Type 1 DM

CME Away

India & Sri Lanka

March 23 - April 7, 2018

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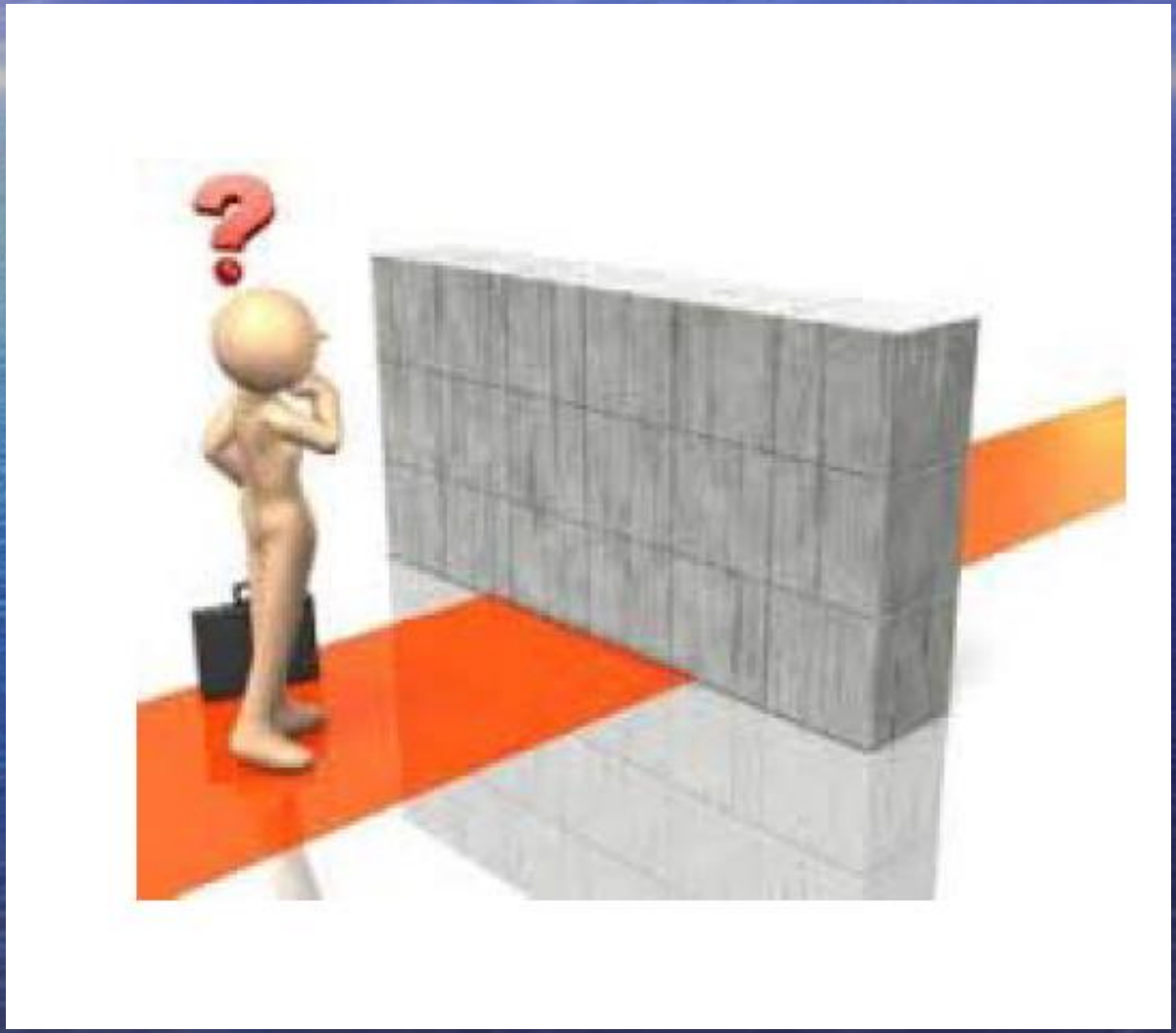
Barriers To Change



Disclosure of Commercial Support

- **This program has not received financial support, or in-kind support, from any Pharmaceutical Company.**

- **<u>Potential for conflict(s) of interest</u>:**
  - **None to declare**

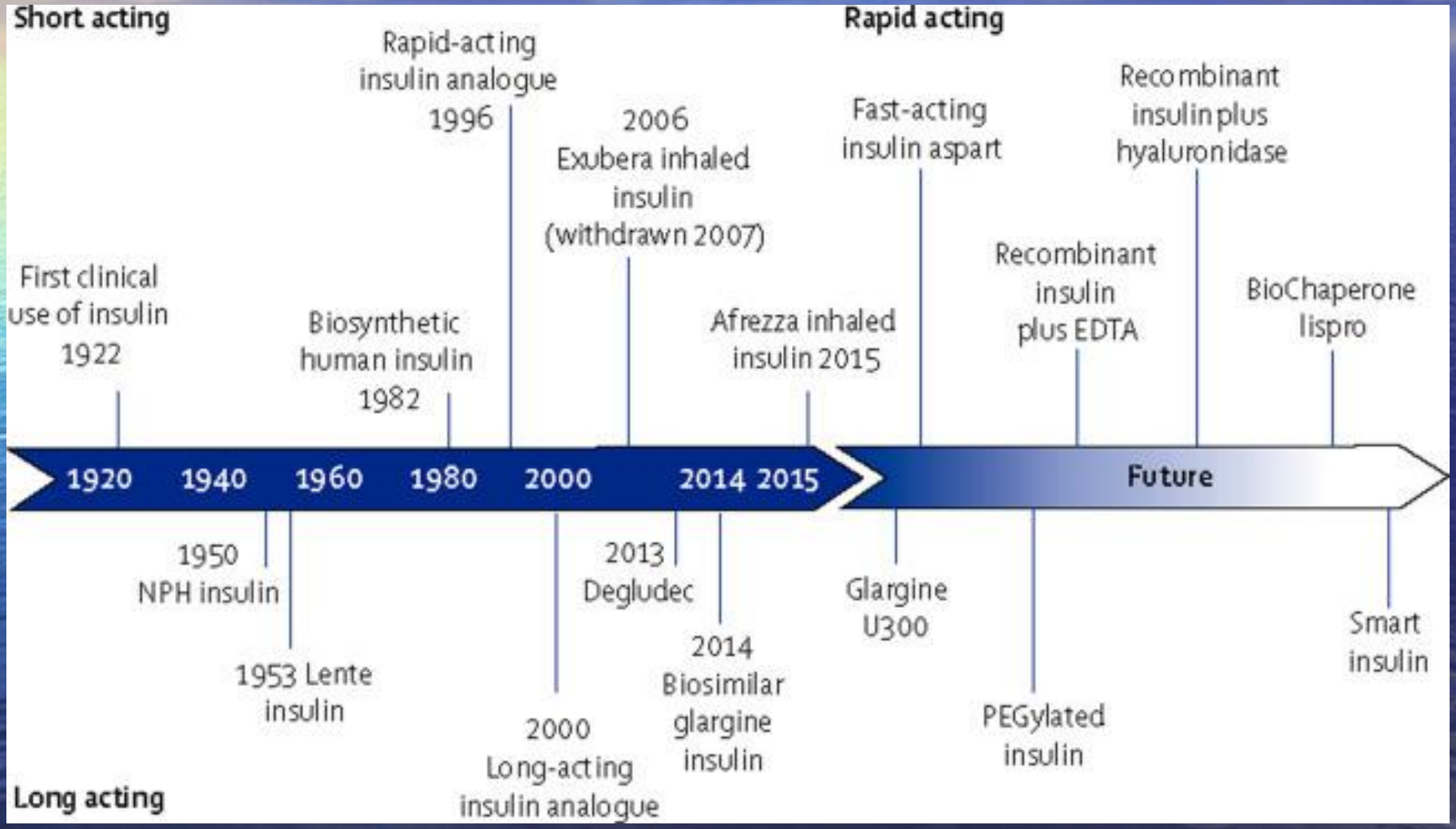
Faculty/Presenter Disclosure

- **Faculty: Richard Bebb**
- **Relationships with commercial interests:**
  - **None to report**

Learning Objectives:

- Insulins: Compare and Contrast
- Other Agents in type 1: Safe?
- Continuous Glucose Monitoring
- Pumps
  - Low glucose Suspend
  - Predictive Suspend
  - Hybrid

Insulin Developments



The long and the short of it

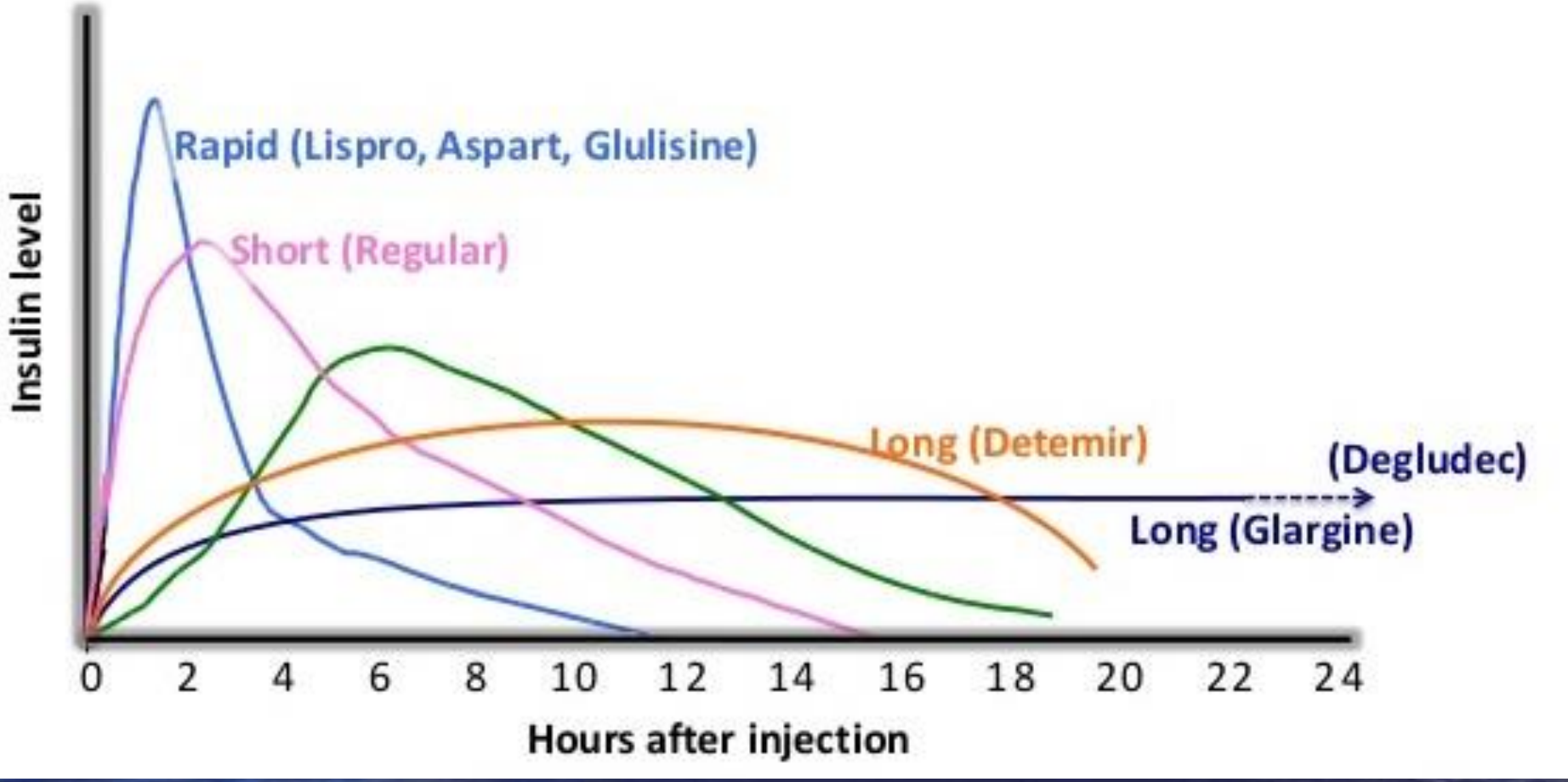
- The *very* long and smooth
  - *Glargine*
  - *U300* Glargine - Toujeo
  - Degludec
  - Subsequent biologic entry glargine
  - Detemir
- The *very* short and sharp
  - Inhaled insulin
  - Fiasp -insulin Asp with niacinamide (vitamin B3)

Basal Insulins Currently Available

	NPH Insulin	Insulin Glargine U-100	Insulin Detemir	Follow-on Insulin Glargine	Insulin Glargine U-300	Insulin Degludec
Insulin type	Human; intermediate-acting	Analog; long-acting	Analog; long-acting	Analog; long-acting	Analog; long-acting	Analog; long-acting
Onset	2-4 hours	1.3 hours	1.3 hours		6 hours	1 hour
Peak	4-10 hours	No pronounced peak	Relatively flat	No pronounced peak	Flat	Flat
Effective duration	10-16 hours	Up to 24 hours	Up to 24 hours	Up to 24 hours	≤36 hours	≤42 hours
Half-life	Unknown*	14 hours	5-7 hours		~23 hours	~25 hours
Time to steady-state	Unknown	2 days	2 days		4 days	2-3 days

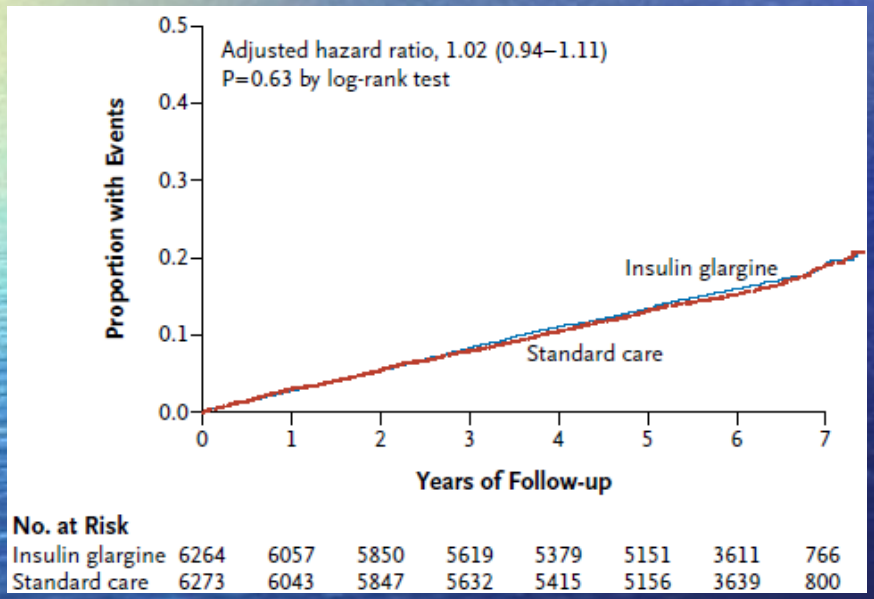
Porcellati F, et al. *Diabetes Care*. 2007;30(10):2447-2452. Lucidi P, et al. *Diabetes Care*. 2011;34(6):1312-1314. Niswender K. *Clin Diabetes*. 2009;27:60-68. Novolin N [package insert]. Indianapolis, IN: Eli Lilly & Co.; January 2017. Lantus [package insert] Bridgewater, NJ: sanofi-aventis US LLC; August 2015. Basaglar [package insert]. Indianapolis, IN: Eli Lilly & Co.; April 2017. Levemir [package insert]. Princeton, NJ: Novo Nordisk US; February 2015. Toujeo [package insert]. Bridgewater, NJ: sanofi-aventis US LLC; October 2015. Becker RH, et al. *Diabetes Care*. 2015;38:637-643. Tresiba [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; December 2016. Heise T, et al. *Diabetes Obes Metab*. 2012;14(10):944-950.

