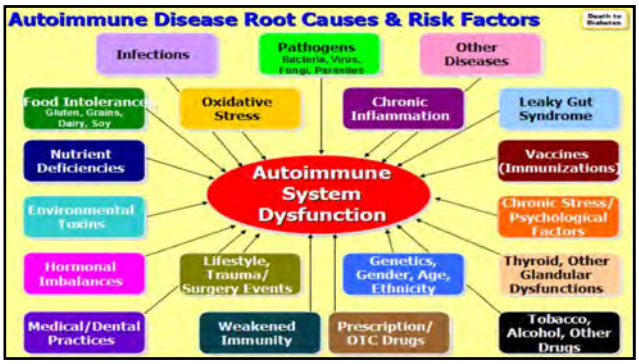
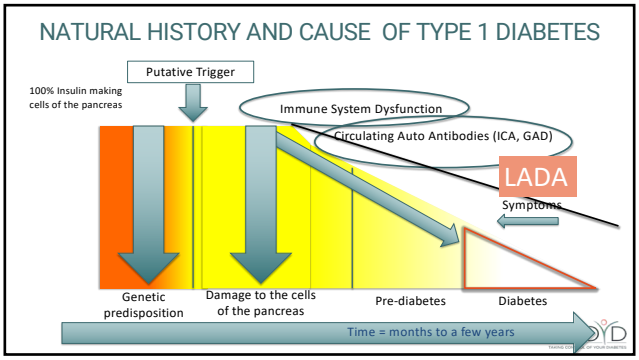
TYPE 1 IS AN AUTOIMMUNE DISEASE: THE IMMUNE SYSTEM ATTACKS HEALTHY BETA CELLS



Natural Progression is months to a few years

TCOYD

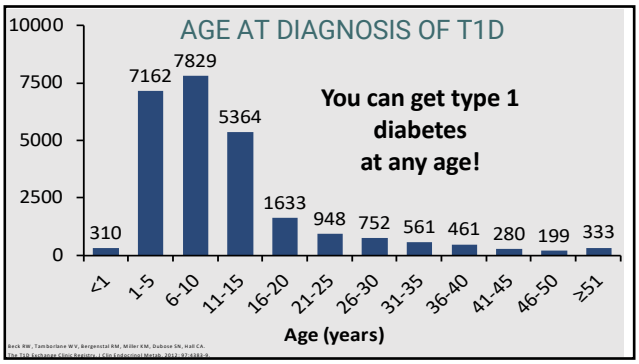


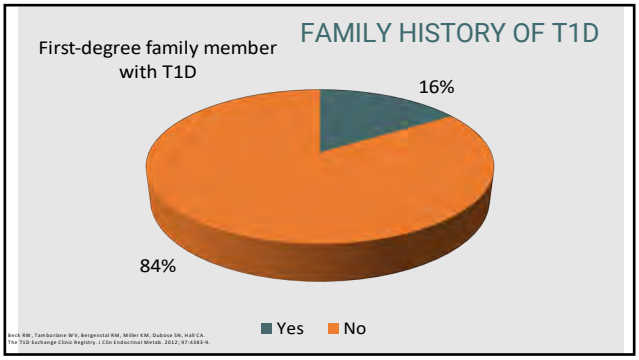


LATENT AUTOIMMUNE DIABETES IN ADULTS (LADA)

- 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



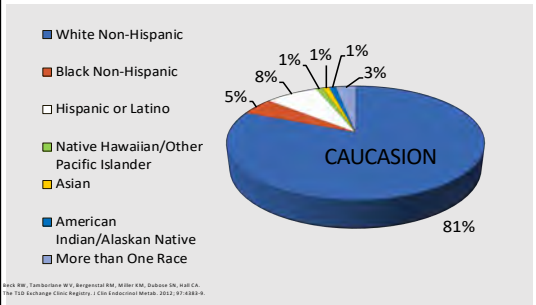


RISK OF DEVELOPING TYPE 1 VS TYPE 2

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%

RACE/ETHNICITY

S



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.

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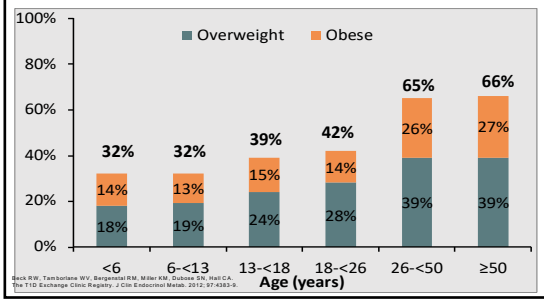
OVERWEIGHT / OBESE



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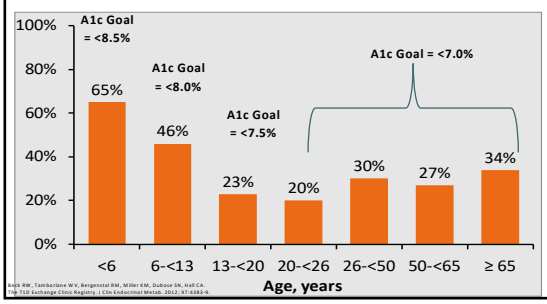
ONLY ~30% OF TYPE 1S REACH ADA GOAL OF AN A1C LESS THAN 7%



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.

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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

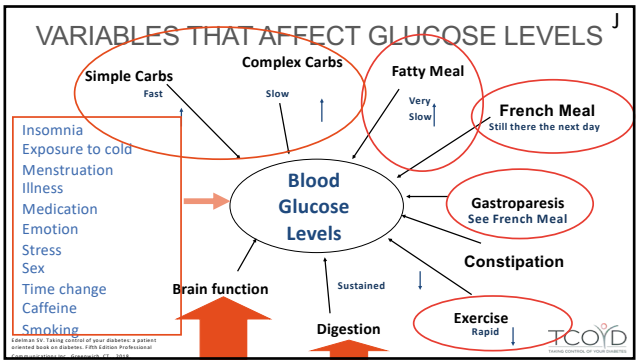
CASE 1: PHIL

- 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.

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

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

VARIABLES THAT AFFECT GLUCOSE LEVELS



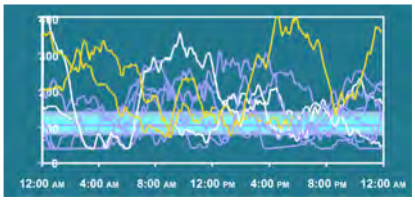
Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT. , 2018.

