Facts or Fiction about Insulin Use

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DISCLOSURE STATEMENT

Speaker:

M. Hamed Farooqi, MD

- Has disclosed that he serves on the Speaker's bureau and receives consulting fees and honoraria from Lilly, Novo Nordisk, MSD, AstraZeneca, J&J and Servier

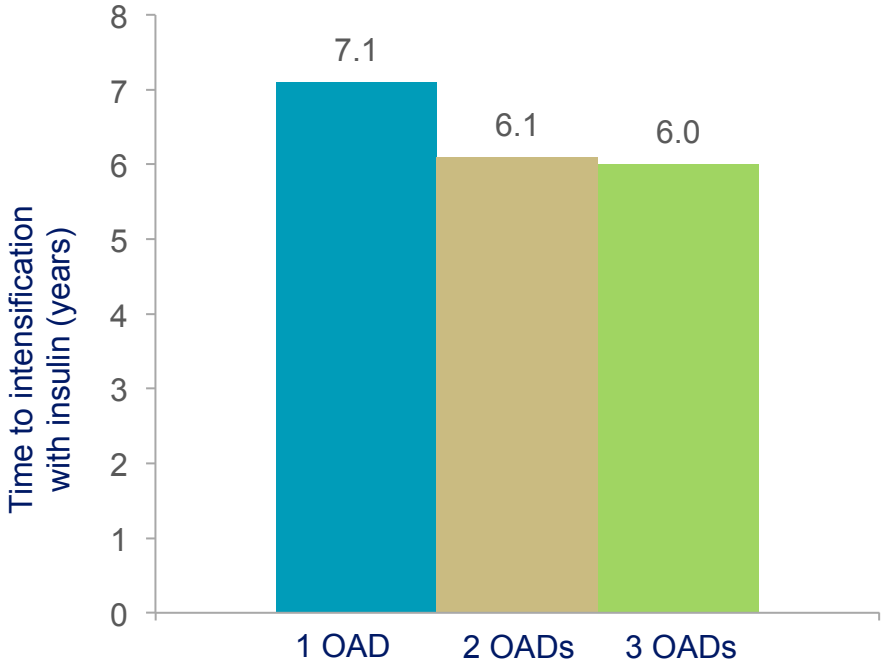
- Will not be discussing the off-label or investigational use of products

Weill Cornell
Medicine-Qatar

Objectives

- Fears of insulin use and how to overcome them
- Dealing with potential risk: Hypoglycemia
- Role of analogues in current setting
- Review of data on new insulins
- Discuss inhaled insulin

Insulin use is delayed despite elevated HbA_{1c}: a retrospective cohort study of 80,000 patients



Clinical Inertia in DM2: It can take up to 7 years to initiate insulin therapy, even in the presence of elevated HbA_{1c}

OAD: oral antidiabetics

Khunti et al. *Diabetes Care* 2013; 36(11):3411-3417

Selected barriers to insulin injection therapy among patients, providers, and health care systems

Strategies for Insulin Injection Therapy in Diabetes Self-Management

American Association of Diabetes Educators, 2011.

Patient Barriers

Psychological resistance

- Myth-based fear of insulin
- Fear of hypoglycemia
- Concern about weight gain
- Fear of needles and pain
- Self-blame
- Loss of control
- Social stigma
- Poor self-efficacy

Patient Barriers

Lifestyle

- Time-consuming; inconvenient
- Travel issues

Physical/mental

- Poor recall/cognitive impairment
- Visual/hearing/dexterity impairment
- Learning difficulties; low literacy/numeracy skills

Financial

- Reimbursement issues

Provider Barriers

- Perceived patient resistance
- Patient's adherence behavior
- Belief that patient's improved status negates need to start insulin therapy
- Concerns about adverse effects (hypoglycemia; weight gain)
- Provider time constraints (instruction; titration)
- Lack of resources/ organizational structure to facilitate guideline adherence

System Barriers

- Overburdened workload among providers
- Access to education
- Limited training of providers in injection technique
- Underutilization of resources
  (within clinical practices, hospitals, and community)
- Reimbursement issues
- Poor follow-up system
- Suboptimal team collaboration; poor chronic care model

Common Patient Concerns When Initiating Insulin Therapy and Suggested Responses for HCPs