Long acting insulin

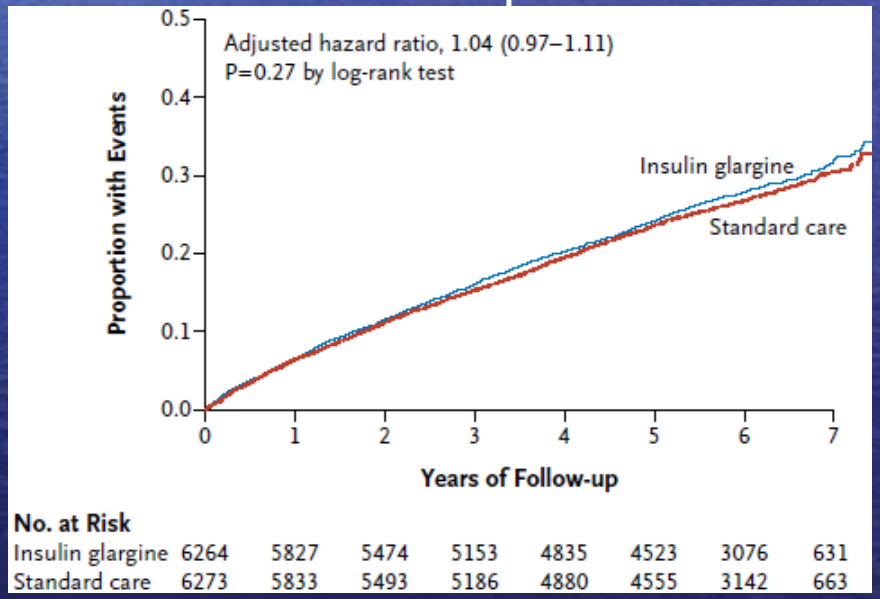


Cardiovascular Safety of Insulin Glargine U-100*: ORIGIN Study

Composite of MI, Stroke, CV Death



Composite of Revascularization or Heart Failure Hospitalization



*12,537 people with increased CV risk plus impaired fasting glucose, impaired glucose tolerance, or T2DM were randomized to insulin glargine U-100 vs standard care. Mean follow-up was 6.2 years.

ORIGIN Investigators. *N Engl J Med*. 2012;367():319-328.

Cardiovascular Safety of Insulin Degludec: DEVOTE Study

Outcome	Hazard Ratio	95% CI
Primary composite[1]	0.91	0.78-1.06
Expanded composite[2]	0.92	0.80-1.05
All-cause death	0.91	0.76-1.11
Non-CV death	0.84	0.60-1.16
CV death	0.96	0.76-1.21
Nonfatal MI	0.85	0.68-1.06
Nonfatal stroke	0.90	0.65-1.23
UA → hospitalization	0.95	0.68-1.31
Severe hypoglycemia	0.60	0.48-0.76
Nocturnal severe hypoglycemia	0.47	0.31-0.73

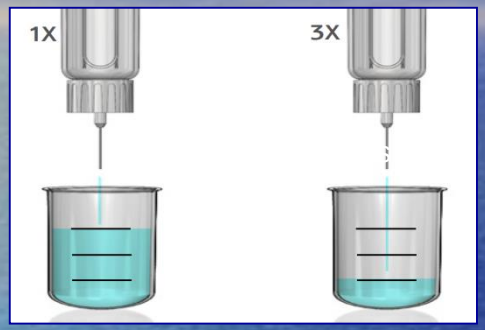
Degludec non-Inferior to glargine for major CV events

[1]CV death, nonfatal MI, nonfatal stroke
[2]CV death, nonfatal MI, nonfatal stroke, unstable angina leading to hospitalization

Marso SP, et al. *N Engl J Med*. 2017;doi:10.1056/NEJMoa1615692.

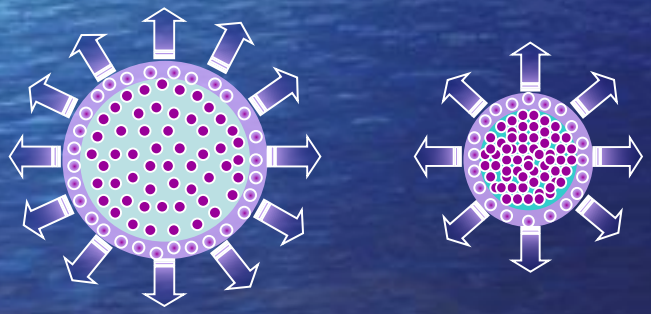
U300 Glargine (Toujeo)

1 **Reduction of volume by 2/3**



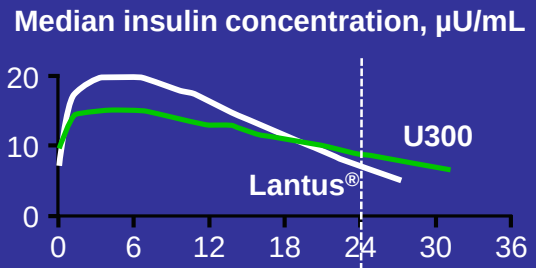
U100 U300

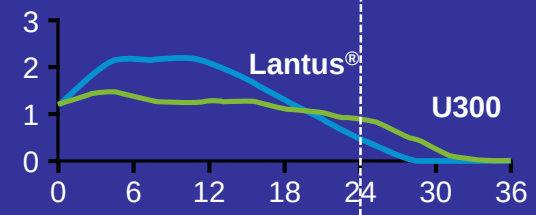
2 **Reduction of depot surface area by 1/2**

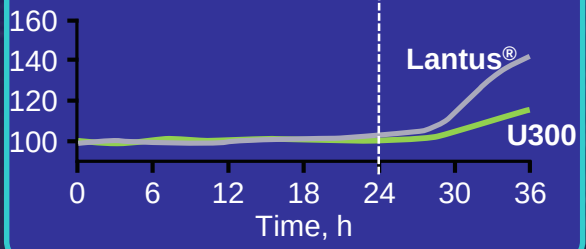


U100 U300

3 **More constant PK/PD profile**





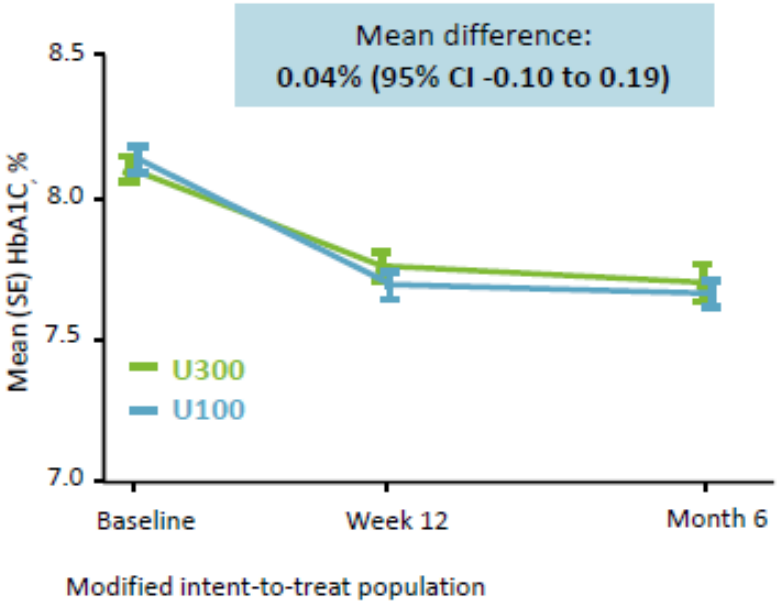


Jax T et al. Poster presented at EASD 2013; Abstract 1029.

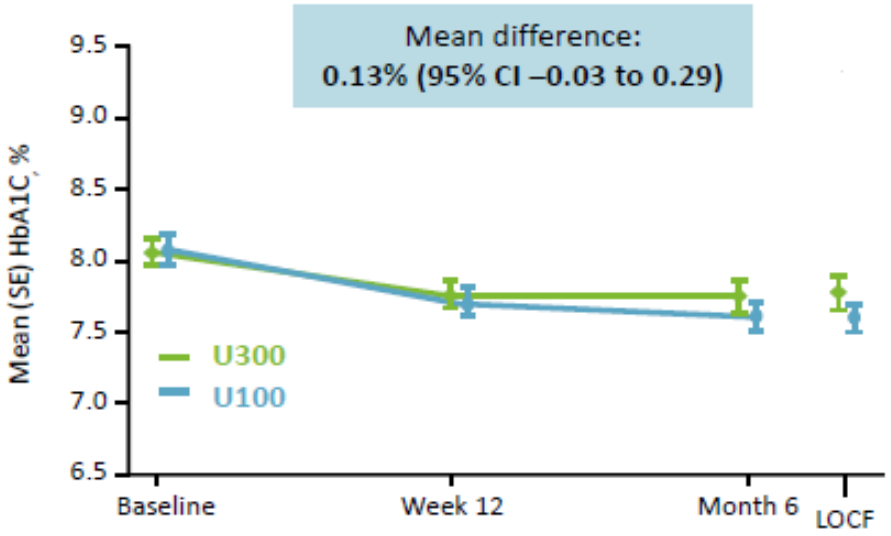
EDITION 4 & JP 1
6 Months

HbA1C

EDITION 4



EDITION JP 1



Modified intent-to-treat population

Primary endpoint of non-inferiority in change in HbA1C was met for each study

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 EASD 2014: P975

LOCF, last observation carried forward

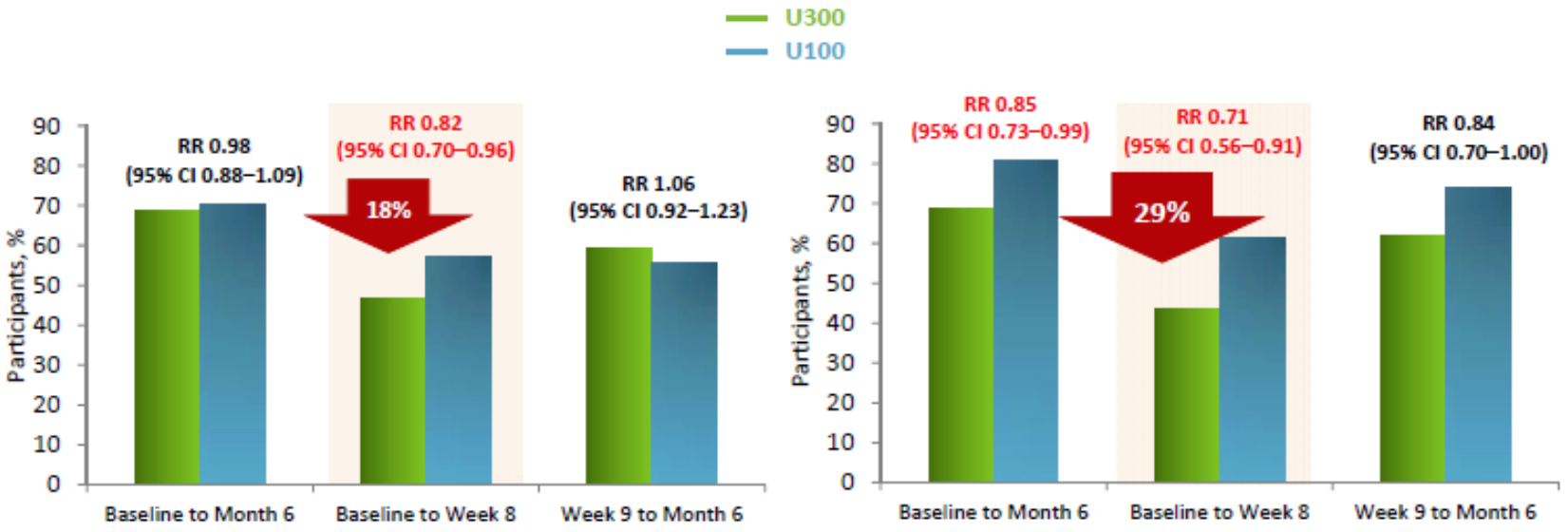
EDITION 4 & JP 1
6 Months

Nocturnal Hypoglycemia

Participants (%) with ≥1 nocturnal*, confirmed¶ and/or severe hypoglycemia

EDITION 4

EDITION JP 1

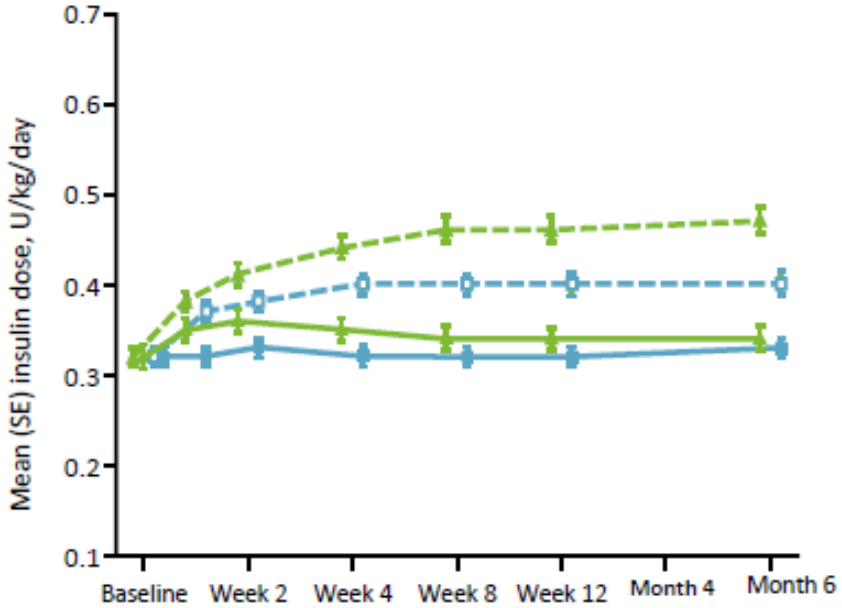


Both studies demonstrated reduced nocturnal hypoglycemia during the first 8 weeks.