THE A1C REPRESENTS ONLY THE AVERAGE BLOOD GLUCOSE OVER TIME

(ALL TREATED WITH FAST-ACTING ANALOGUES)

Mean A1C=6.7%

Glucose Concentration (mg/dL)

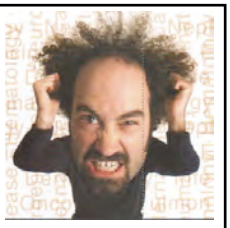


24-hour CGMS glucose sensor data
Type 1 diabetes (N=9)

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

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



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

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

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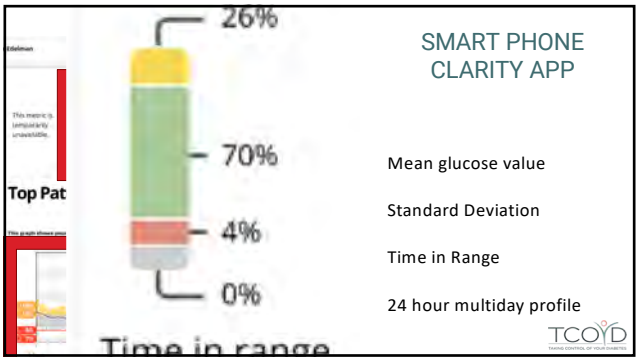


SMART PHONE CLARITY APP

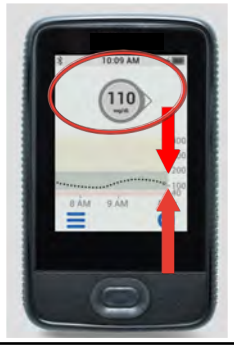
Mean glucose value

Standard Deviation

Time in Range

24 hour multiday profile

S



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

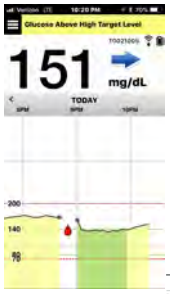
Mobile App

No extra device to carry

iOS and Android platform

Alarm settings & reports

EVERSENSE IMPLANTABLE CGM



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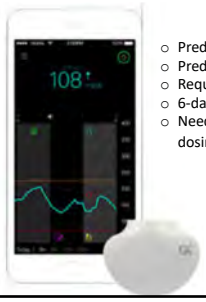
GUARDIAN CONNECT



- 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

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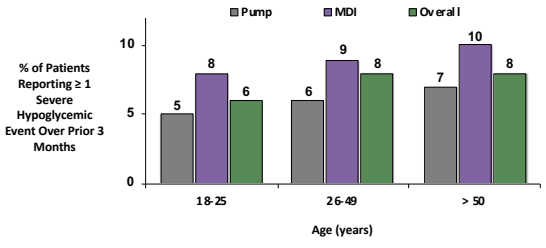
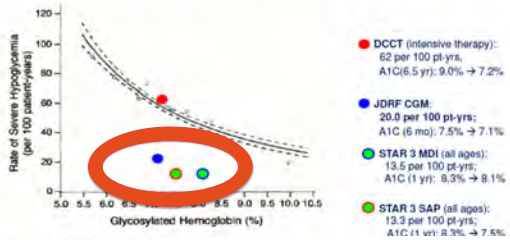
SEVERE HYPOGLYCEMIA – SERIOUS AE IN T1D DUE TO TOO MUCH INSULIN



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

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



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

J

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

Hermanas K, Fras JP, Edelman SV, I... undergoing continuous subcutaneous insulin infusion therapy. *Postgraduate Medicine*. 123(2), 2011.

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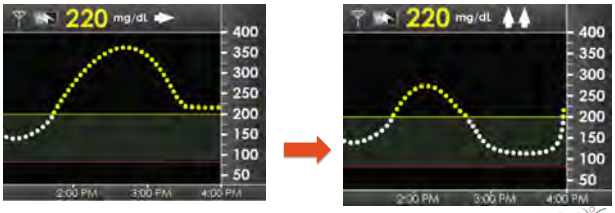
MEAN CHANGE IN INSULIN DOSE BASEDON 2 ARROWS UP: SURVEY OF 300 CGM USERS

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
Rapidly rising: Your glucose is rising more than 3 mg/dL each minute — **6.8 units**	140% Mean Increase
Rapidly falling: Your glucose is falling more than 3 mg/dL each minute — **1.5 units**	48% Mean Decrease

S

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

AUDIENCE RESPONSE SYSTEM

Text TCOYD to the number 22333

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

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.

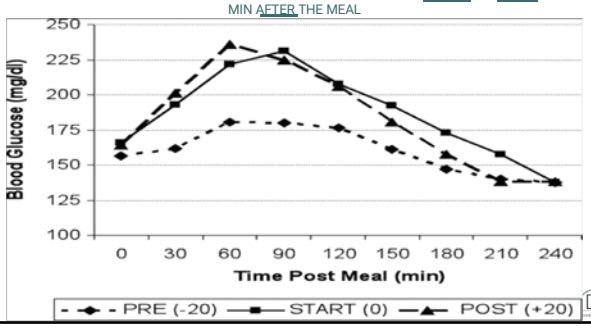
Add 50 mg/dl

Add 75 mg/dl

Add 100 mg/dl

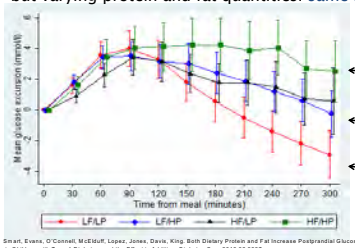
Wait until trend arrow becomes horizontal

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



BOTH DIETARY FAT AND PROTEIN INCREASE POST MEAL GLUCOSE CONCENTRATIONS

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

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

A	3 units
B	6 units
C	12 units
D	More than 6 units

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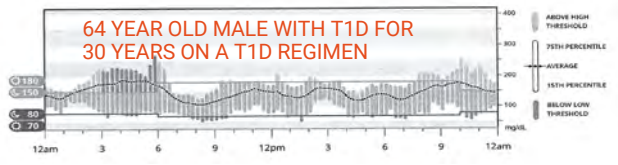
64 YEAR OLD MALE WITH T1D FOR 30 YEARS ON A T1D REGIMEN



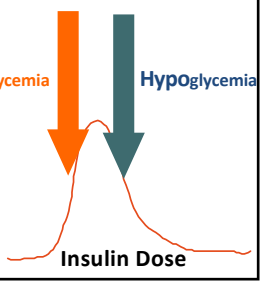
What is/are the possible causes of this patients glucose profiles overnight?

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

S

SUBCUTANEOUS INSULIN HAS A VERY NARROW THERAPEUTIC WINDOW

- Too little insulin leads to postprandial hyperglycemia
- Too much leads to hypoglycemia
- Very difficult to get it just right