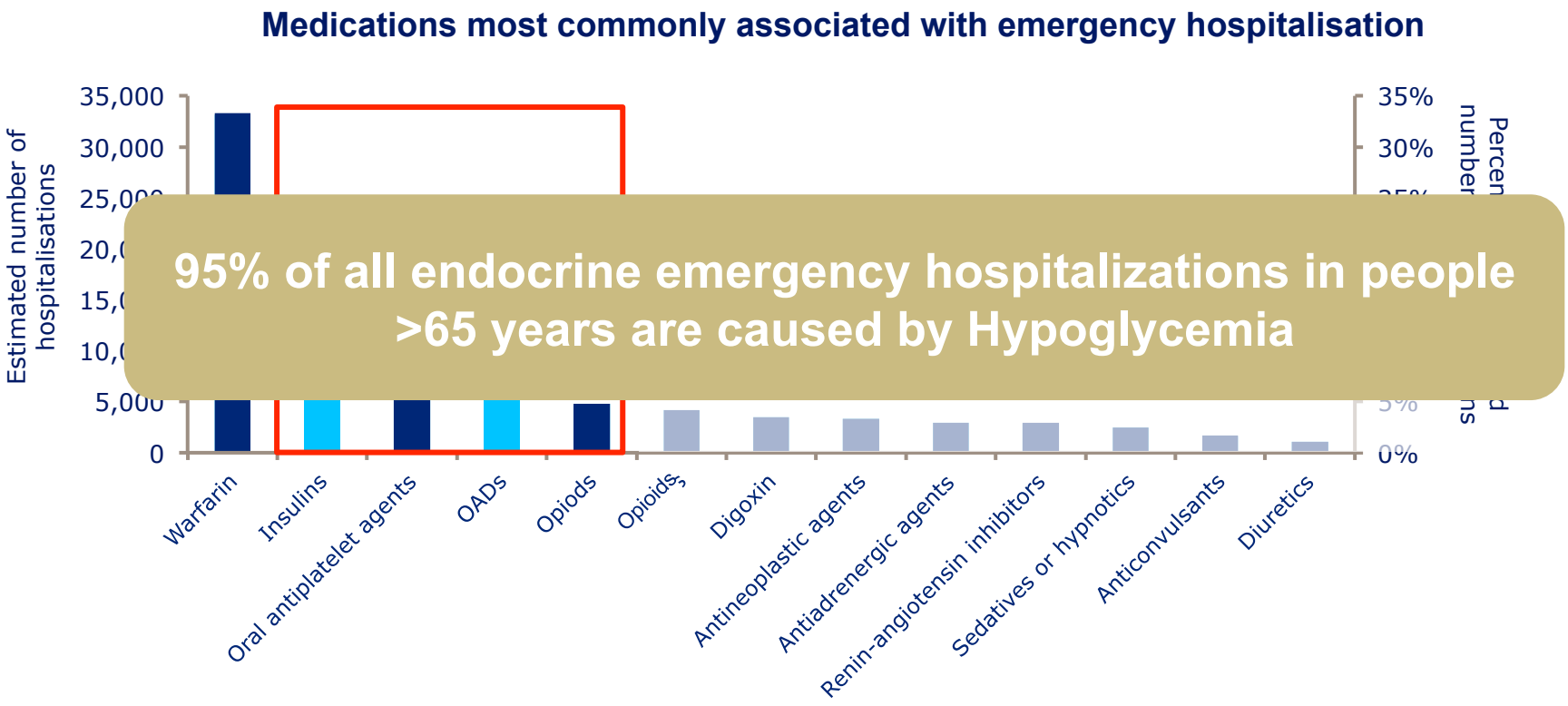
Patient Concern	Reassurance
"I need insulin because I have failed."	HCPs should present insulin in a positive light at the time of diagnosis, explaining that type 2 diabetes is a progressive disease with a gradual decline in β-cell function, meaning that most patients will eventually require insulin. Emphasize that oral anti-diabetic agents have failed the patient rather than this situation being related to any failure on the patient's part.
"Insulin injections are painful."	Modern needles are very fine, laser-sharpened, and silicone-coated for ease of entry. They are practically pain-free. A demonstration needle can usually dispel this concern.
"I have needle phobia."	A number of injection aids are available, such as needle shields. A demonstration needle can usually dispel this concern. For genuine needle phobia, jet injectors deliver a high-pressure jet of insulin directly through the skin; however, HCPs should point out that jet injectors are not completely pain-free and can cause bruising in some patients if not used correctly.
"Insulin regimens are complex, restrictive, and intrusive."	There are many insulin formulations and dosage combinations that can be tailored to suit each patient's lifestyle with minimum disruption. For example, new insulin analogs mimic natural insulin much more closely than human insulins, and the rapid-acting formulation can be given just before mealtimes. Pre-filled insulin pens containing insulin analogs can be carried discreetly to work, school, or social activities. These devices are also particularly suitable for patients with visual or dexterity difficulties, cognitive impairment, or compliance issues.

Funnell MM. Overcoming barriers to the initiation of insulin therapy. Clin Diabetes. 2007;25:36-38

"Insulin causes complications."	This misconception may arise because the patient knows people who started insulin therapy late in their disease, when the adverse effects of long-term hyperglycemia were just becoming evident. Assure the patient that the opposite is true by discussing the evidence from studies demonstrating that good glycemic control can reduce microvascular complications such as nephropathy, neuropathy, and visual deterioration, as well as possibly reducing cardiovascular events.
"I will experience severe hypoglycemia."	Because the new insulin analogs are more similar to natural insulin than older formulations, the risk of hypoglycemia is reduced with these agents. Patients should be reassured that severe hypoglycemia is rare and affects only about 0.5% of patients with type 2 diabetes. Patients can also take various precautions against low blood glucose such as taking their insulin as scheduled, learning to recognize the signs of hypoglycemia, always carrying low-glucose treatment, and learning to adjust their insulin dose, food intake, or exercise level according to any divergence from the agreed schedule.
"I will gain weight."	Insulin analogs are much less likely to cause weight gain than human insulins; patients who eat sensibly and exercise should not experience excessive weight gain. HCPs can arrange for a meeting with a diabetes educator or dietitian to discuss strategies to prevent weight gain.

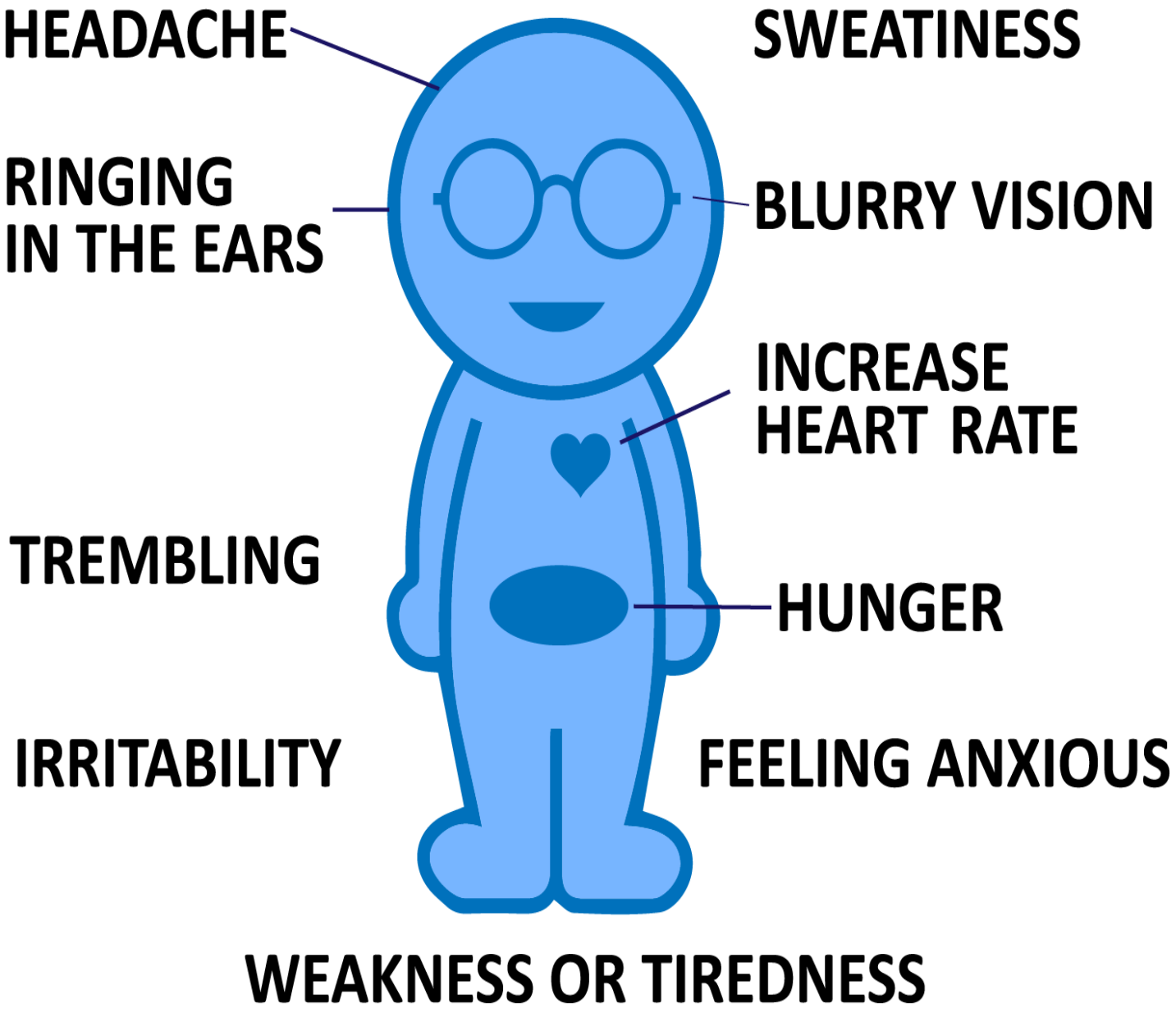
Funnell MM. Overcoming barriers to the initiation of insulin therapy. Clin Diabetes. 2007;25:36-38