* Nocturnal = 00:00–05:59 h
¶ Confirmed ≤3.9 mmol/L
RR, relative risk

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 EASD 2014: P975

Daily Insulin Dose



Mealtime insulin (U300)
Mealtime insulin (U100)
Basal insulin (U300)
Basal insulin (U100)

U300 vs. U100 change in dose from baseline (U/kg at month 6)
U300: **+0.19**
U100: **+0.10**

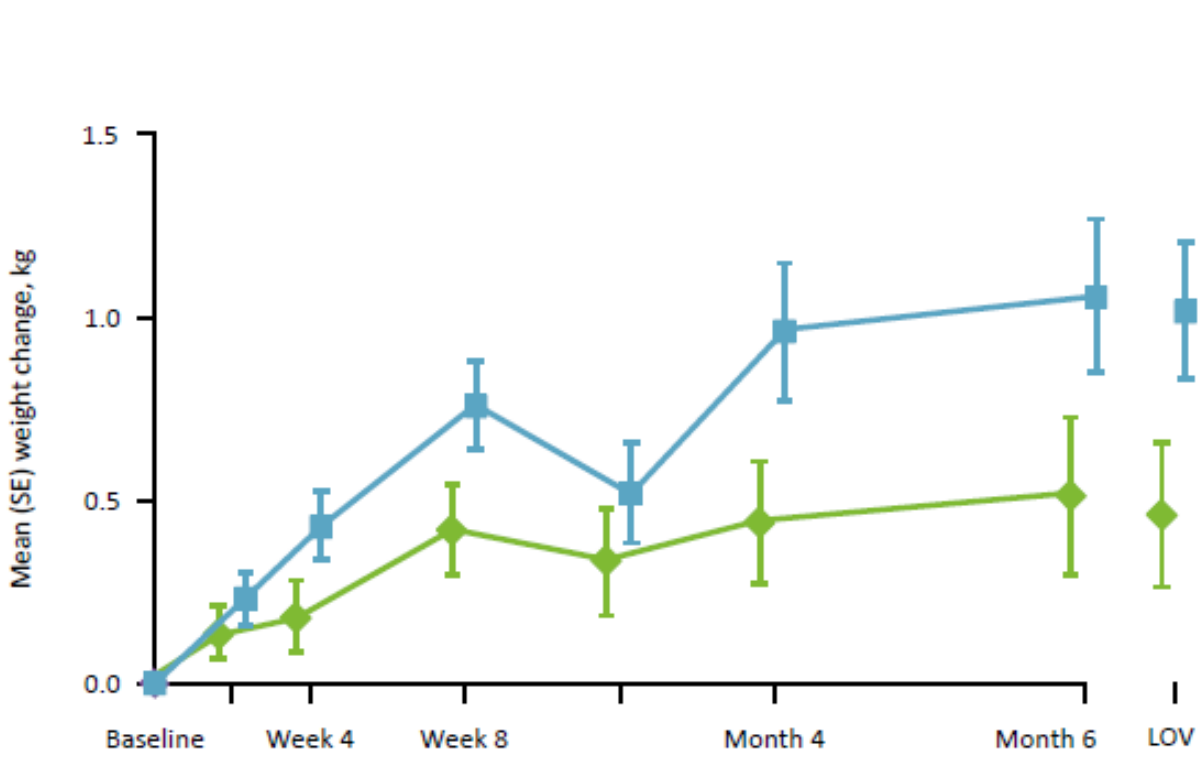
Home P *et al*. Abstract presented at EASD 2014: 0148; Bajaj H *et al*. Poster presented at CDA 2014: P112
Matsuhisa M *et al*. Poster presented at EASD 2014: P975

LOCF, last observation carried forward

EDITION 4

6 Months

Weight Change



Mean difference for U300 vs. U100 at Month 6:
-0.56 kg (95% CI -1.09 to -0.03)
P=0.037

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 EASD 2014: P975

LOV, last on-treatment value

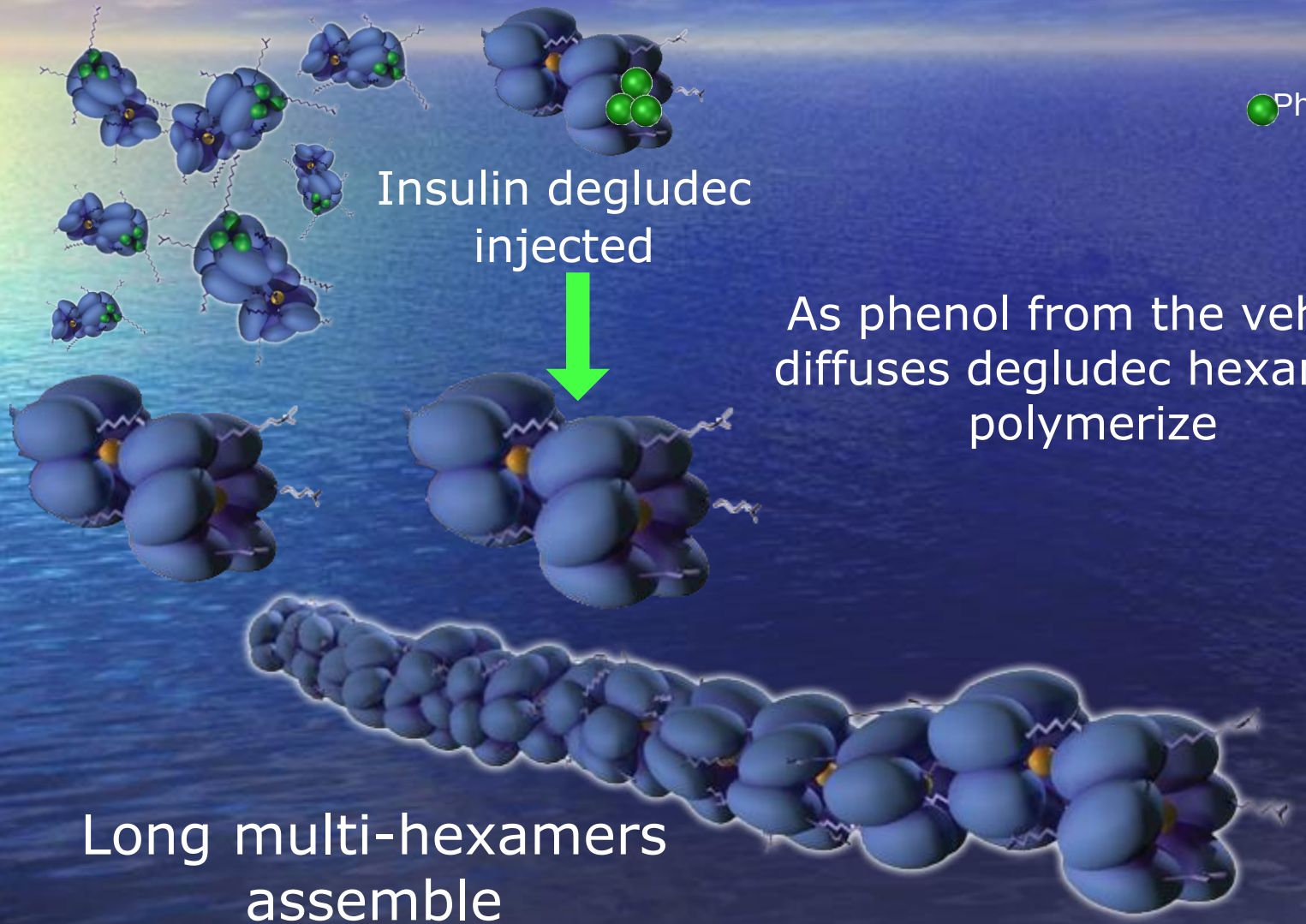
EDITION 4

Summary

In people with T1D:

- U300 was as effective as U100 in improving glycemic control
- Insulin dose requirement was greater for U300 than U100
- Rate and % of participants **with hypoglycemia did not differ** between groups for any time (24 h) or nocturnal hypoglycemia over the **6-month period**
  - **Nocturnal hypoglycemia** was lower with U300 **during the first 8 weeks** of treatment, when most of the up-titration of the basal insulin dose occurred
- **Less weight gain** was observed with U300 compared with U100
- Timing of U300 or U100 injections (morning or evening) did not show any significant differences in glucose-lowering efficacy or hypoglycemia

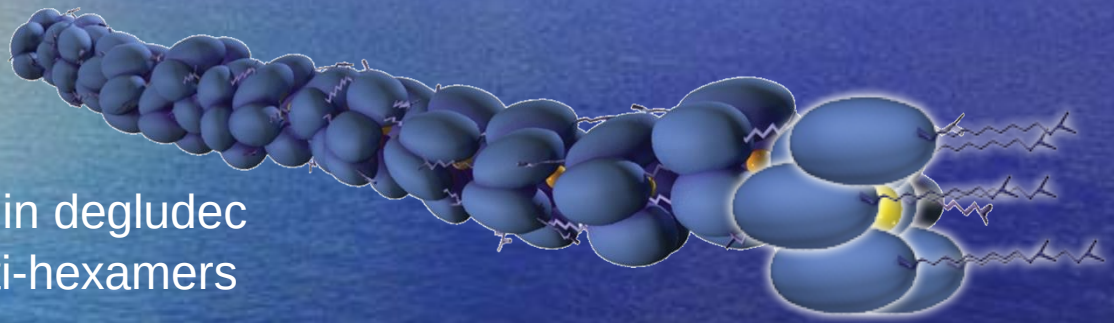
Insulin degludec forms a subcutaneous depot



Insulin degludec: slow release

Subcutaneous depot

Zn^{2+}

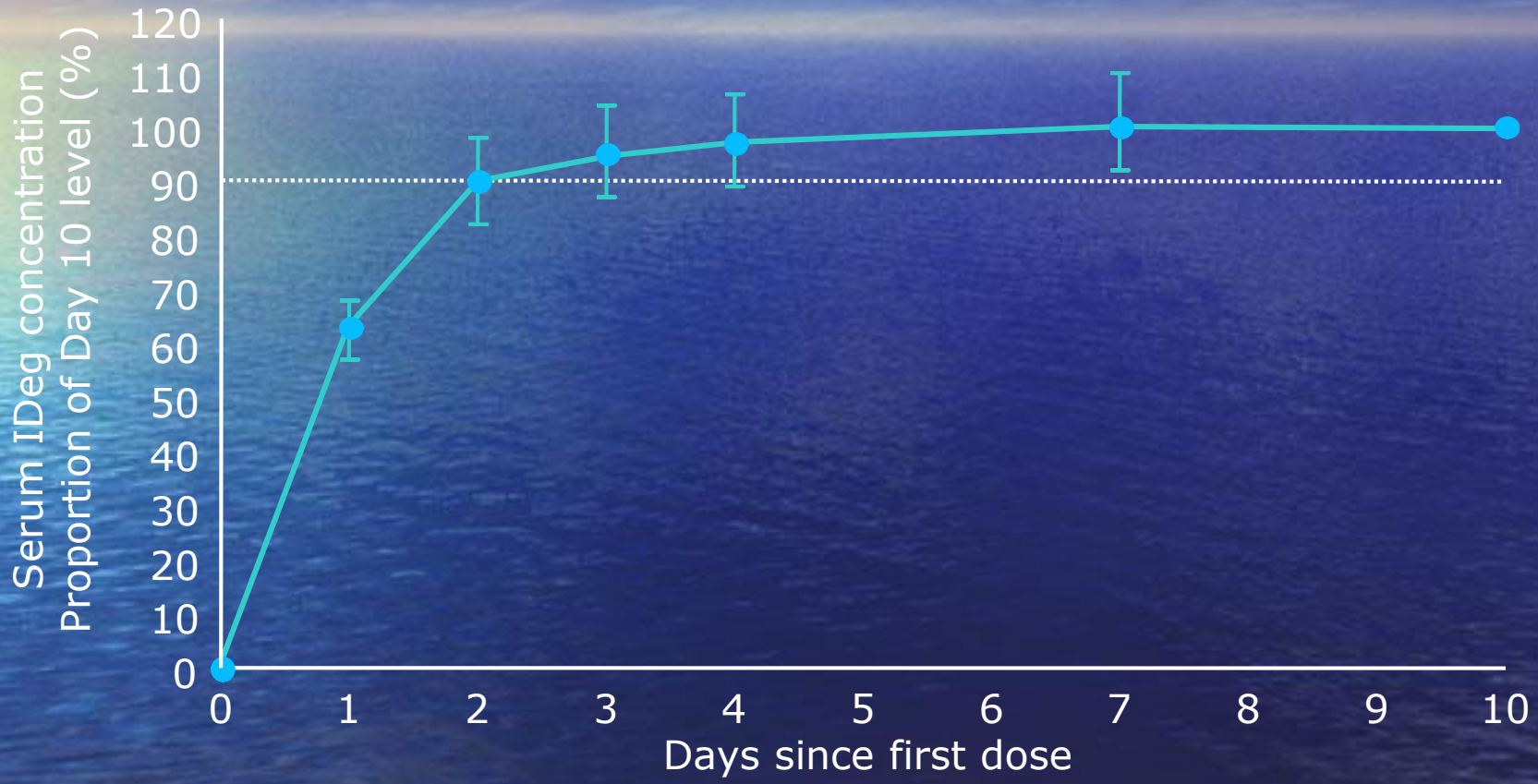


Insulin degludec multi-hexamers

Zinc diffuses slowly causing individual hexamers to disassemble, releasing monomers