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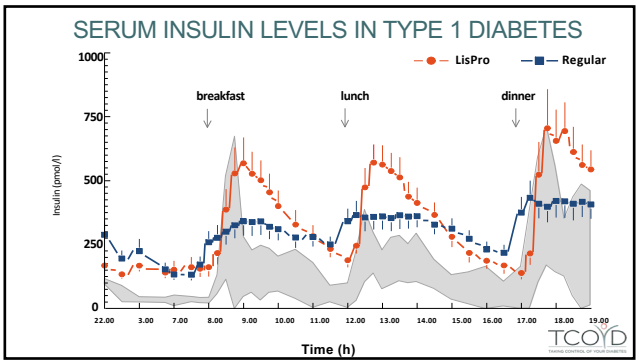
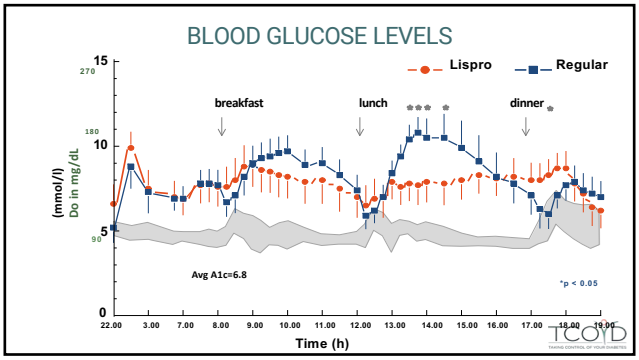
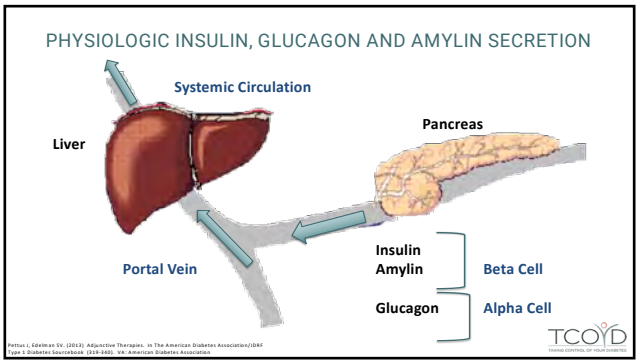
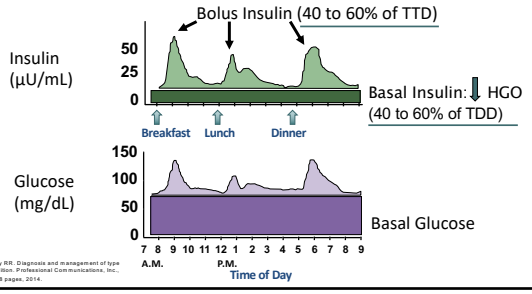

SERUM INSULIN LEVELS IN TYPE 1 DIABETES
LisPro
Regular
breakfast
lunch
dinner
Insulin (pmol/l)
1000
750
500
250
0
22.00 3.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00
Time (h)
TCOYD


BLOOD GLUCOSE LEVELS
Lispro
Regular
breakfast
lunch
dinner
(mmol/l)
Do in mg/dL
15
270
180
10
5
90
0
Avg A1c=6.8
*p < 0.05
22.00 3.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00
Time (h)
TCOYD


PHYSIOLOGIC INSULIN, GLUCAGON AND AMYLIN SECRETION
Systemic Circulation
Liver
Pancreas
Portal Vein
Insulin
Amylin
Beta Cell
Glucagon
Alpha Cell
TCOYD

PHYSIOLOGIC INSULIN SECRETION AND GLUCOSE LEVELS IN HEALTHY SUBJECTS



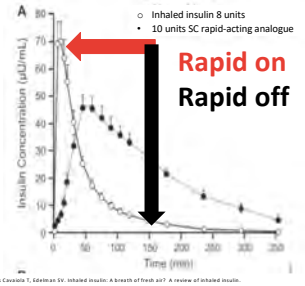
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages. 2014.

GENERIC AND TRADE NAMES: INSULIN

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

INHALED INSULIN

J



- Inhaled insulin 8 units
- 10 units SC rapid-acting analogue

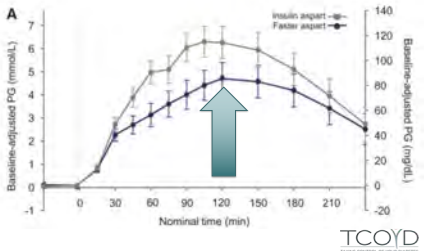
Rapid on
Rapid off

- 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



Rodé et al DTT Vol 19 2017

TCOYD

SHORTCOMINGS OF BASAL INSULINS INCLUDE:

S

- 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

TCOYD

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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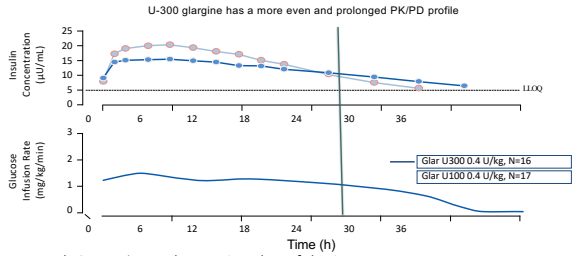
U-300 GLARGINE

- 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
Bolli GB *et al*. Poster presented at EASD 2014: P947; 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: P978

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

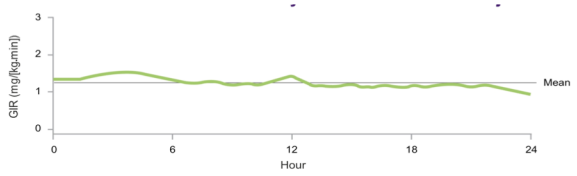
U-300 glargine has a more even and prolonged PK/PD profile



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

Becker RH, et al. *Diabetes Care*. 2015;4;639-643.

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

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.
Heise T et al. Diabetes Obes Metab. 2012;14:944-950.
Heise T et al. Diabet Med. 2013;30:487-494.
Jonassen I et al. Pharm Res. 2012;29:2104-2114.
Press release:
http://www.ngvnordisk.com/include/asp/exe_news_attachment.asp?sAttachmentGUID=a1 b5d012-cfcb-4b58-9925-b8c7790d1d0e Accessed December 15, 2014.

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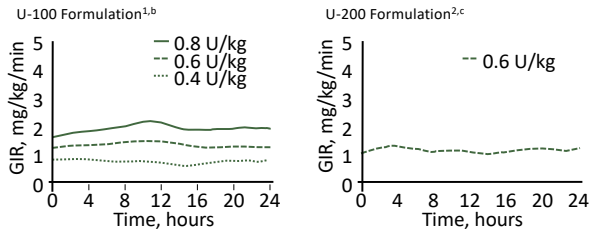
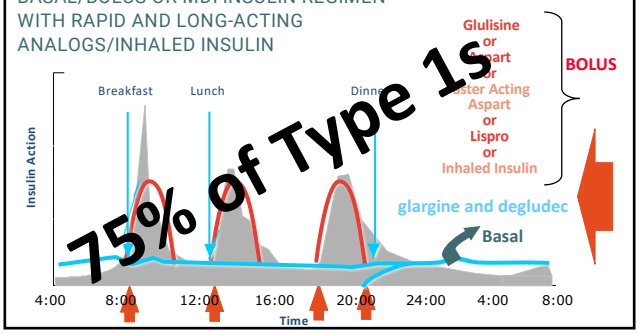
PHARMACODYNAMICS OF INSULIN DEGLUDEC U-100 AND U-200 IN PATIENTS WITH T2DM: SAME TIME COURSE OF ACTION



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].

[a,b] Glucose clamp study in patients with T2DM (n = 49).
[c] Glucose clamp study in patients with T2DM (n = 16).

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



75% of Type 1s

SOFTWARE PROGRAMS AS PUMPS

- 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. 144 pages, 2013.

TCOYD

J

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

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.