Hypoglycemia is a problem with diabetes therapy



Data given are number and percentage of annual national estimates of hospitalisations. Data from the NEISS-CADES project.
ER visits n=265,802/Total cases n=12,666. ER, emergency room

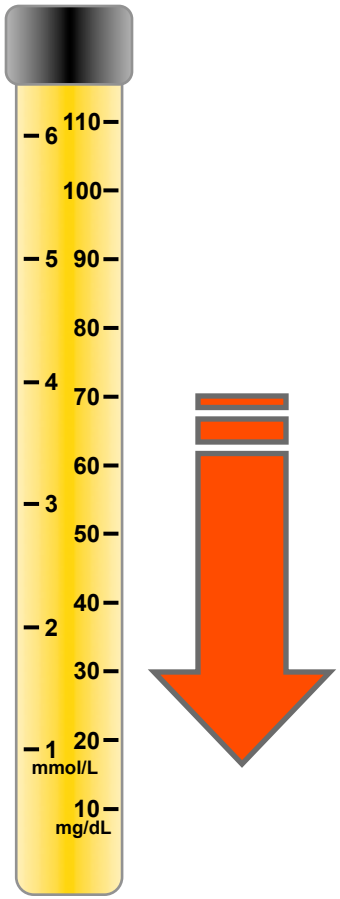
Budnitz *et al*. *N Engl J Med* 2011;365:2002–12

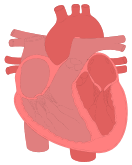


http://www.qualityandsafety.va.gov/ChoosingWiselyHealthSafetyInitiative/Images/HYPOGLYCEMIA_RISK.png

Potential Complications and Effects of Severe Hypoglycemia

Plasma glucose level





Arrythmia[1]	Neuroglycopenia[2]
▪ Abnormal prolonged cardiac repolarization — ↑ QTc and QT dispersion ▪ Sudden death	▪ Cognitive impairment ▪ Unusual behavior ▪ Seizure ▪ Coma ▪ Brain death