Monomers are absorbed from the depot into the circulation

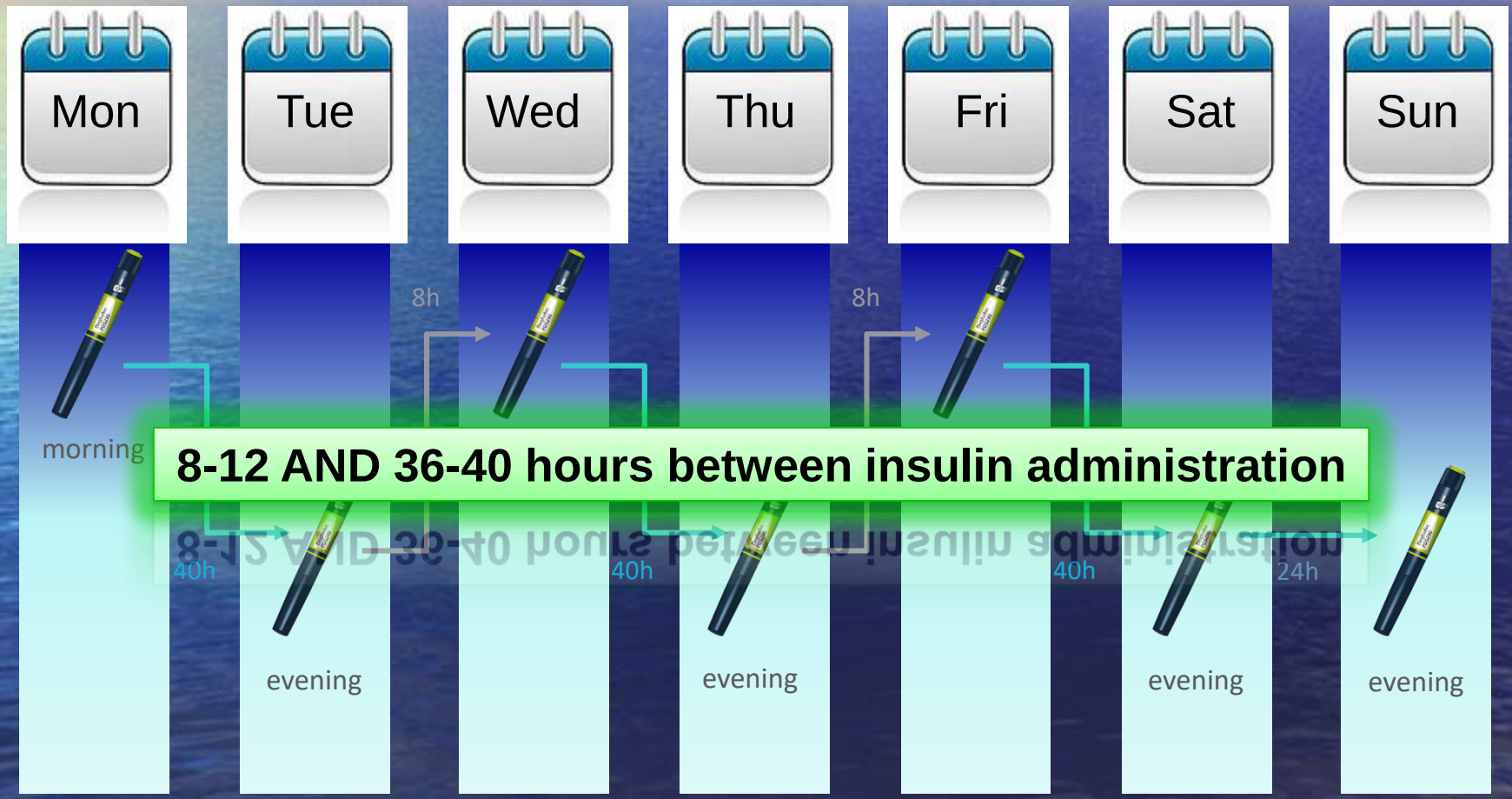
Insulin degludec steady state is reached within 2–3 days of once-daily dosing



Relative serum IDeg trough concentrations during initiation of once-daily (0.4 U/kg) dosing in patients with T1DM

Heise T *et al. IDF 2011 21st World Congress Abstract Book.* IDF: Dubai, 2011; Poster 1453

Timing of flexible degludec administration



Flexible Dosing with Degludec

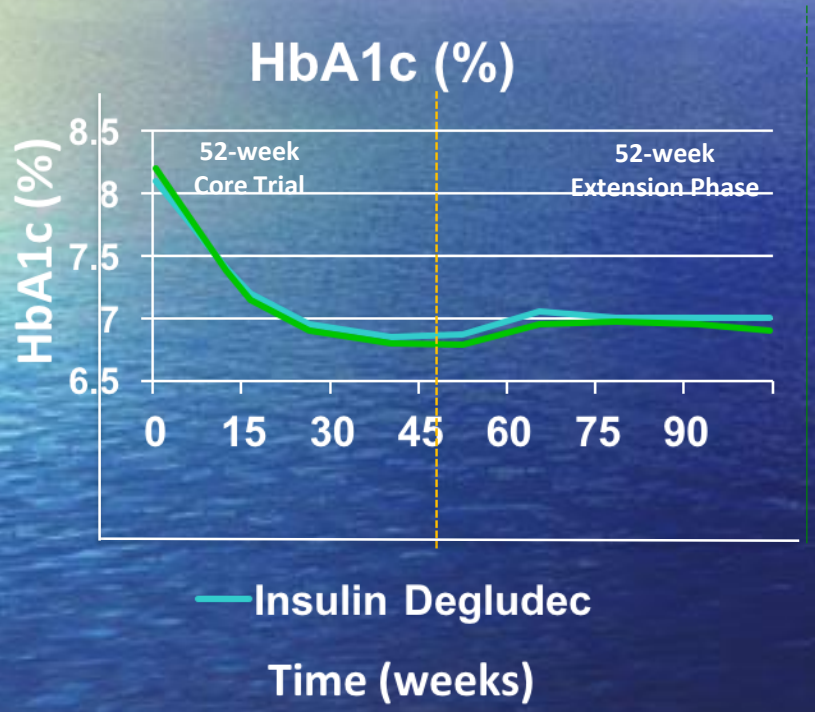
- 26-wk randomized, open-label, treat-to-target trial (N=687)
- Glargine once daily at same time each day
- Degludec once daily
  - Fixed: same time each day
  - Flexible: schedule to create 8-40 hour dosing intervals

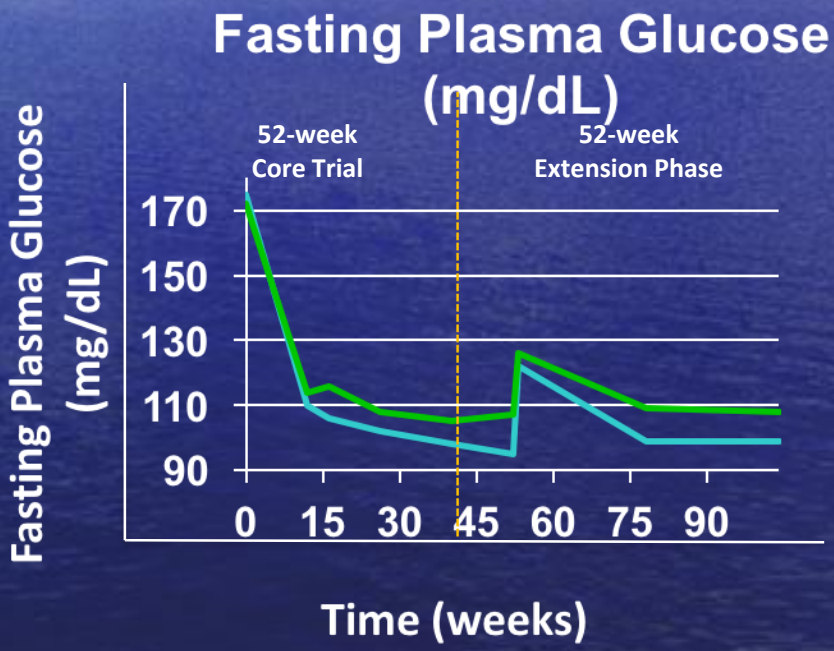
Change from baseline* to 26 weeks	Degludec		Glargine
	Flexible	Fixed	
HbA1c (%)	-1.28	-1.07	-1.26
FPG (mg/dL)	-58	-54	-50
Confirmed or severe hypoglycemia (events/patient-year)	3.6	3.6	3.5
Confirmed or severe nocturnal hypoglycemia (events/patient-year)	0.6	0.6	0.8

*HbA1c 8.4-8.5% at baseline

Meneghini L, et al. *Diabetes Care*. 2013;36:858-864.

Insulin Degludec vs Insulin Glargine U-100: Glycemic Efficacy





N=725

Rodbard HW, et al. *Diabet Med*. 2013;30:1298-1304.

Hypoglycemia with Degludec and Glargine U-300 vs Glargine U-100

Meta-analyses of phase 3 clinical studies in T2DM

	Degludec[1]	Glargine U-300[2]
# Studies	5	3
# Participants	3372	2496
Definition of confirmed hypoglycemia	<56 mg/dL and severe	≤70 mg/dL or severe
Anytime events [Rate ratio vs glargine U-100 (95% CI)]	0.83 (0.74-0.94)	0.86 (0.77-0.97)
Nocturnal events [Rate ratio vs glargine U-100 (95% CI)]	0.68 (0.57-0.82)	0.69 (0.57-0.84)

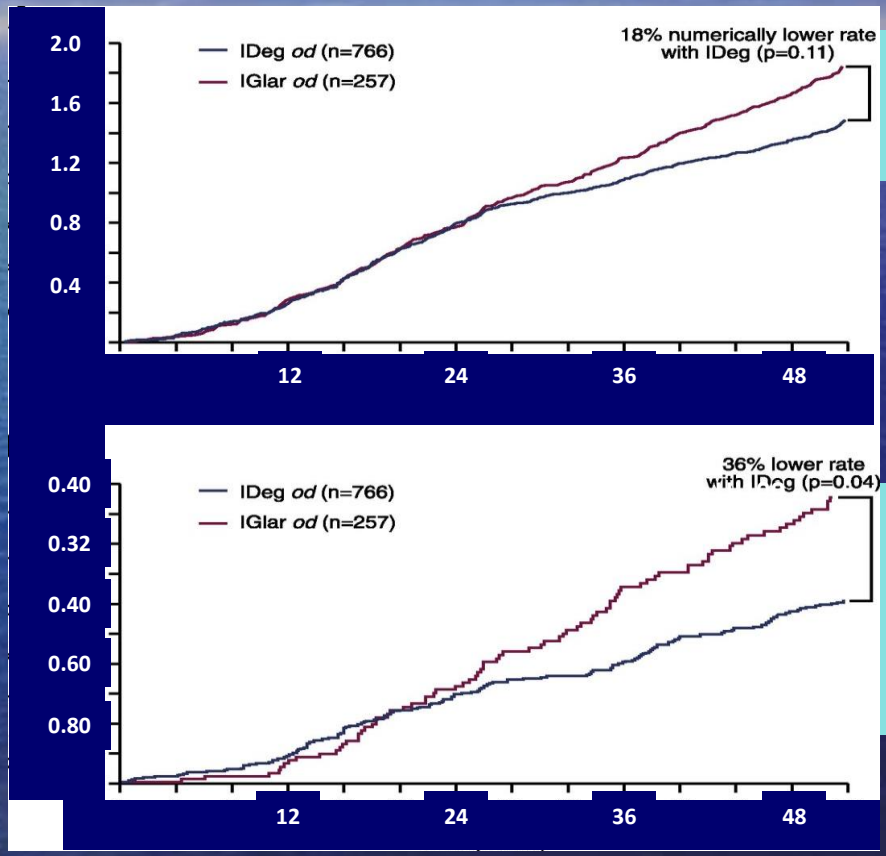
With both insulins, ~15% fewer overall and ~30% fewer nocturnal events vs glargine U-100

1. Ratner RE, et al. *Diabetes Obes Metab*. 2013;15(2):175-184.
2. Ritzel R, et al. *Diabetes Obes Metab*. 2015;17(9):859-867.

Insulin Degludec vs Insulin Glargine U-100

Cumulative hypoglycemic events (confirmed <56 mg/dL)

Anytime events/patient



18% lower with degludec *P*=0.11

Nocturnal events/patient

36% lower with degludec *P*=0.04

1023 insulin-naïve patients with T2DM

Zinman B, et al. Diabetes Care. 2012;35:2464-2471.

Imitation is the sincerest form of flattery

- Subsequent entry biologic
  - Lilly insulin glargine

What is a “subsequent entry biologic”??