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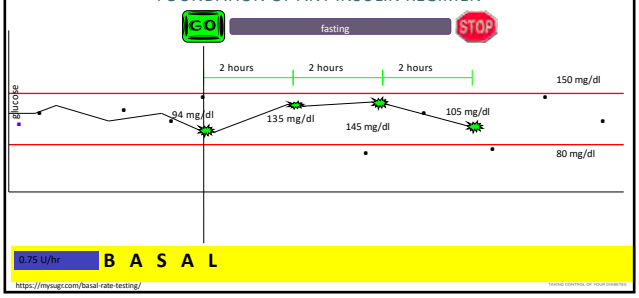
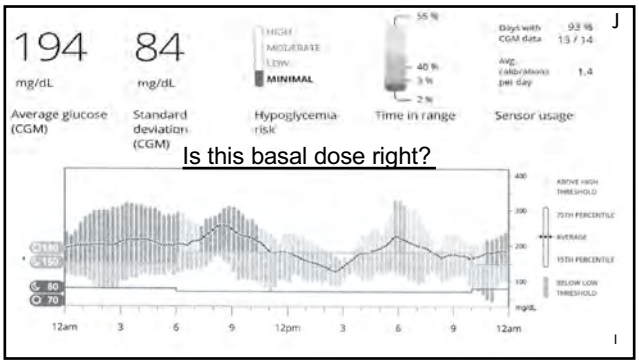
TESTING A BASAL SEGMENT IN T1D:

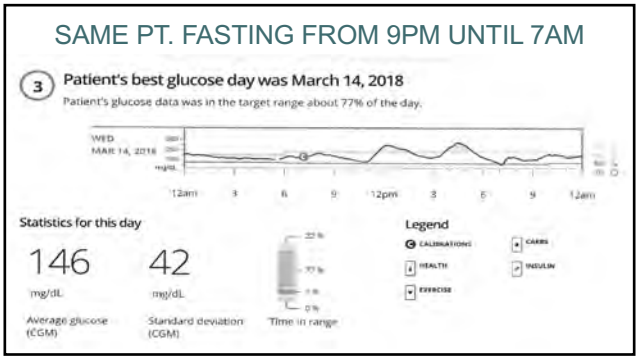
FOUNDATION OF ANY INSULIN REGIMEN

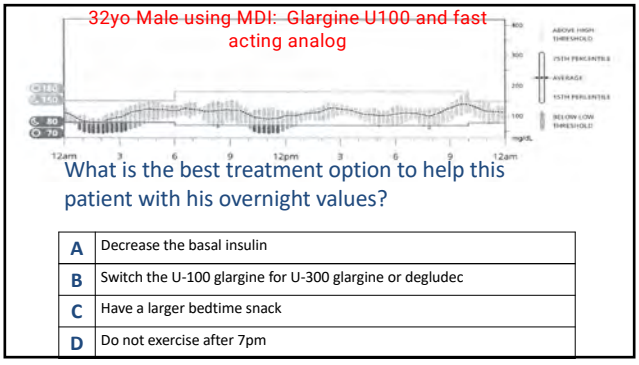


https://mysugrr.com/basal-rate-testing/



SAME PT. FASTING FROM 9PM UNTIL 7AM





ADJUNCTIVE THERAPIES FOR PEOPLE WITH TYPE 1 DIABETES

S

- 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

DPP-4 INHIBITORS IN T1D

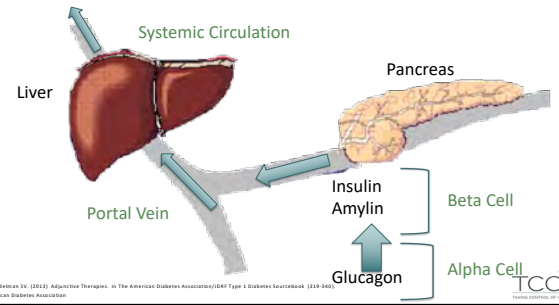
- No statistically significant differences compared to placebo

METFORMIN IN T1D

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

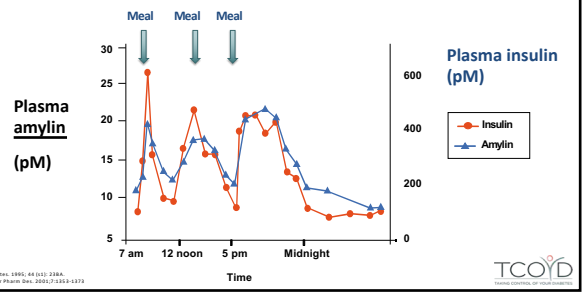
Petrie et al. Lancet DE 2017; 5:597-609
Garg et al. Endocrine Practice, 2013

PHYSIOLOGIC INSULIN, GLUCAGON AND AMYLIN SECRETION



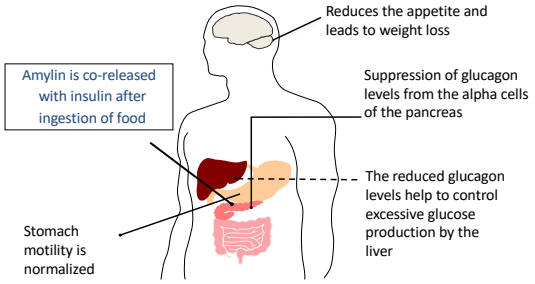
Pettus J, Edelman SV. (2013). Adjunctive Therapies. In The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook (319-340). VA: American Diabetes Association

PHYSIOLOGIC INSULIN AND AMYLIN SECRETION AFTER MEALS

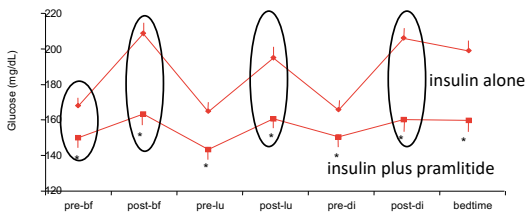


Koda et al, Diabetes. 1995; 44 (s1): 298A.
Weyer et al. Curr Pharm Des. 2003;7:1353-1373

REGULATION OF BLOOD GLUCOSE LEVELS AFTER MEALS BY AMYLIN

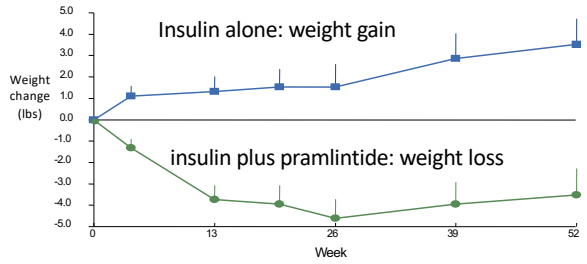


PRAMLINTIDE REDUCES FBG, PPG AND GLUCOSE FLUCTUATIONS

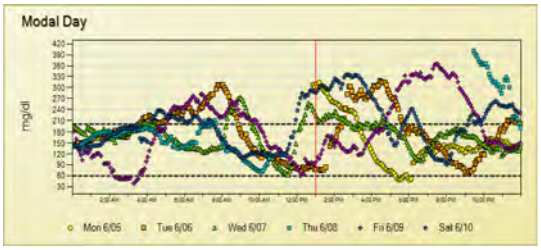


Clinical Practice Study, 120 µg SYMLIN
bf, breakfast; lu, lunch; di, dinner
N=166; *p-values for all data points <0.05
Data on file, Amylin Pharmaceuticals, Inc.