1. Landstedt-Hallin L et al. *J Intern Med*. 1999;246:299–307.

2. Cryer PE. *J Clin Invest*. 2007;117:868–870.

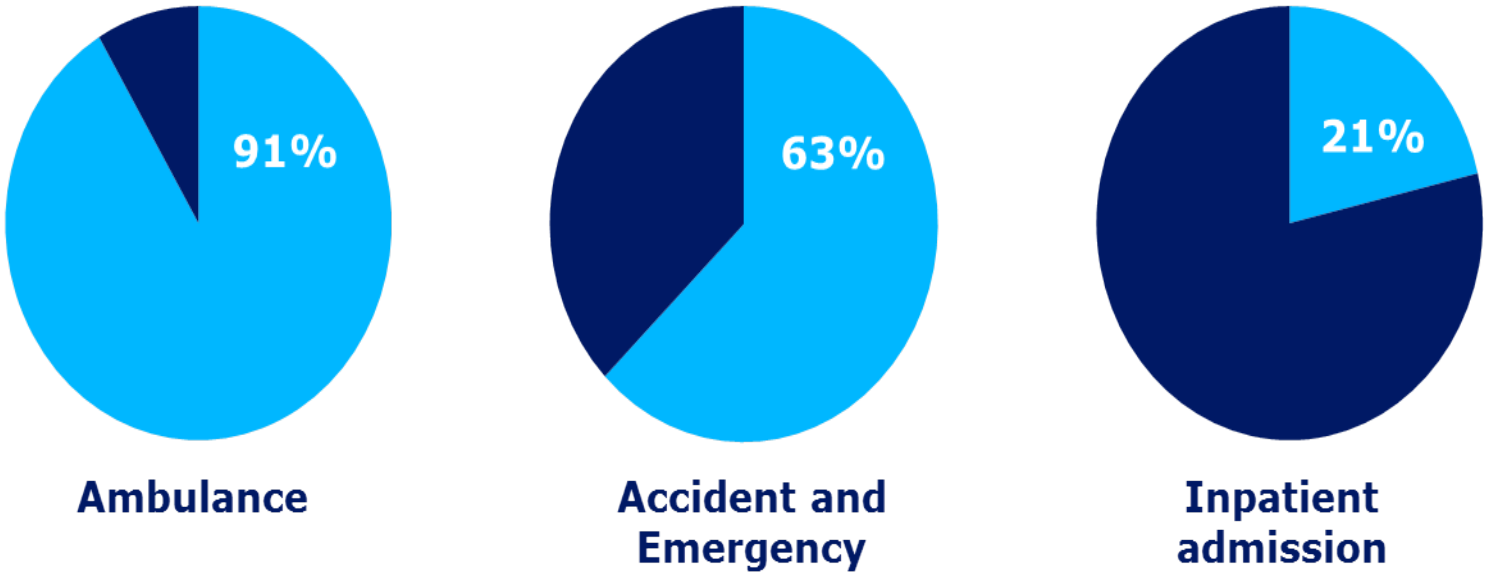
Management of Hypoglycemia

● Patients with asymptomatic or symptomatic hypoglycemia should ingest carbohydrates. 15 to 20 grams of oral glucose is typically sufficient.
Glucose may be ingested in the form of tablets, juice, milk, other snacks, or a meal.
● For the treatment of hypoglycemia in a person with impaired consciousness and no established intravenous (IV) access, administer glucagon, The usual dose is 0.5 to 1.0 mg given SC or IM. Education and training for clinicians, friends, and family on the recognition and treatment of severe hypoglycemia, including the use of glucagon kits, is necessary.
●IV dextrose (25 g of 50% glucose [dextrose]) can be administered to treat hypoglycemia in patients with impaired consciousness and established IV access (typically in a hospital).
●A subsequent glucose infusion (or food, if patient is able to eat) is often needed, depending upon the cause of the hypoglycemia, to prevent recurrence of symptoms.

Uptodate

Severe events often require hospitalisation and inpatient care

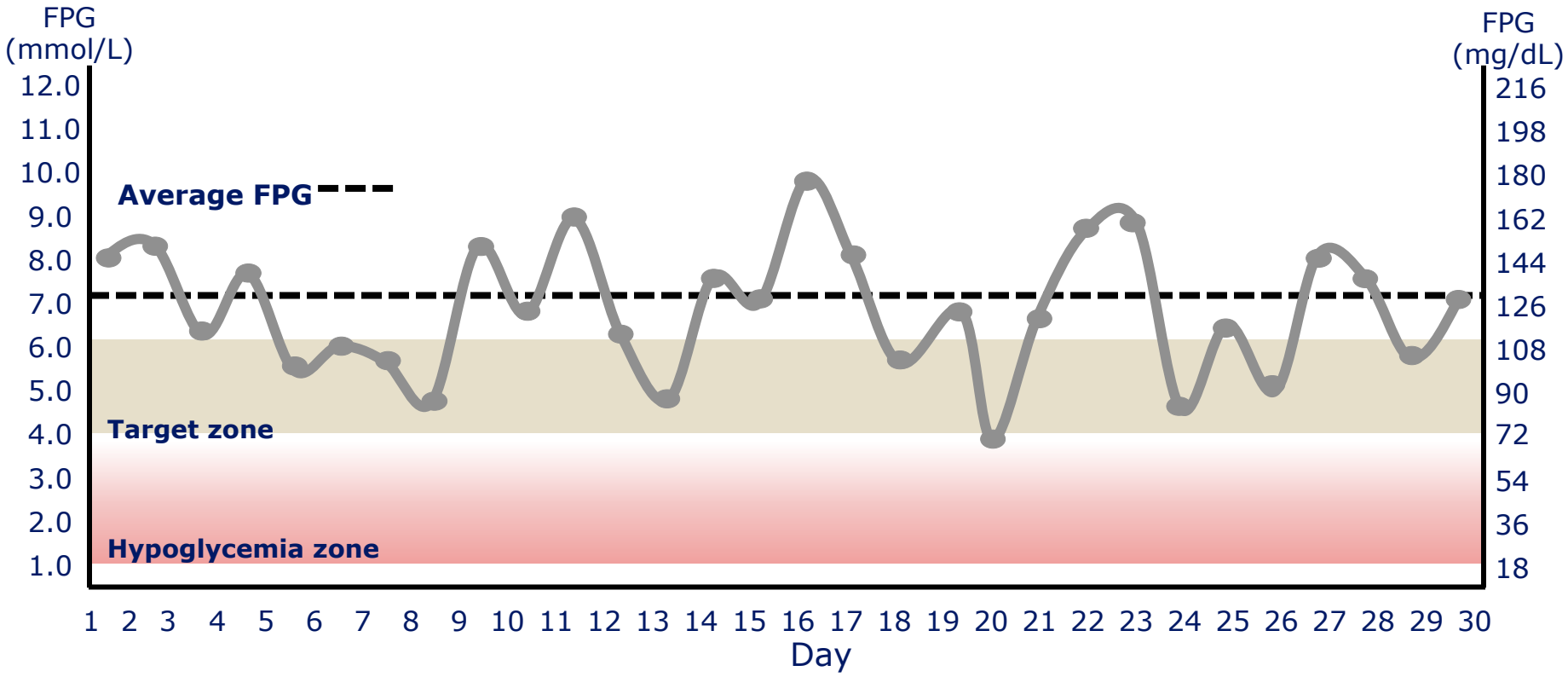
Percentage of severe events requiring hospital services