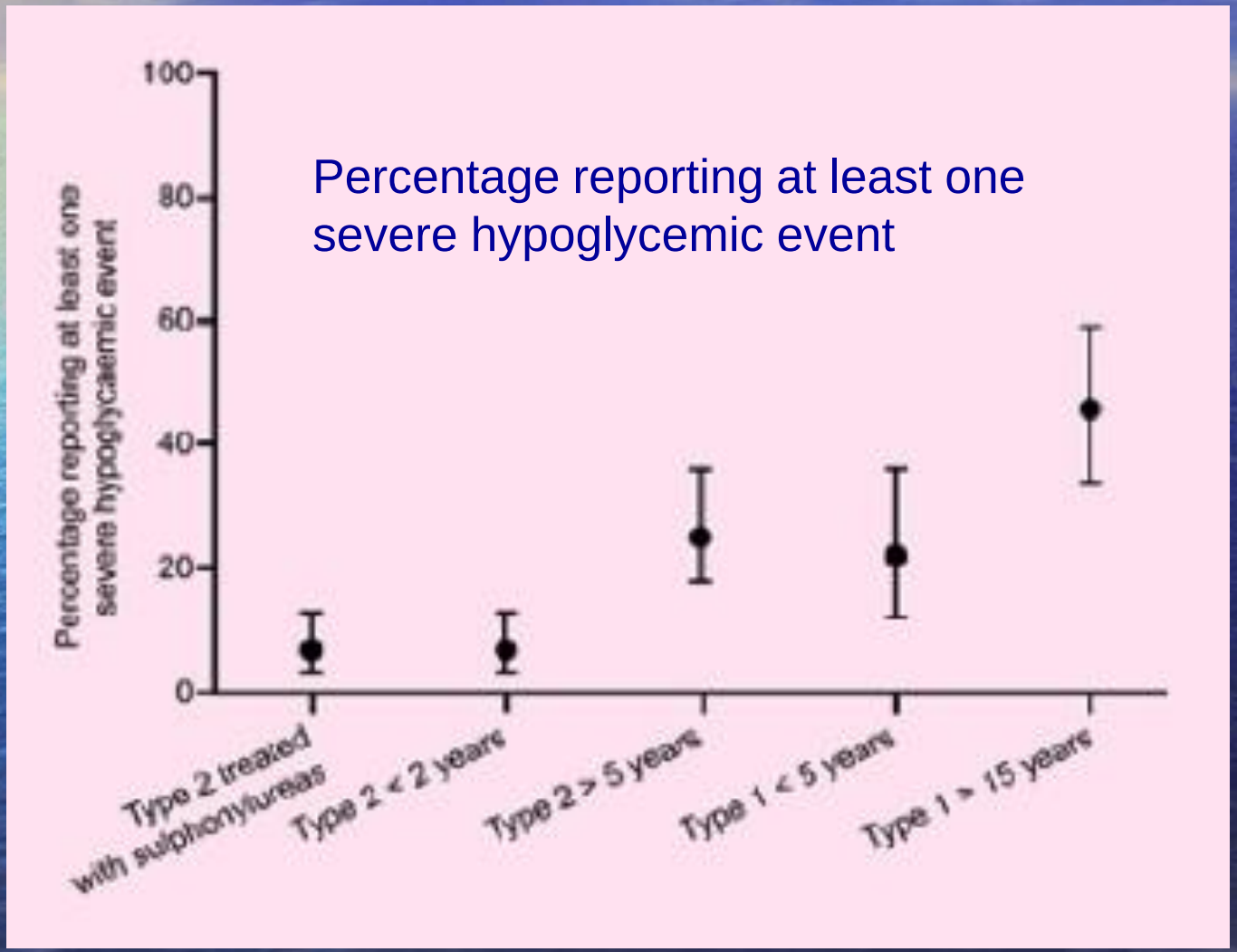
- a biologic product that would be similar to and would enter the market subsequent to an approved innovator biologic
- other terms used include "similar biological medicinal products" in the European Union and "follow-on protein products" in the United States

The very short

- Ideal bolus insulin:
  - Faster onset
  - More rapid clearance

Increasing attention to hypoglycemia

- Hypoglycemia varies by disease type and stage



Amiel. Diabetic Medicine 2008; 25: 245-254

afrezza

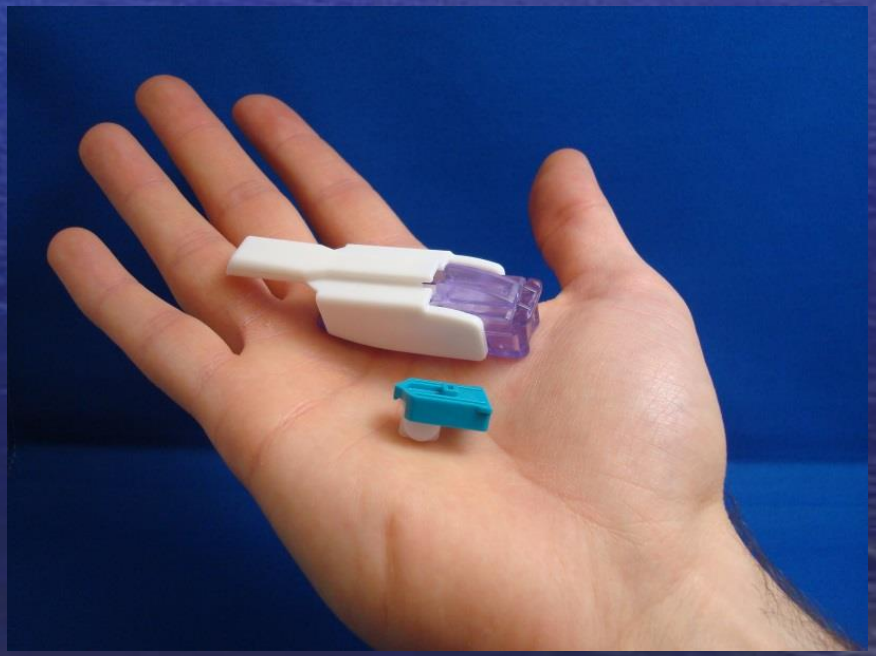
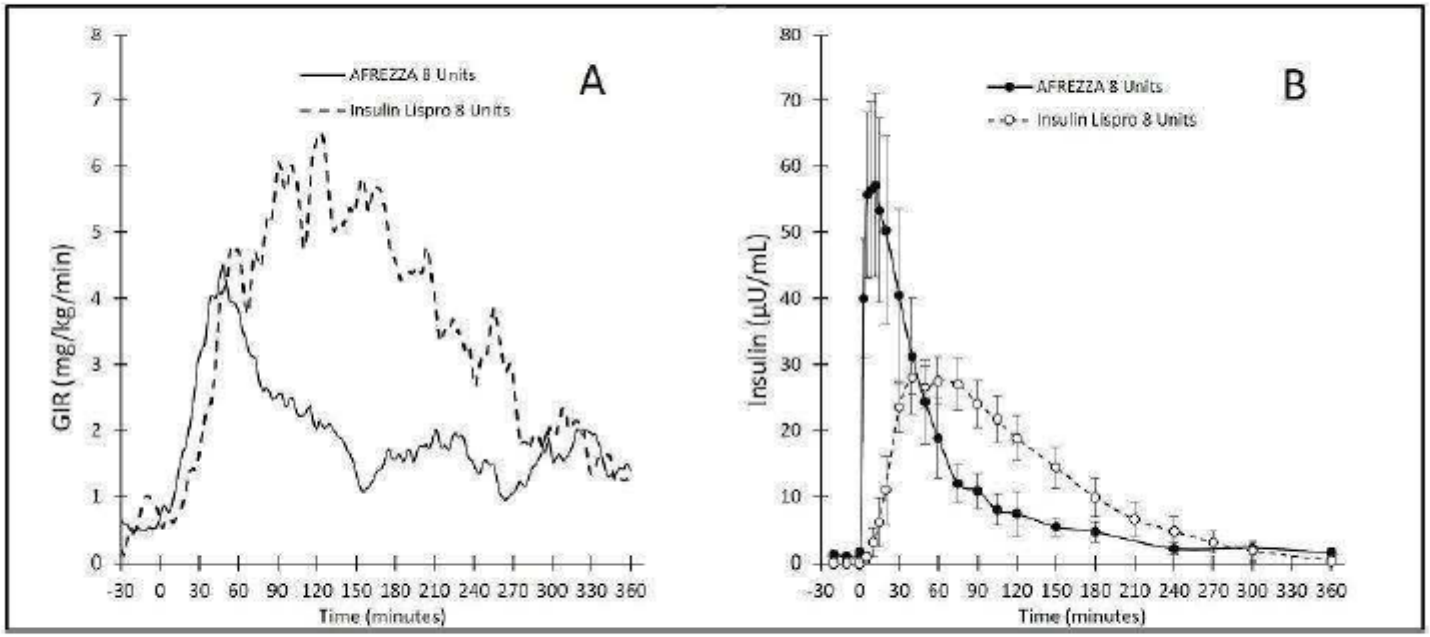


Figure 3. Baseline-Corrected Glucose Infusion Rate (A) and Baseline-Corrected Serum Insulin Concentrations (B) after Administration of AFREZZA or Subcutaneous Insulin Lispro in Type 1 Diabetes Patients*



*Despite the faster absorption of insulin (PK) from Afrezza, the onset of activity (PD) was comparable to insulin lispro.

Afrezza product monograph: afrezza.com

Table 1. Common Adverse Reactions in Patients with Type 2 Diabetes Mellitus (excluding Hypoglycemia) Treated with AFREZZA

	Placebo* (n = 290)	AFREZZA (n = 1991)	Non-placebo comparators (n=1363)
Cough	19.7%	25.6%	5.4%
Throat pain or irritation	3.8%	4.4%	0.9%
Headache	2.8%	3.1%	1.8%
Diarrhea	1.4%	2.7%	2.2%
Productive cough	1.0%	2.2%	0.9%
Fatigue	0.7%	2.0%	0.6%
Nausea	0.3%	2.0%	1.0%

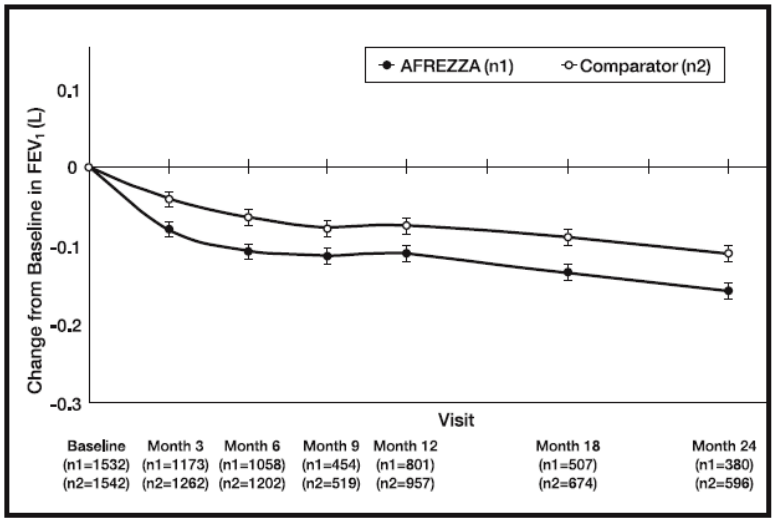
*Carrier particle without insulin was used as placebo *[see Description (11)]*.

Afrezza product monograph: afrezza.com

WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE

- Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA. *[see Warnings and Precautions (5.1)]*.
- AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD. *[see Contraindications (4)]*.
- Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV_1) to identify potential lung disease in all patients *[see Dosage and Administration (2.5), Warnings and Precautions (5.1)]*.

Figure 2. Mean (+/-SE) Change in FEV_1 (Liters) from Baseline for Type 1 and Type 2 Diabetes Patients



Afrezza product monograph: afrezza.com

The FDA is requiring the following post-marketing studies for Afrezza:

- a clinical trial to evaluate pharmacokinetics, safety and efficacy in pediatric patients;

- a clinical trial to evaluate the potential risk of pulmonary malignancy with Afrezza (this trial will also assess cardiovascular risk and the long-term effect of Afrezza on pulmonary function);

- two pharmacokinetic-pharmacodynamic euglycemic glucose-clamp clinical trials, one to characterize dose-response and one to characterize within-subject variability.

Fiasp Insulin

Released March 2017 Canada
Sept 2017 USA

Insulin aspart with nicotinamide keeps insulin in monomers
Faster absorption (inject 2 min prior to eating)
Head to head study with Insulin Aspart in type 1 DM:

- Better pc sugar control
- Trend to reduction of HgA1c in some studies
- Non - inferior with regards hypoglycemia

May have a role as insulin of choice in insulin pumps?

Diabetes Care. 2017 Jul;40(7):951-957
Diabetologia 2016; 59(Suppl. 1):S1-S581

SGLT2 Agents for type 1??

1) EMPAREG CV event reduction in type 2 DM

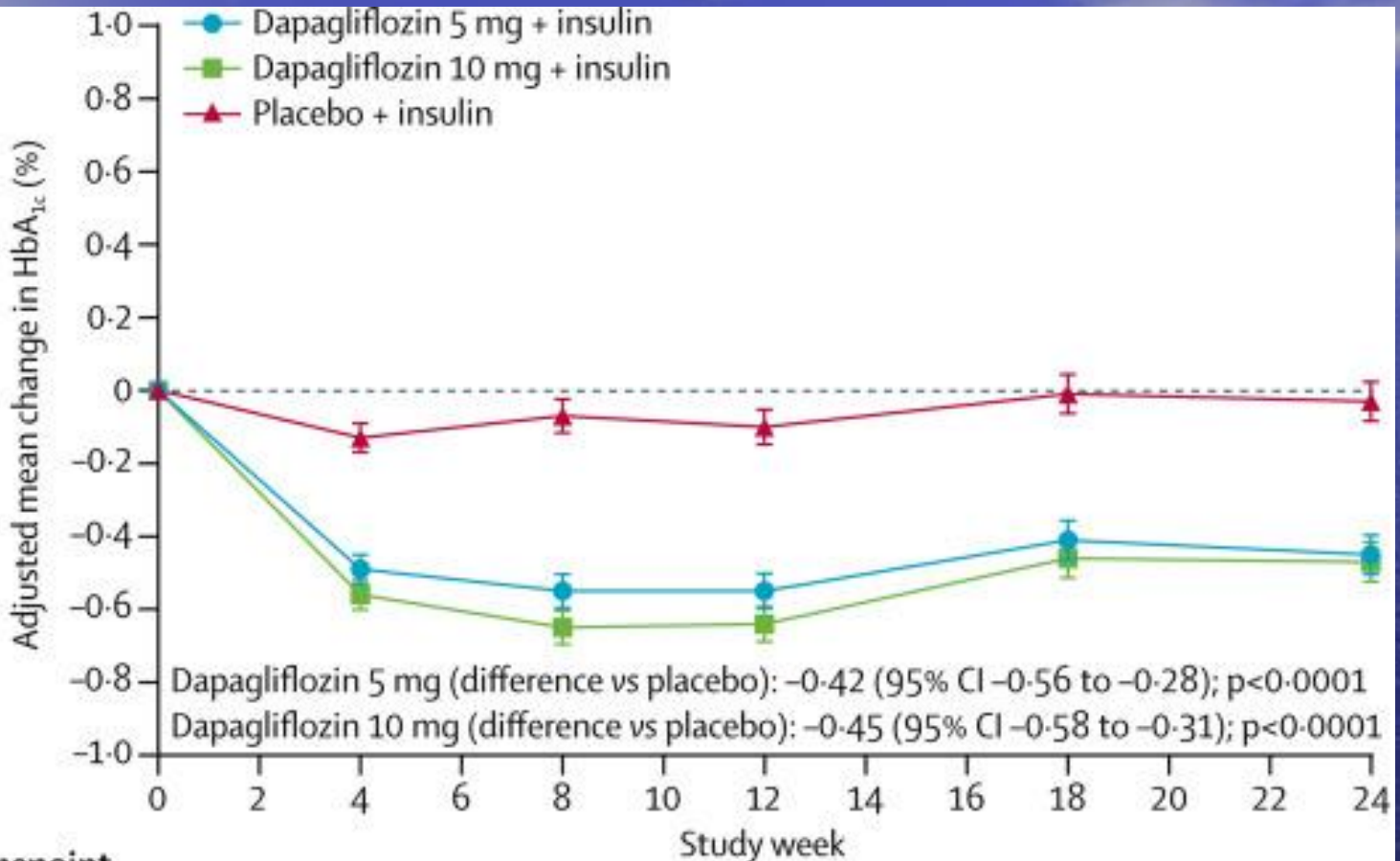
2) SGLT2 agents work independently from insulin