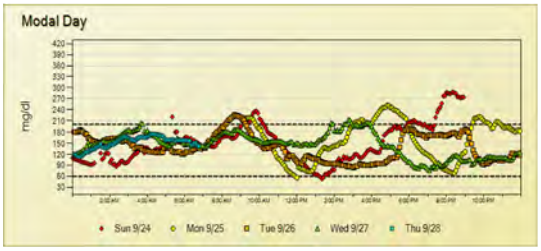
PRAMLINTIDE + INSULIN: EFFECT ON SUSTAINED WEIGHT LOSS



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



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



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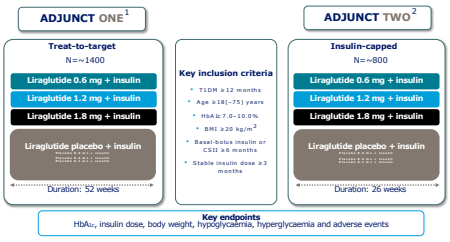
GLP-1 RECEPTOR AGONIST IN T1D

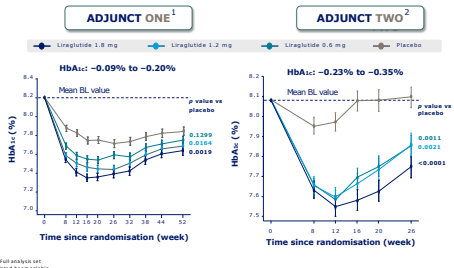
- There were small very early studies with exenatide
- One large well controlled study looking at liraglutide
- Many of the clinical effects in type 1 are similar to what is seen with SGLT ½ inhibitors
- No agent is actively being studied for FDA approval in type 1 diabetes

ADJUNCT ONE AND TWO: LIRAGLUTIDE IN T1DM – PHASE 3A TRIAL DESIGNS



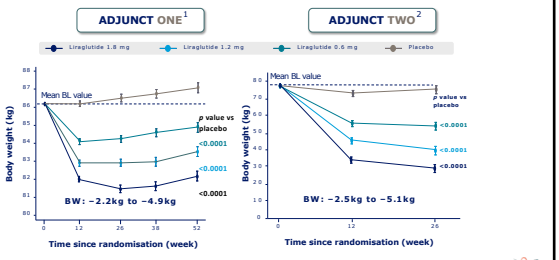
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA1c, glycosylated haemoglobin; T1DM, type 1 diabetes mellitus
1. Mathieu C et al. *Diabetes Care* 2016;39:1702–1710; 2. Ahrén B et al. *Diabetes Care* 2016;39:1693–1701

CHANGE IN HBA$_{1C}$ FROM BASELINE TO END OF TREATMENT



Data are estimated means. Full analysis set
BL, baseline, HbA1c, glycosylated haemoglobin
1. Mathieu C et al. *Diabetes Care* 2016;39:1702–1710; 2. Ahrén B et al. *Diabetes Care* 2016;39:1693–1701

CHANGE IN BODY WEIGHT FROM BASELINE TO END OF TREATMENT



Data are estimated means. Full analysis set
BL, baseline, BW, body weight
1. Mathieu C et al. *Diabetes Care* 2016;39:1702–1710; 2. Ahrén B et al. *Diabetes Care* 2016;39:1693–1701

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CHANGE IN TOTAL INSULIN DOSE FROM BASELINE TO END OF TREATMENT

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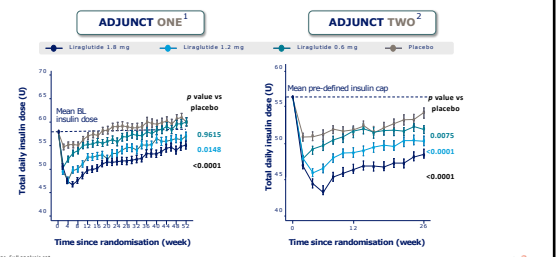
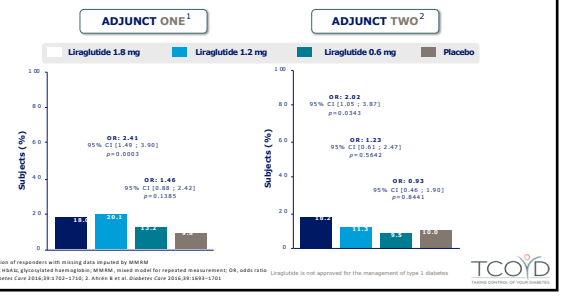


Data are estimated means. Full analysis set
U, units
1. Mathieu C et al. *Diabetes Care* 2016;39:1702–1710; 2. Ahrén B et al. *Diabetes Care* 2016;39:1693–1701

TCOYD

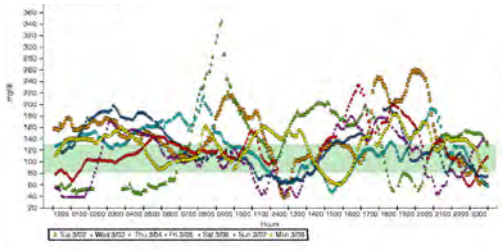
SUBJECTS ACHIEVING HBA_{1C} <7.0% AND NO SEVERE HYPOGLYCAEMIA



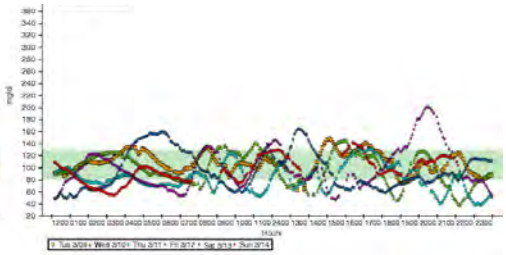
On-treatment; proportion of responders with missing data imputed by MMRM
CI, confidence interval; HbA1c, glycosylated haemoglobin; MMRM, mixed model for repeated measurement; OR, odds ratio
Liraglutide is not approved for the management of type 1 diabetes
1. Mathieu C et al. *Diabetes Care* 2016;39:1702–1710; 2. Ahrén B et al. *Diabetes Care* 2016;39:1693–1701

TCOYD

WEEKLY CGM RECORD FOR ONE PATIENT PRIOR TO LIRAGLUTIDE



WEEKLY CGM RECORD FOR ONE PATIENT FOLLOWING LIRAGLUTIDE



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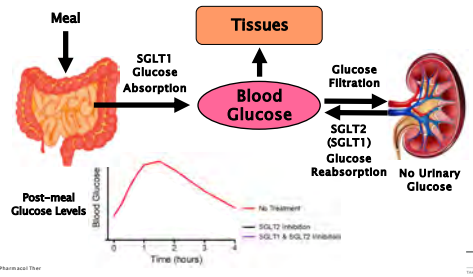
SGLT 1/2 INHIBITORS IN T1D