Based on 8,655 patients with diabetes experiencing 244 events

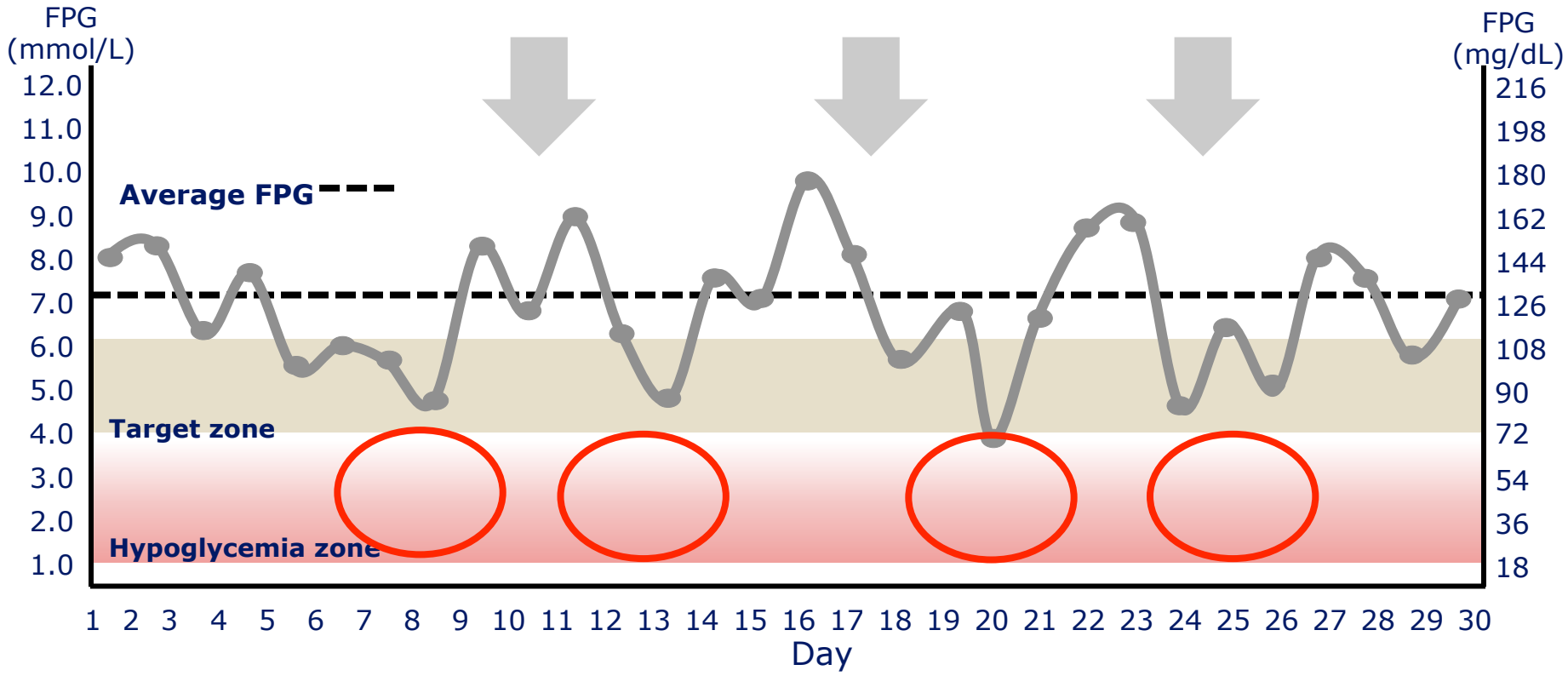
Leese *et al*. *Diabetes Care* 2003;26:1176–80

Glucose variability and the risk of Hypoglycemia



Vora & Heise. *Diabetes Obes Metab* 2013;15,701−12

Glucose variability and the risk of Hypoglycemia



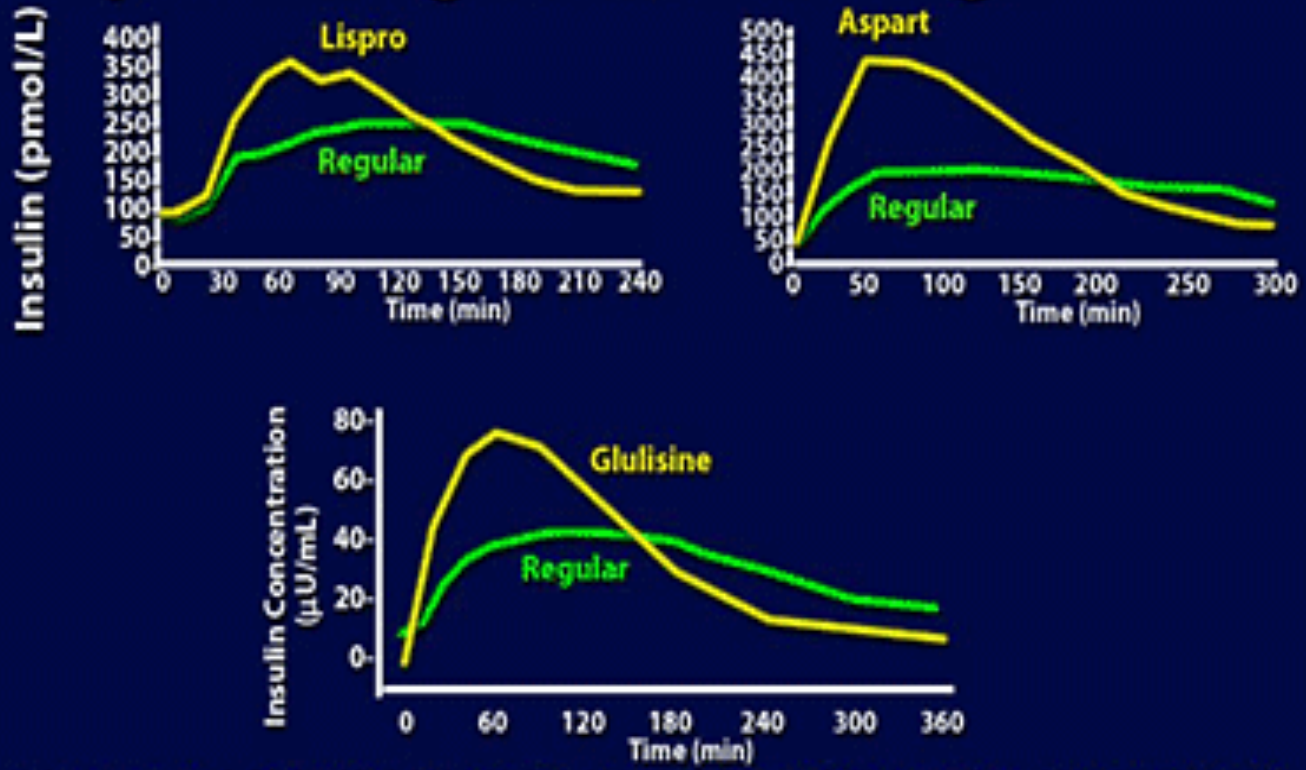
Vora & Heise. *Diabetes Obes Metab* 2013;15,701–12