DEPICT: dapagliflozin for T1DM

- Population: 778 DM1, mean A1c 8.5%
- Intervention: dapagliflozin vs placebo
- Outcome: A1c at 24 weeks
- Both dapa doses reduced A1c by 0.4%, lower TDD insulin by 9-13%; no increase in severe or overall hypos, DKA in 4, 5, and 3 per grp

Dandona P, Lancet Diab Endo, Sept 14, 2017

Reduction in HgA1c

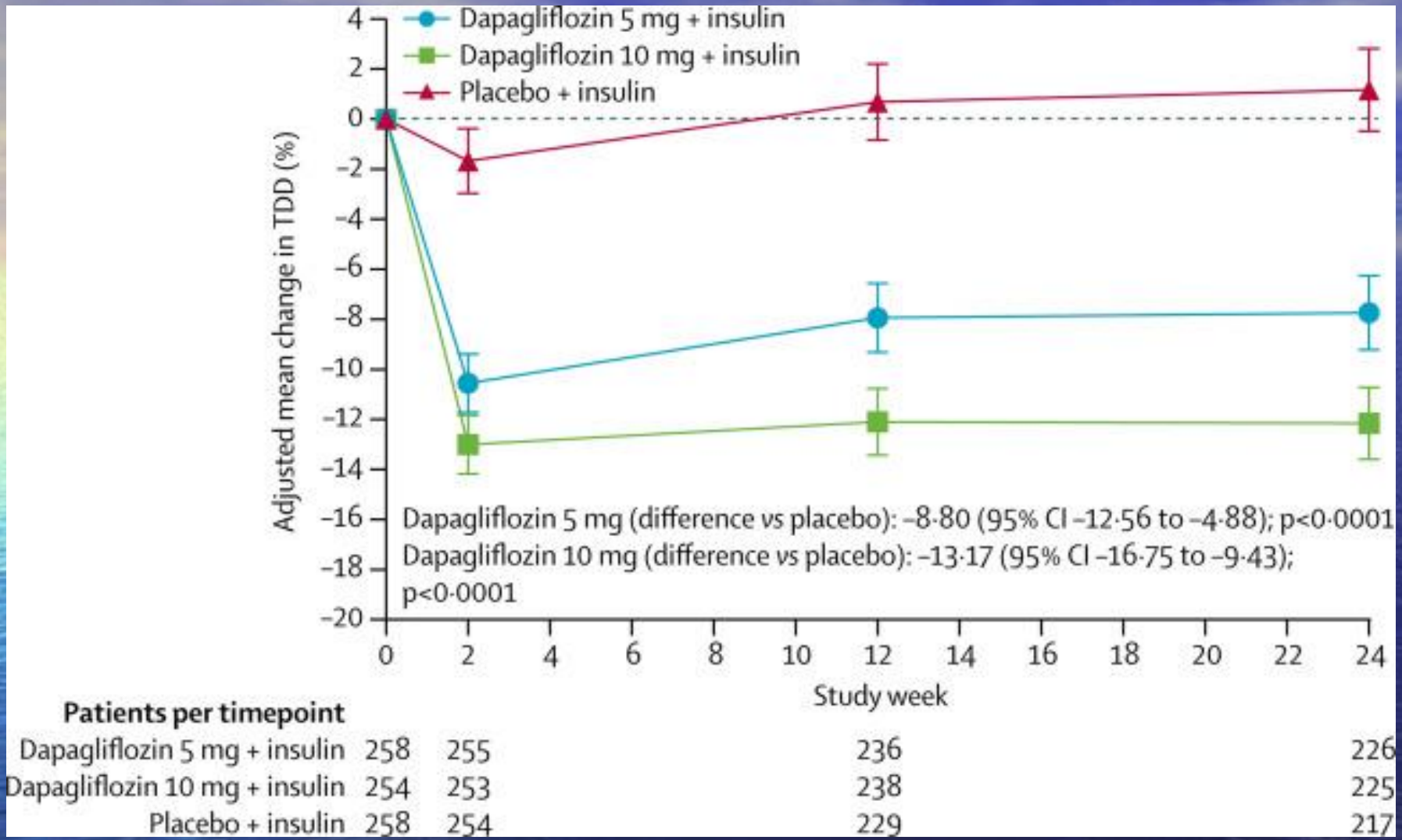


Patients per timepoint

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

The Lancet Diabetes & Endocrinology DOI: (10.1016/S2213-8587(17)30308-X)

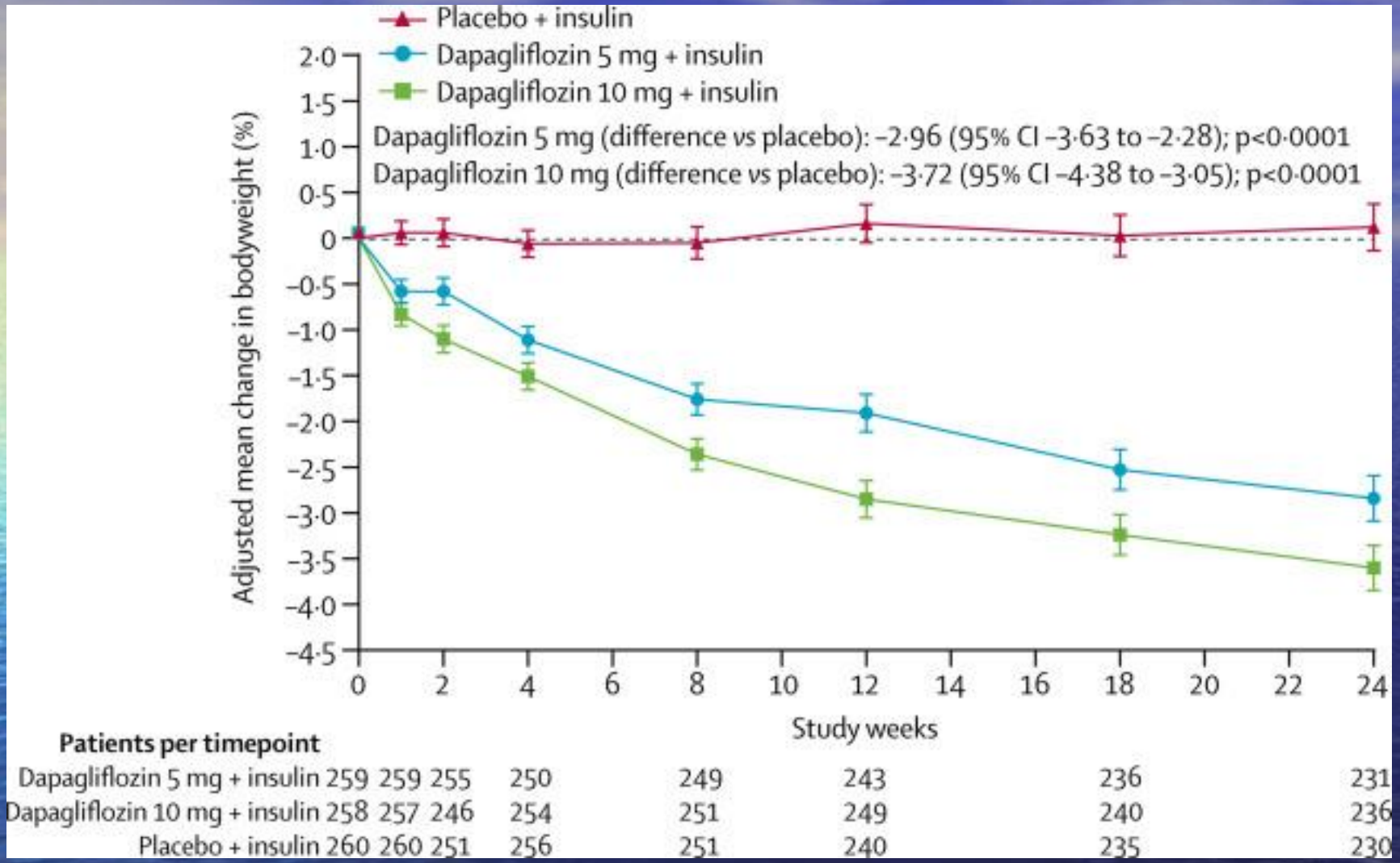
Total Daily Insulin Dose



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

The Lancet Diabetes & Endocrinology DOI: (10.1016/S2213-8587(17)30308-X)

Body Weight

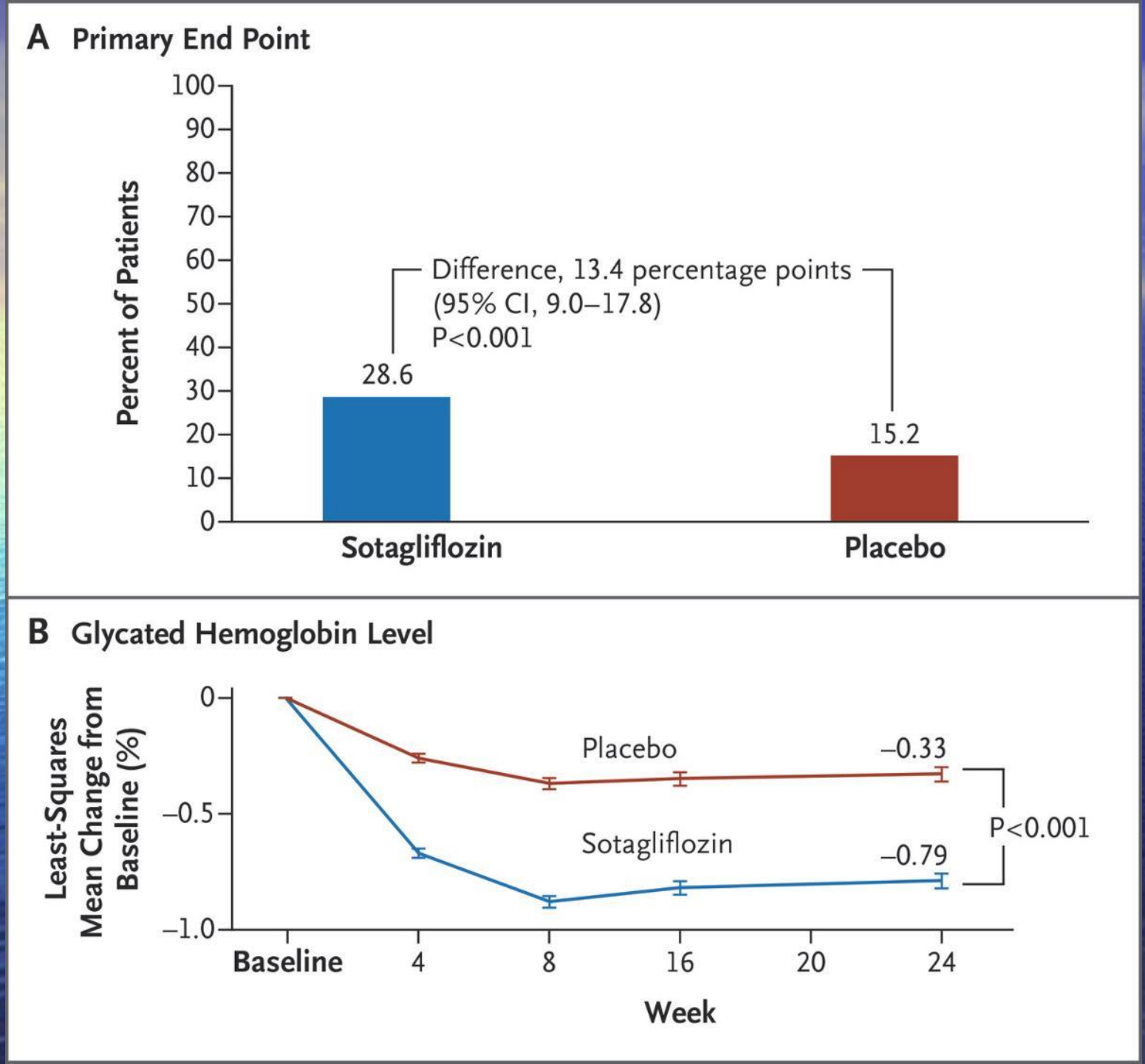


The Lancet Diabetes & Endocrinology DOI: (10.1016/S2213-8587(17)30308-X)

INTANDEM3

- Population: 1402 DM1
- Intervention: sotagliflozin 400mg OD vs placebo
- Outcome:A1c<7 at week 24 w/o hypo or DKA
- Result: 29 vs. 15%, P<0.001.
- Notes: higher severe hypos (3 vs. 2.4%) and DKA (3 vs 0.6%) in sotagliflozin group despite ketone monitoring