- 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

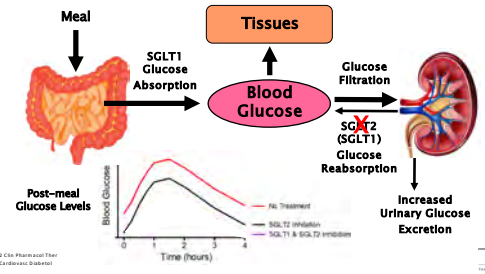
INTESTINAL SGLT1-MEDIATED GLUCOSE ABSORPTION
RENAL SGLT2 (SGLT1) MEDIATED GLUCOSE REABSORPTION



Zambrowicz et al 2012 Clin Pharmacol Ther

TCOYD

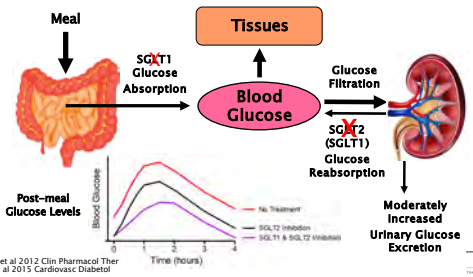
GLUCOSE ABSORPTION AND REABSORPTION IN PATIENTS WITH DIABETES TREATED WITH A SELECTIVE SGLT2 INHIBITOR:
CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN, ERTUGLIFLOZIN



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

TCOYD

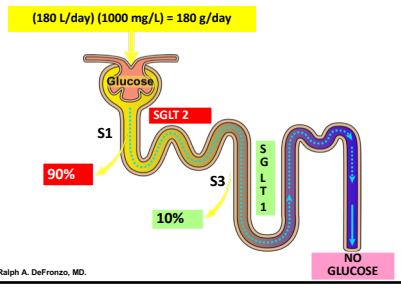
GLUCOSE ABSORPTION/REABSORPTION IN PATIENTS TREATED WITH A DUAL SGLT1& SGLT2 INHIBITOR (SOTAGLIFLOZIN):
INHIBITS SGLT1 LOCALLY IN THE GI TRACT AND SGLT2 SYSTEMICALLY IN THE KIDNEY



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

TCOYD

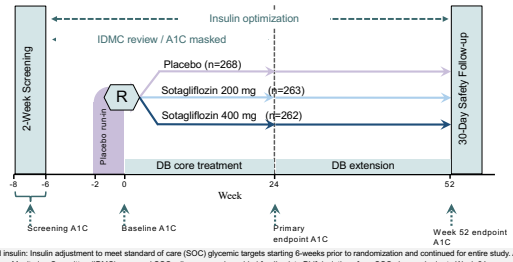
RENAL HANDLING OF GLUCOSE



Slide courtesy of Ralph A. DeFronzo, MD.

INTANDEM STUDY DESIGN

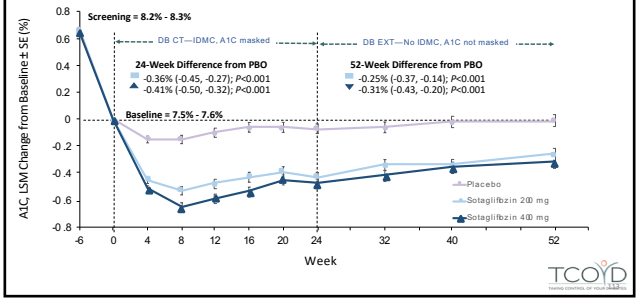
J



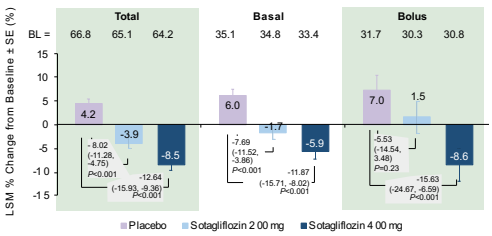
Optimized insulin: Insulin adjustment to meet standard of care (SOC) glycemic targets starting 6-weeks prior to randomization and continued for entire study. An independent Insulin Dose-Monitoring Committee (IDMC) assessed SOC adherence and provided feedback to PI if deviations from SOC observed prior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

DB, double-blind; R, randomized.

INTANDEM1: A1C



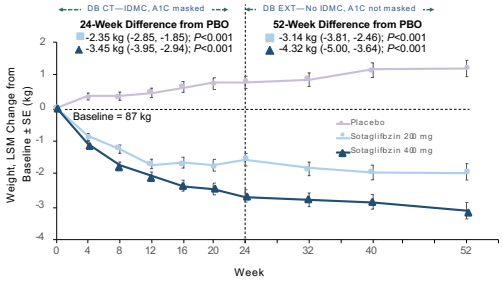
INTANDEM1: INSULIN DOSE



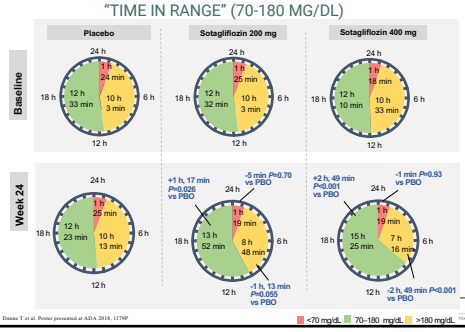
LSM, least squares mean.

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

INTANDEM1: WEIGHT



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



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

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

TCOYD

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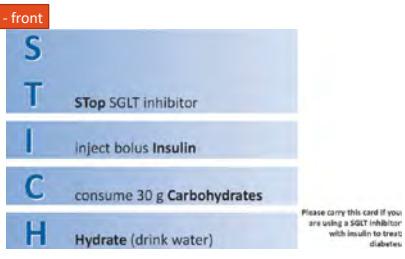
RISK MITIGATION OF DKA WITH SGLT INHIBITORS

- 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.

TCOYD

APPROACH TO REDUCE DKA RISK WITH SGLTIS: STICH PROTOCOL

Wallet Card - front



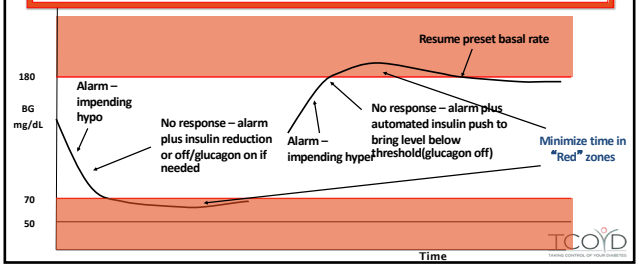
Garg S, et al. *Diab Tech Ther* 2018; epub.