Analogue	Modification	Mechanism
A		
Lispro (Humalog®) Eli Lilly and Co	$Pro^{B28} \rightarrow Lys$ $Lys^{B29} \rightarrow Pro$	IGF-I-related motif impairs dimerization
Aspart (NovoLog®) Novo-Nordisk	$Pro^{B28} \rightarrow Asp$	Charge repulsion at dimer interface
Glulisine (Apidra®) Sanofi-Aventis	$Asn^{B3} \rightarrow Lys$ $Lys^{B29} \rightarrow Glu$	Decreased zinc-free self-association
B		
Glargine (Lantus®) Sanofi-Aventis	Arg^{B31}-Arg^{B32} tag $Asp^{A21} \rightarrow Gly$	Shift in pI to pH 7 leads to isoelectric precipitation on injection
Detemir (Levemir®) Novo-Nordisk	Modification of Lys^{B29} by a tethered fatty acid	Stabilization of hexamer and binding to serum albumin

[a]Panel A describes rapid-acting analogues employed in prandial regimens and in insulin pumps whereas B lists basal insulin analogues with protracted action. Table is reprinted from Berenson *et al*. with permission of the authors.[6]

Weiss MA. Design of ultra-stable insulin analogues for the developing world. J Health Spec 2013;1:59-70

Rapid-acting Insulin Analogs

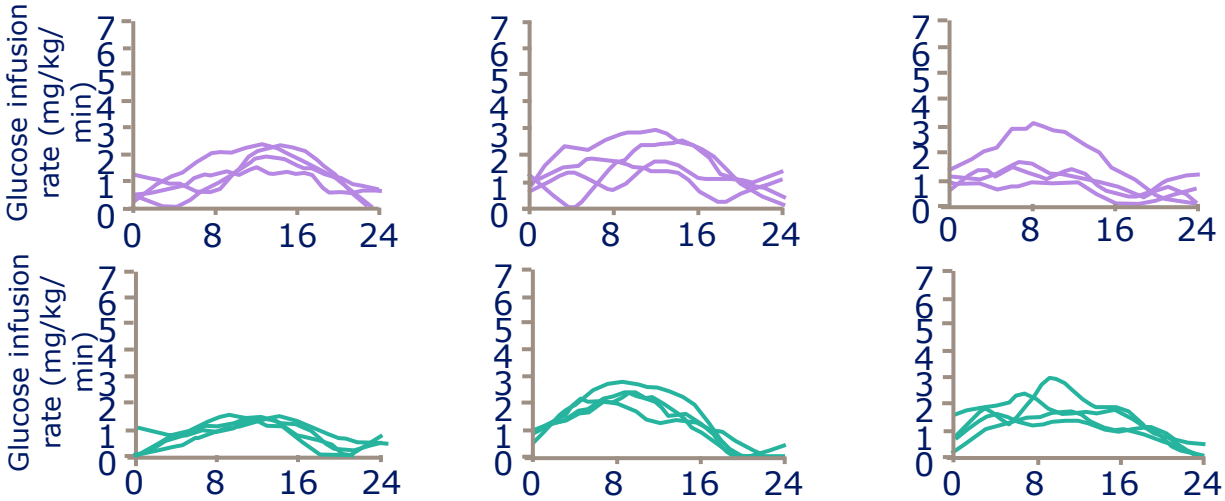


Heinemann, et al. *Diabet Med.* 1996;13:625-629; Mudaliar, et al. *Diabetes Care.* 1999;22:1501-1506. Program at 64th meeting of the ADA. Orlando, Fl: 2004.

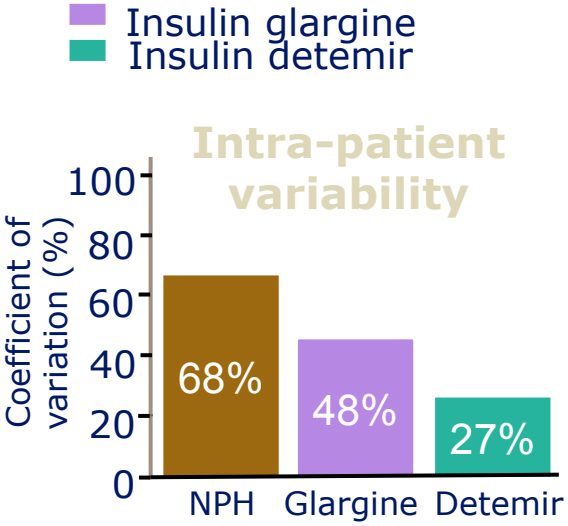
Current basal analogs: less hypoglycemia but still room for improvement

Most of the time I feel fine, but sometimes my blood glucose values are all over the place without any apparent reason