Garg S. NEJM Sept 13 2017



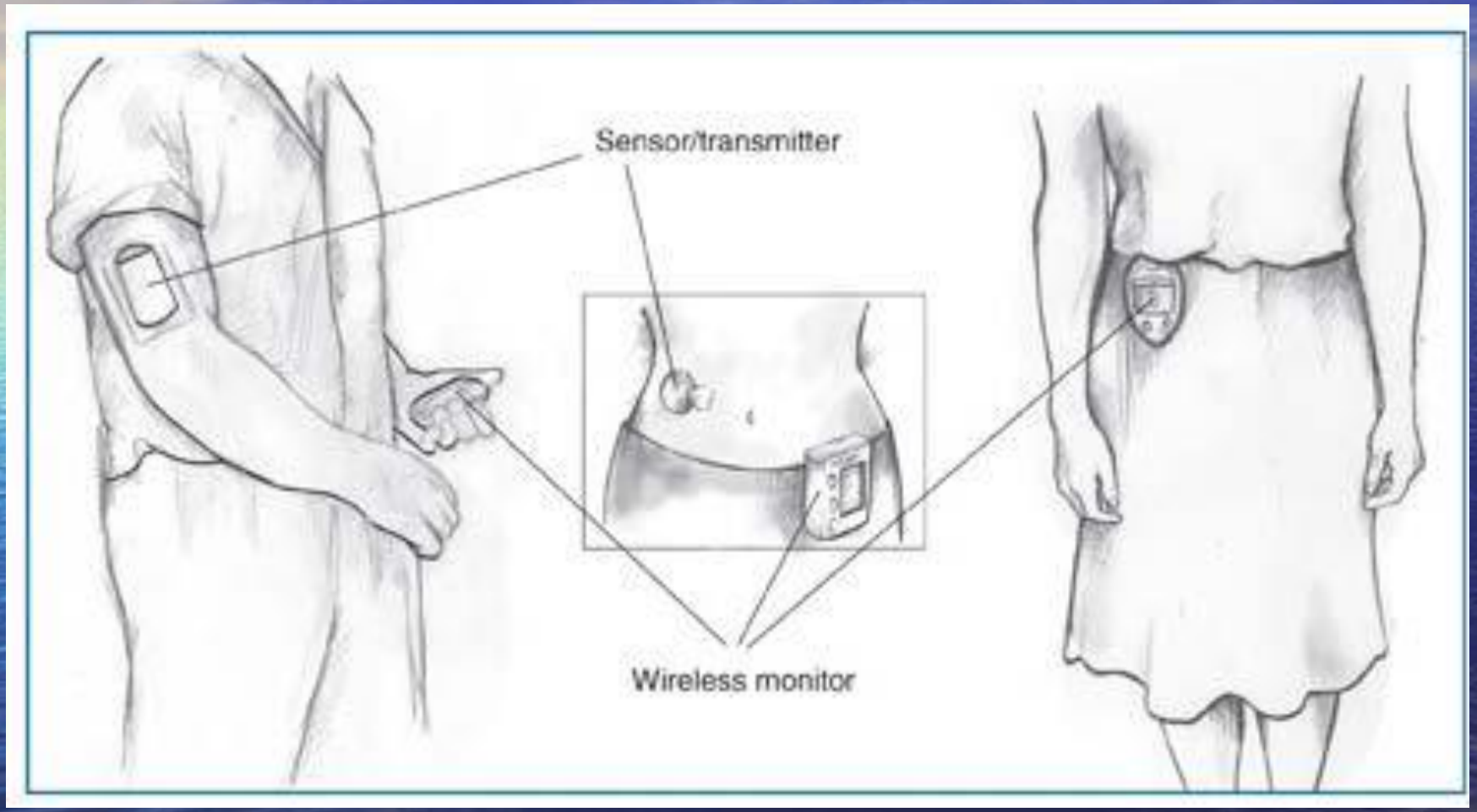
Primary Endpoint HgA1c <7

American Association
of Clinical Endocrinologists (AACE)
American College of Endocrinology (ACE)

2016 Outpatient Glucose Monitoring Consensus Statement

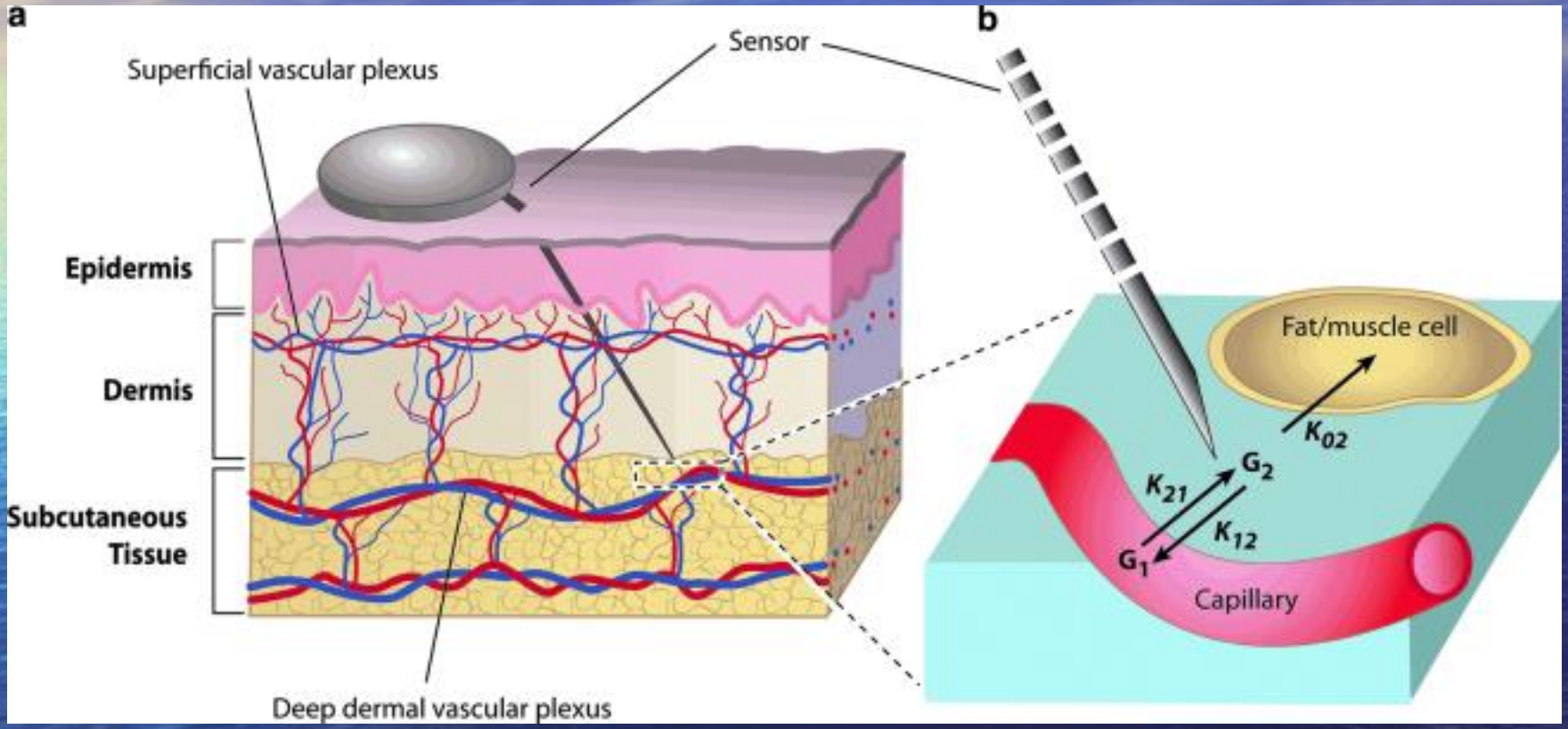
ENDOCRINE PRACTICE Vol. 21 No. 2 February 2016 Pages 231-261.

Continuous Glucose Monitoring



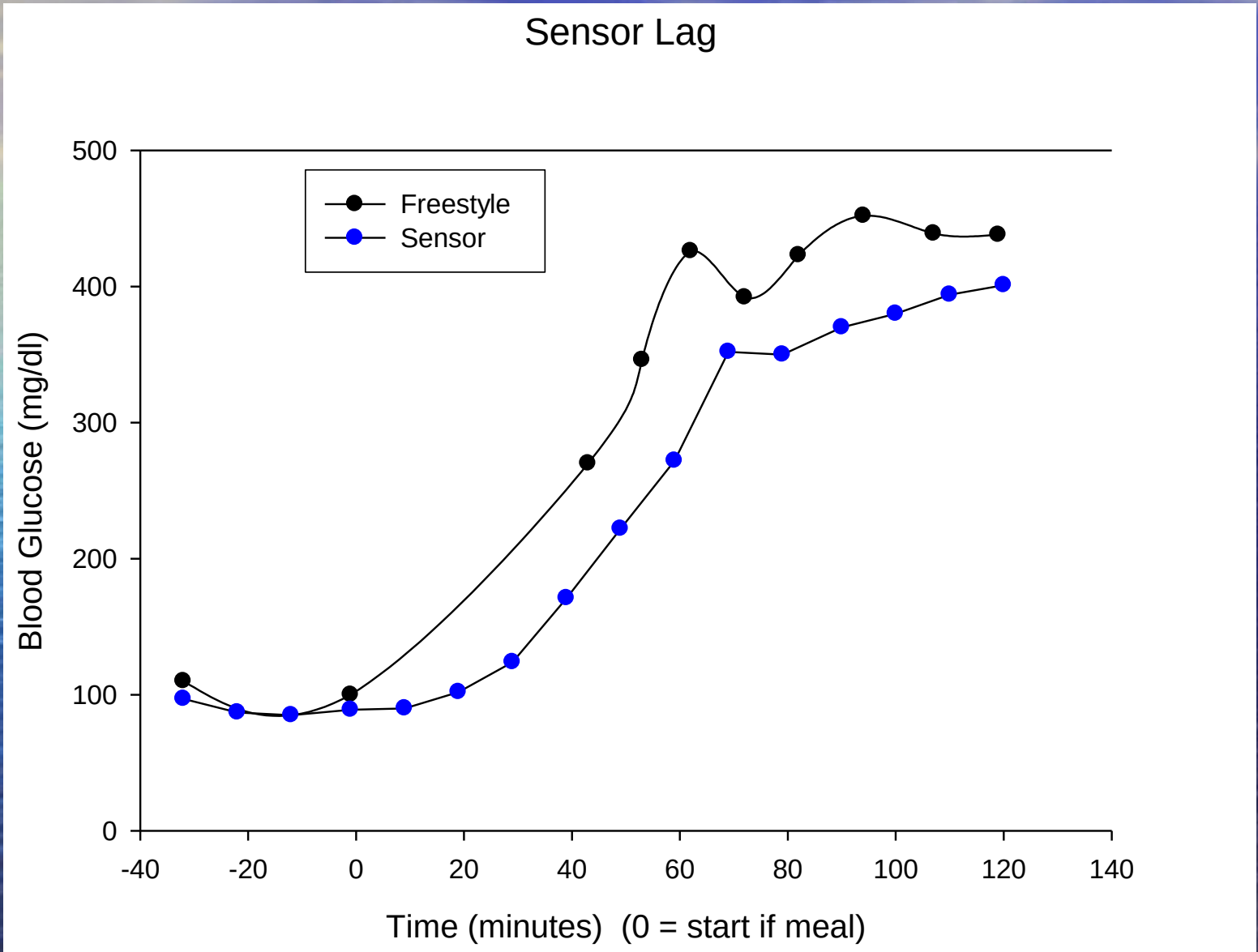
Sensor/transmitter plus Monitor (may be a watch or cell phone)

The Sensor is in Interstitial Tissue so it relies on diffusion



The diffusion imparts a delay in the detecting of true capillary or venous blood glucose