TCOYD

AN ARTIFICIAL PANCREAS IS COMING FASTER THAN WE THOUGHT POSSIBLE

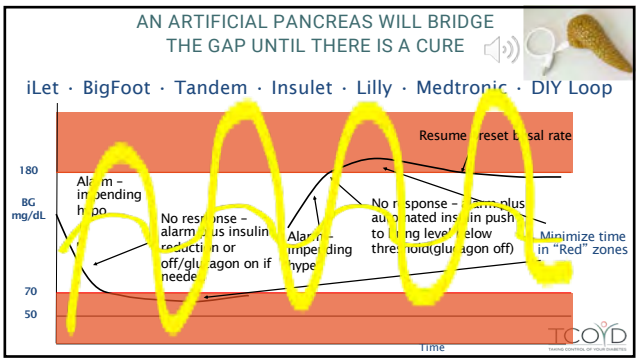
J

iLet • BigFoot • Tandem • Insulet • Lilly • Medtronic



AN ARTIFICIAL PANCREAS WILL BRIDGE THE GAP UNTIL THERE IS A CURE

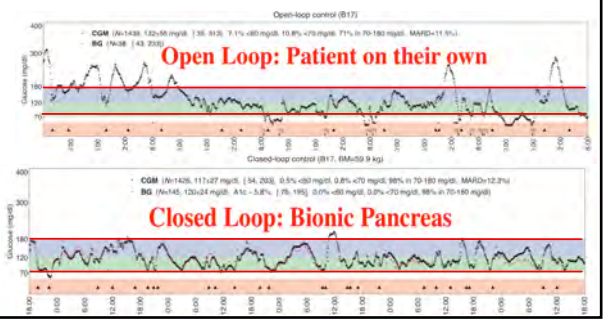
iLet · BigFoot · Tandem · Insulet · Lilly · Medtronic · DIY Loop



EXAMPLE OF AN APILET: BIONIC PANCREAS

2 ports for insulin and glucagon

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

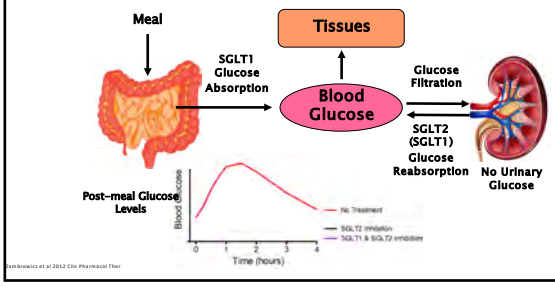
SUPPLEMENTAL DATA SLIDES

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

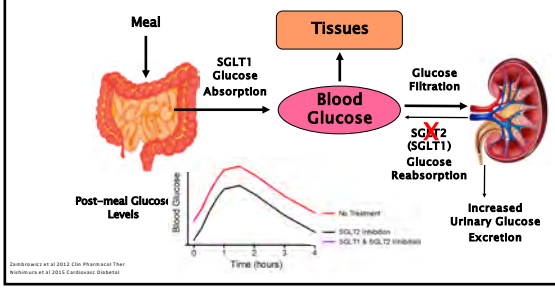
WWW.TCOYD.ORG
Taking Control Of Your Diabetes, TCOYD is a non-for-profit educational organization.

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



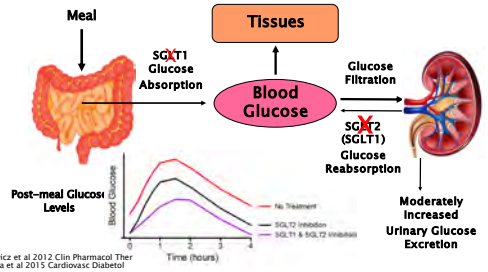
Zambrowicz et al 2012 Clin Pharmacol Ther

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



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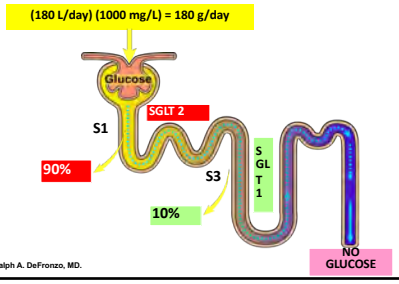
RENAL HANDLING OF GLUCOSE



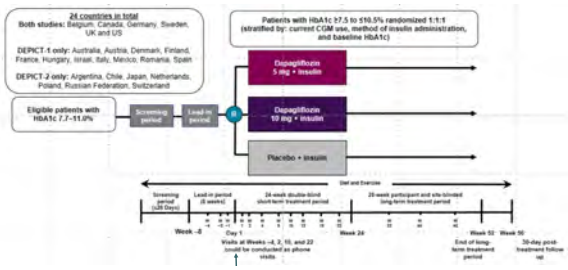
Slide courtesy of Ralph A. DeFronzo, MD.

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

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

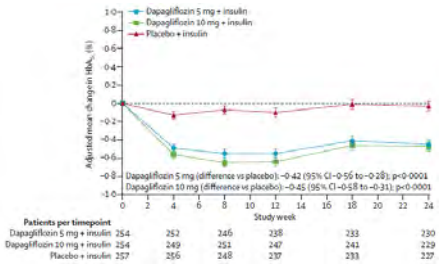
1. Dandona P, et al. Lancet Diabetes Endocrinol. 2017;5:864-876.
2. Matthaei C, et al. Diabetes Care. 2018;41:1938-1946.
3. Garg SK, et al. N Engl J Med. 2017;377:2337-2348.
4. Buse JB, et al. Diabetes Care. 2018;41:1970-1980.
5. Danne T, et al. Diabetes Care. 2018;41:1981-1990.
6. Rosenstock J, et al.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

DEPICT STUDIES (DAPAGLIFLOZIN): DESIGN



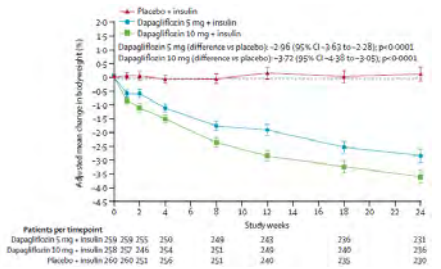
Insulin dose reduced 20% at randomi

DEPICT1 – A1C



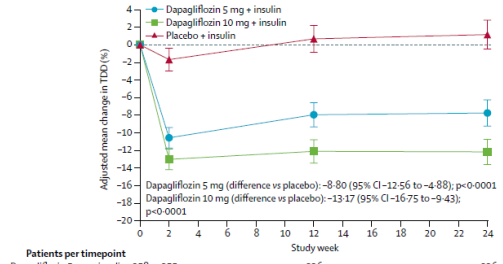
Dapagliflozin 5 mg: mean baseline HbA1c was 8·52% (SD 0·72) and mean week 24 HbA1c was 8·04% (SD 0·90); adjusted mean change, −0·45% (SE 0·05).
Dapagliflozin 10 mg: mean baseline HbA1c was 8·50% (SD 0·62) and mean week 24 HbA1c was 8·04% (SD 0·83); adjusted mean change, −0·47% (SE 0·05).
Placebo: mean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



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

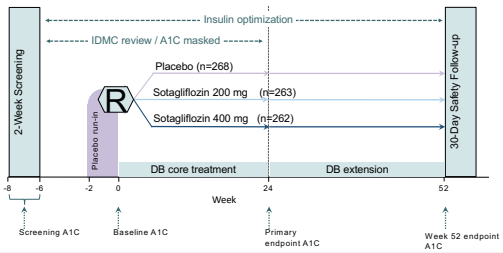


Patients per timepoint				
Dapagliflozin 5 mg + insulin	258	255	236	226
Dapagliflozin 10 mg + insulin	254	253	238	225
Placebo + insulin	258	254	229	217