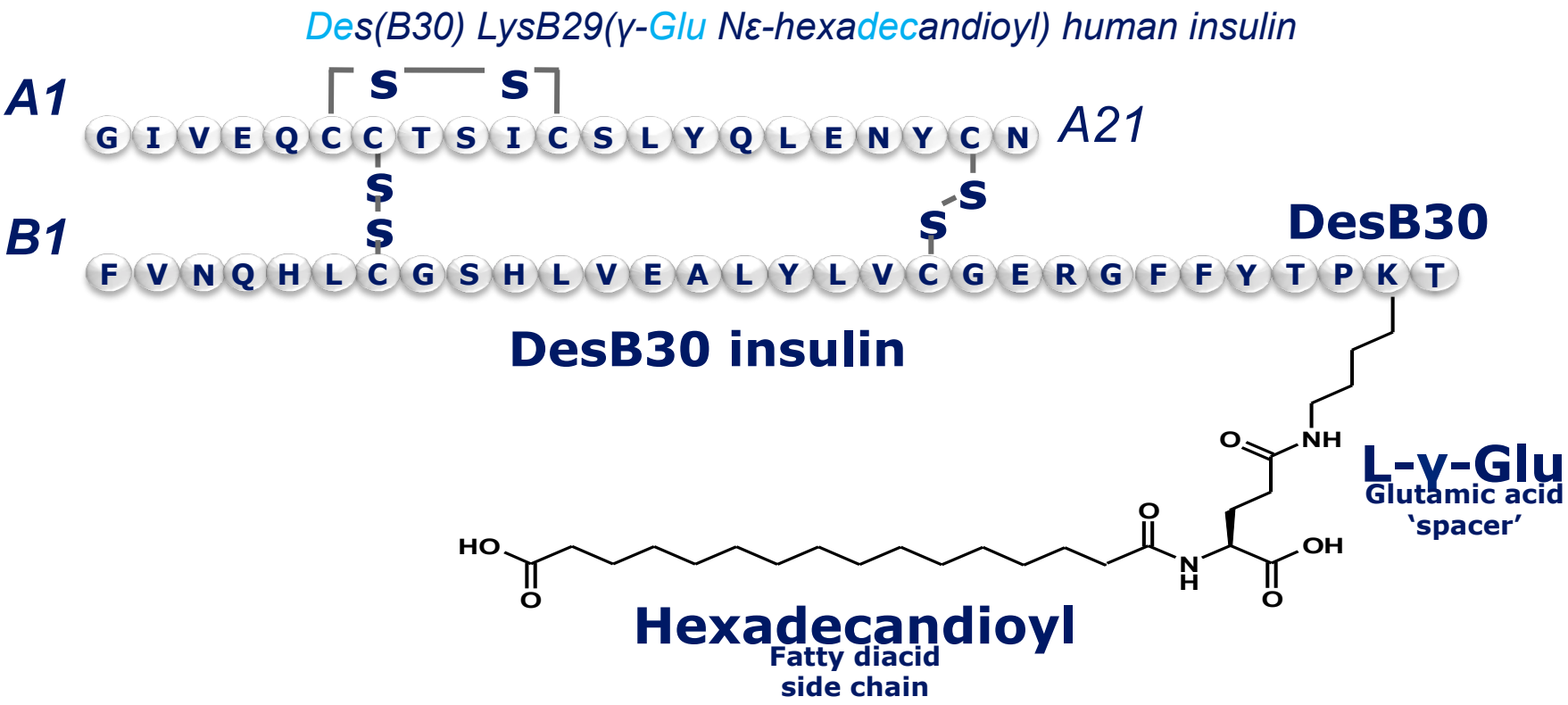
Intra-patient daily profiles



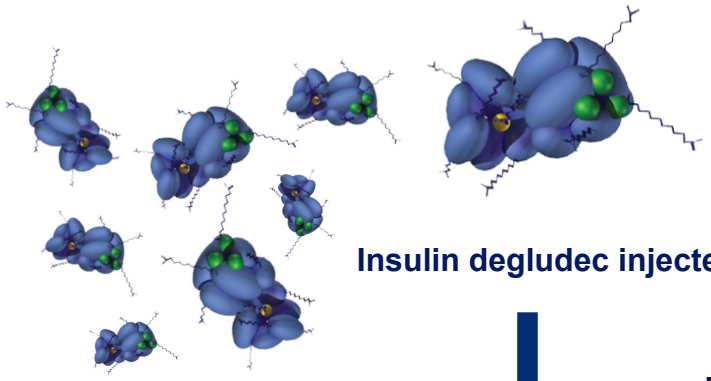
Heise *et al. Diabetes* 2004;53:1614–20



Insulin degludec: rationally designed, beyond sequence modification



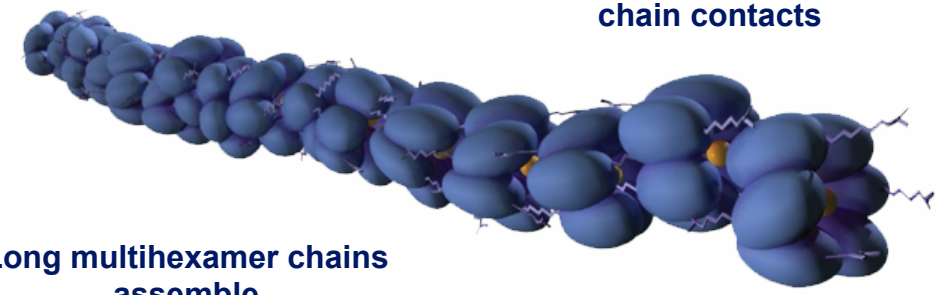
Insulin degludec: immediately after injection



Phenol; Zn^{2+}]

Insulin degludec injected

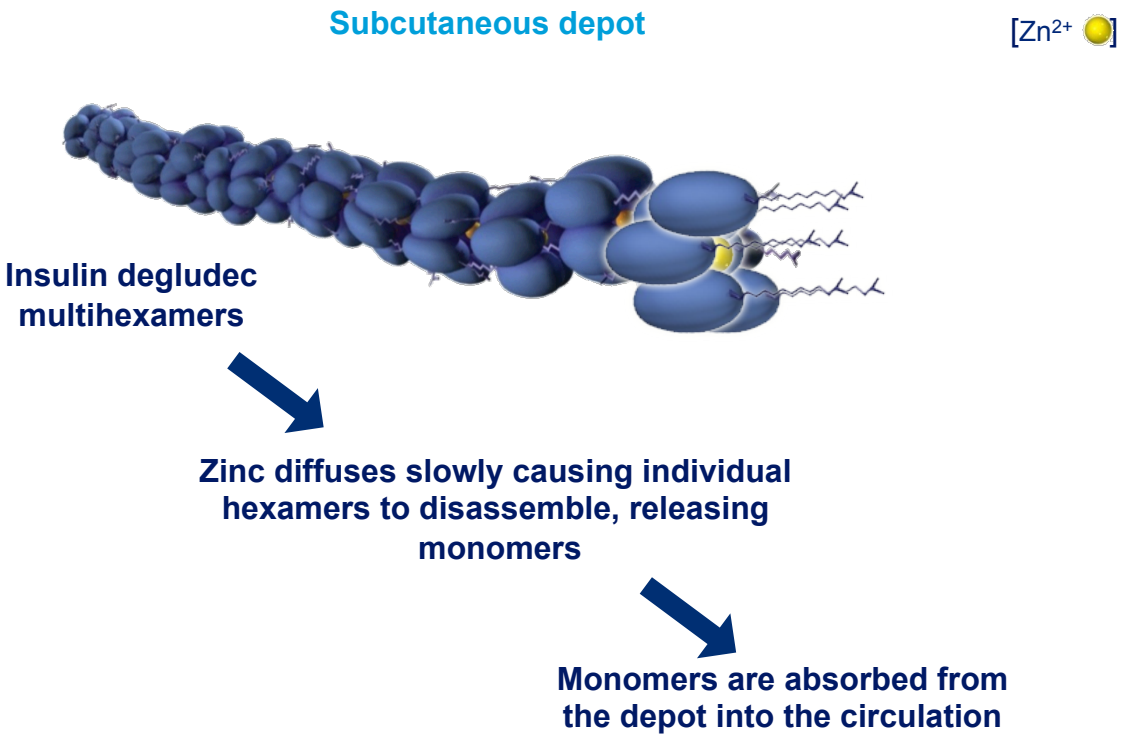
Phenol from the vehicle diffuses quickly, and insulin degludec links up via single side-chain contacts