Sensor lag is approximately 15-20 minutes

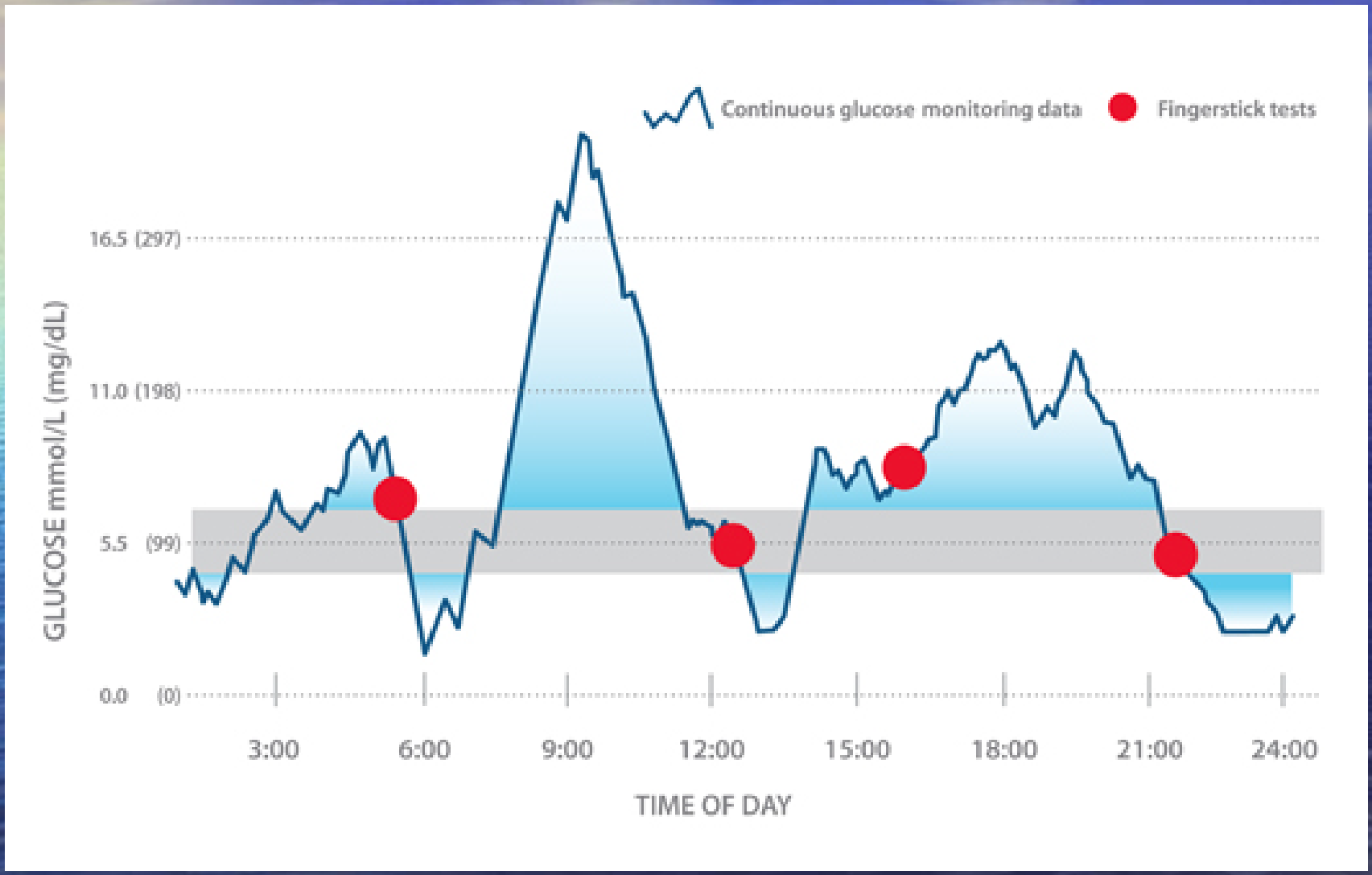


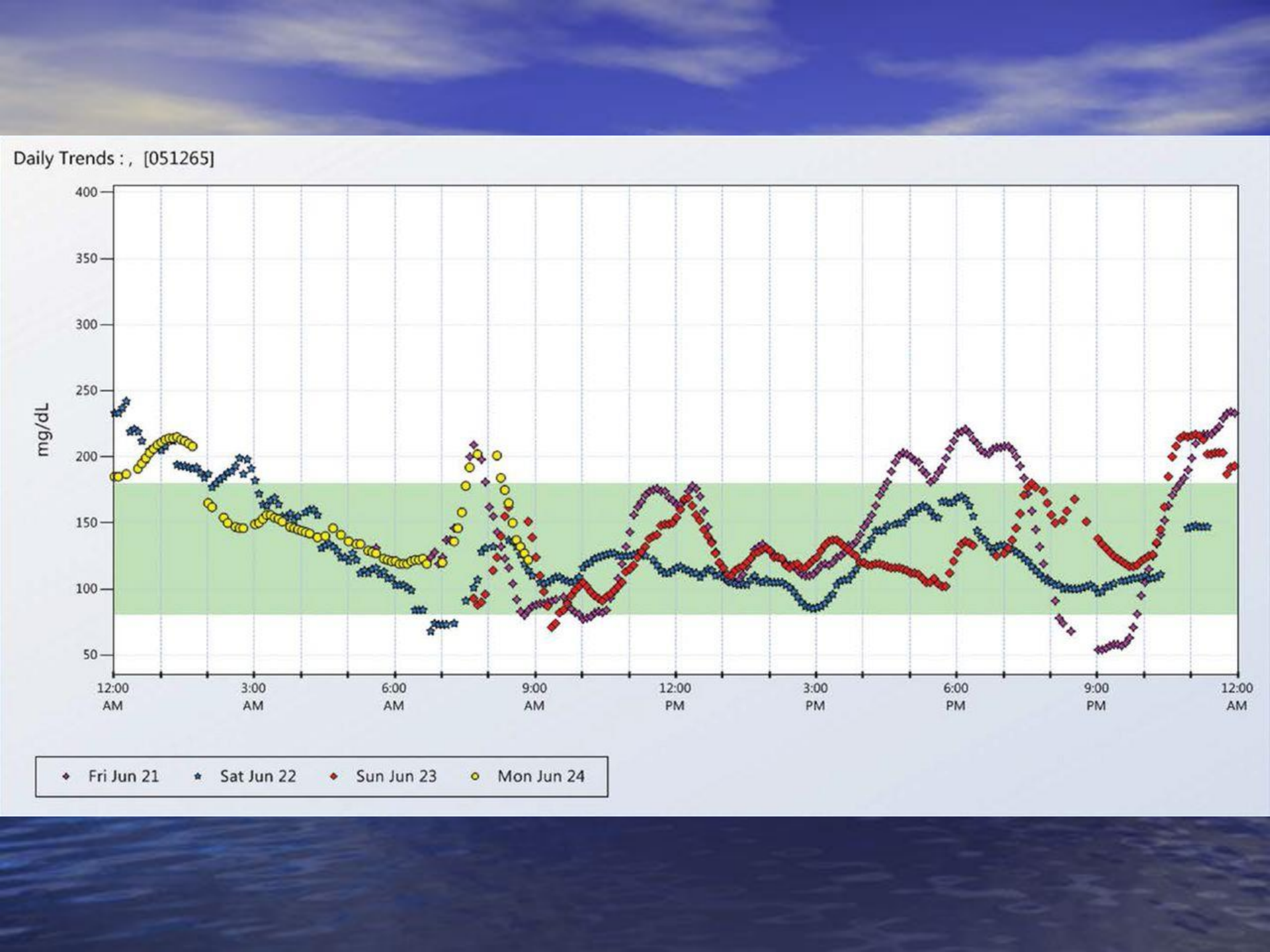
Continuous Glucose Monitoring

- Provides real time interstitial glucose values
- Measures every 5 minutes
-
- High and low alerts

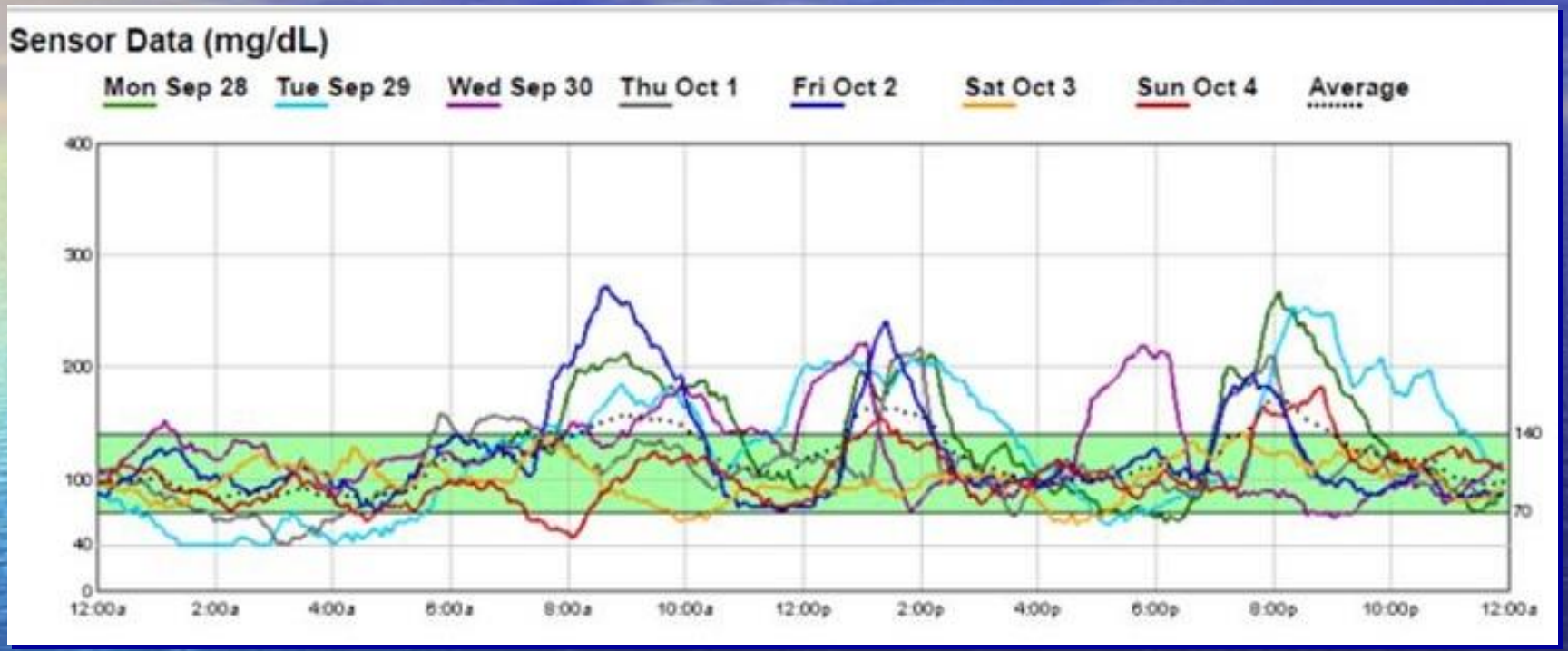
- Provides direction
- Programming for analysis of glucose values
  - -advise on insulin doses (eg bolus wizard)
  - -low glucose suspend
  - -predictive low glucose suspend
  - -Hybrid pump: basal control

CGM vs SMBG with fingerstick tests




Daily Trends : , [051265]
400
350
300
250
200
150
100
50
mg/dL
12:00 AM
3:00 AM
6:00 AM
9:00 AM
12:00 PM
3:00 PM
6:00 PM
9:00 PM
12:00 AM
Fri Jun 21
Sat Jun 22
Sun Jun 23
Mon Jun 24

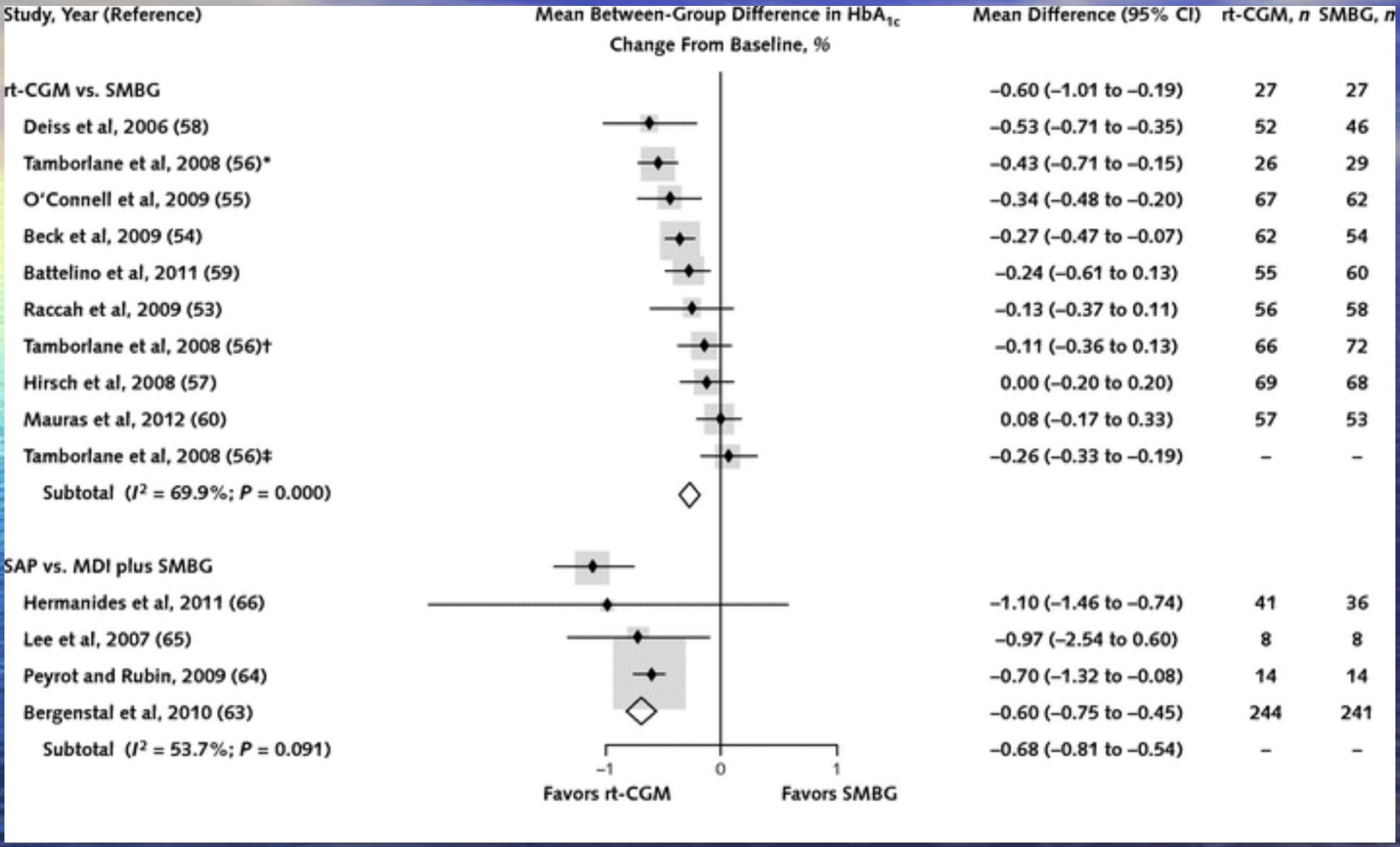
T1DM pt: basal 0.6 u/hr, carb ratio: 1:12



Your Advice?

- A. Change carb ratio to 1:10
- B. Change carb ratio to 1:15
- C. Change 24-hr basal to 0.7 u/hr

Comparison of CGM vs SMBG



Ann Intern Med. 2012;157(5):336-347.

Indications for CBG Monitoring:

1) Type 1 DM with:
    a) Hypoglycemic unawareness or severe hypoglycemia

    b) HbA1c reduction without increased hypoglycemia

2) Preconception and pregnancy

3) Data with type 2 DM is not as strong

Continuous Glucose Monitoring

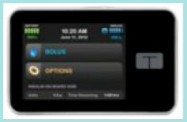
Pros	Cons
Alerts patients to • Episodes of hypoglycemia and hyperglycemia • *Predicts* episodes of hypoglycemia and hyperglycemia	Issues related to • Accuracy • Comfort • Convenience • Patient acceptance • Expense
Device displays help patients with clinical decision making	Most devices require frequent calibration

Insulin Pumps

Insulin Pumps on the Market






Accu-Chek Combo System	Asante Snap Insulin Pump System	MiniMed Paradigm Real-Time Revel System (523/723)	MiniMed 530G with Enlite (551/751)	OmniPod Insulin Manage-ment System	OneTouch Ping	t:slim Insulin Pump	V-Go Disposable Insulin Delivery Device
Roche Health Solutions	Asante Solutions	Medtronic MiniMed	Medtronic MiniMed	Insulet Corporation	Animas	Tandem Diabetes Care	Valeritas, Inc.

Current Developments in Insulin Pump Technology

- Data supporting the feasibility of locating infusion sets and CGM catheters in close proximity make it likely that combination sensor and infusion sets will be developed
- Insulin pumps can now display CGM data on the same screen and share display data on other remote devices
- Medtronic's MiniMed 530G with Enlite (approved in 2013) is the first device that alters insulin delivery in response to CGM sensor data

CGM: continuous glucose monitoring

Type 1 Diabetes

- A 2010 Cochrane review of CSII vs. MDI (23 RCT n=976 patients with T1DM)
  - Significantly lower HgA1c in CSII cf. MDI
  - CSII had better quality of life measures
  - Severe hypoglycemia reduced in CSII

Misso ML, et al. *Cochrane Database Syst Rev*. 2010;(1):CD005103. doi(1):CD005103

CSII: continuous subcutaneous insulin infusion
MDI: multiple daily injection
T1DM: type 1 diabetes mellitus

Type 2 Diabetes

- Fewer studies of CSII vs MDI in T2DM
- In an analysis of 4 RCT in T2DM:
  - No benefit in HgA1c, hypoglycemia or weight in studies as long as one year

Bode BW. *Diabetes Technol Ther*. 2010;12 Suppl 1:S17-21.

The Ideal Pump Patient Candidate:

- The ideal CSII candidate is:
  - Type 1
  - Intelligent
  - Motivated
  - Asks to be on a pump
  - Tests more that 6 times a day