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

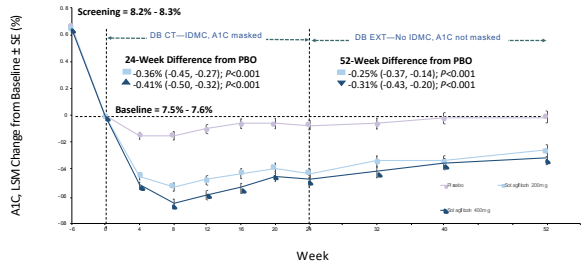
INTANDEM STUDY DESIGN



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



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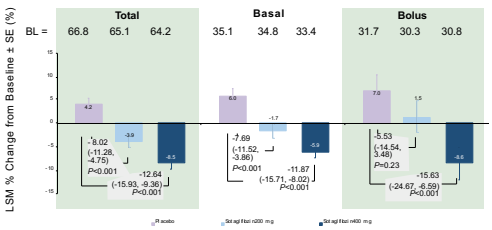
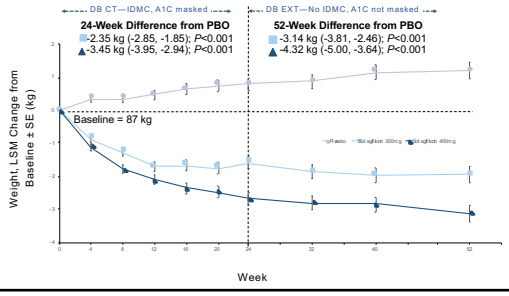
INTANDEM1: INSULIN DOSE

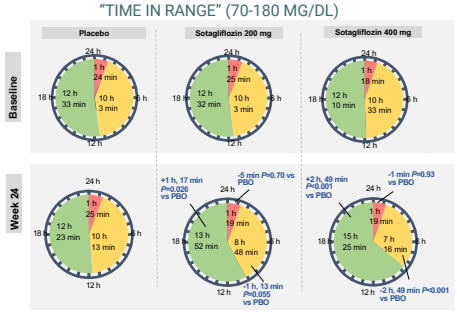


LSM, least squares mean.
Data presented as the mean change from baseline in insulin dose (95% CI), *P*-value.

INTANDEM1: WEIGHT

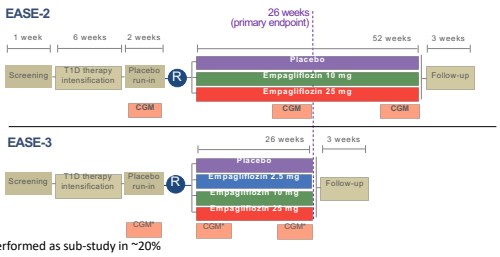


INTANDEM 1&2 (POOLED): CONTINUOUS GLUCOSE MONITORING "TIME IN RANGE" (70-180 MG/DL)



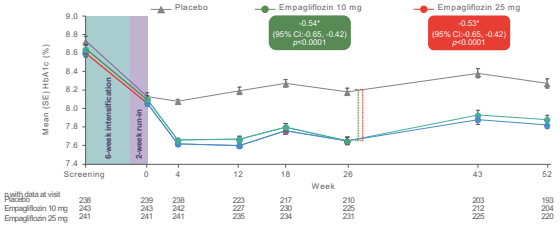
Dunne T et al. Poster presented at ADA 2018, 1179P

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



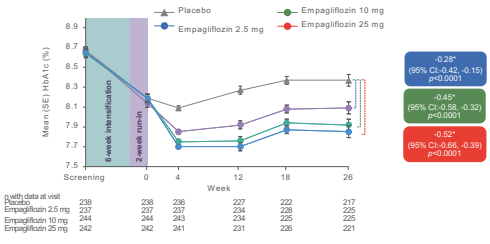
*CGM performed as sub-study in ~20% patients; R, randomisation

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

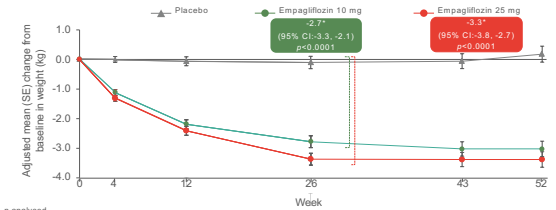
EASE-3: A1C



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).

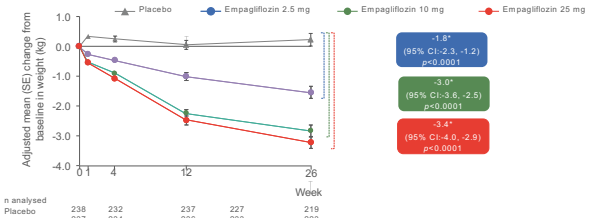
EASE-3: WEIGHT



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

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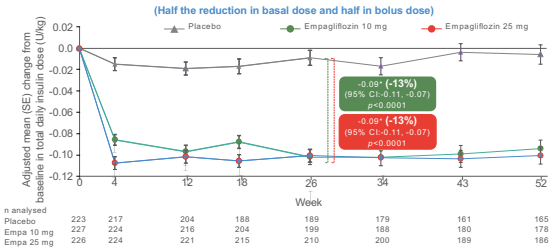
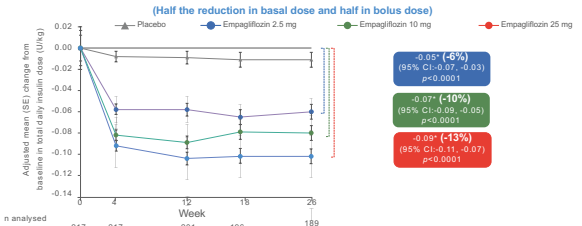
EASE-2: TOTAL DAILY INSULIN DOSE REDUCTION OVER TIME



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).

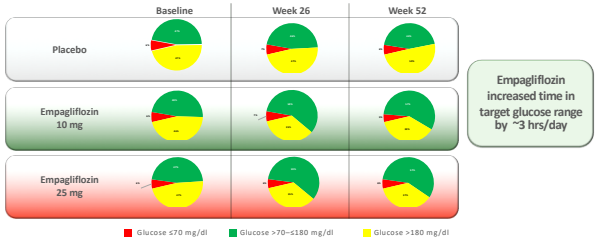
EASE-3: TOTAL DAILY INSULIN DOSE REDUCTION OVER TIME



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).

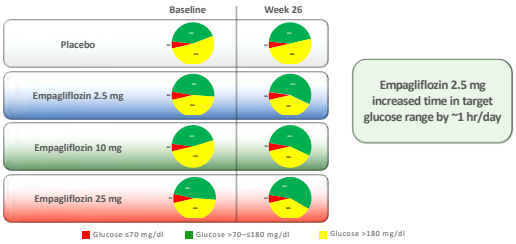
EASE-2: CGM RESULTS



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

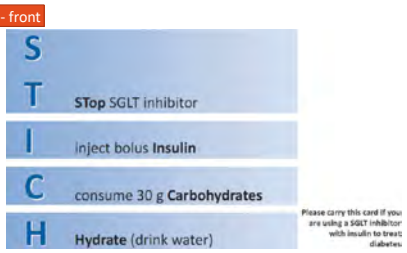
* Lower doses retain much of the glycemic efficacy with lesser effect on weight and blood pressure

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.