Long multihexamer chains assemble

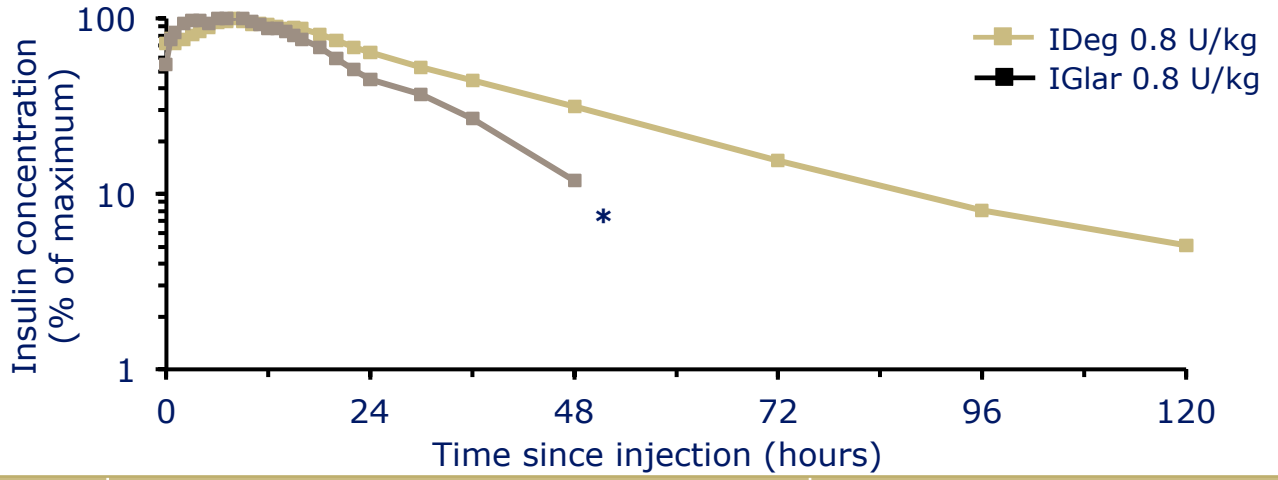
Jonassen *et al. Pharm Res* 2012;29:2104–14

Insulin degludec: slow release following injection



Jonassen *et al. Pharm Res* 2012;29:2104–14

Half-life of insulin degludec is twice as long as that of insulin glargine



	Insulin degludec			Insulin glargine		
	0.4 U/kg	0.6 U/kg	0.8 U/kg	0.4 U/kg	0.6 U/kg	0.8 U/kg
Half-life (hours)	25.9	27.0	23.6	11.5	12.9	11.9
Mean half-life	**25.4**			**12.1**		

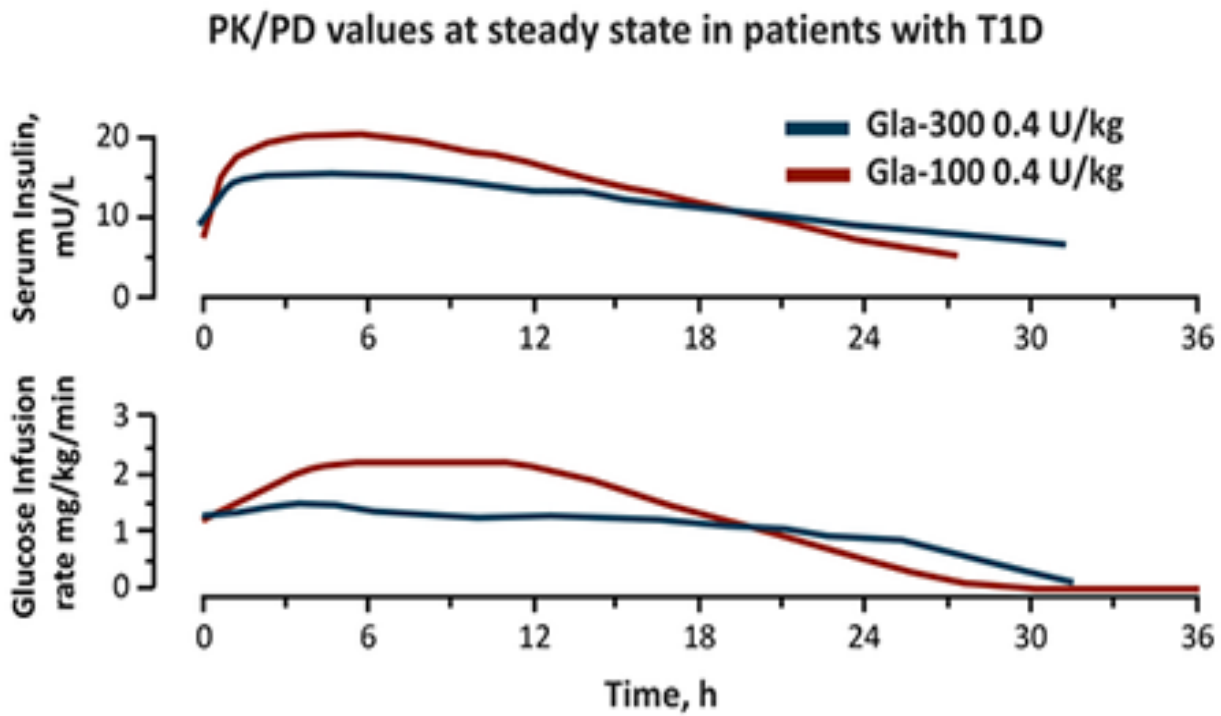
*Insulin glargine was undectable after 48 hours

Results from 66 patients with type 1 diabetes (T1D)

IDeg, insulin degludec; IGlar, insulin glargine

Heise *et al. Diabetes* 2011;60(Suppl. 1):LB11; Heise *et al. Diabetologia* 2011;54(Suppl. 1):S425

Insulin Glargine U300



Gla-300 = glargine U300. Gla-100 = glargine U100.

Tillner J, et al. *Diabetologia*. 2013;56(suppl 1):A1033.[12]

Jax T, et al. *Diabetologia*. 2013;56(suppl 1):A1029.[13]

Basaglar

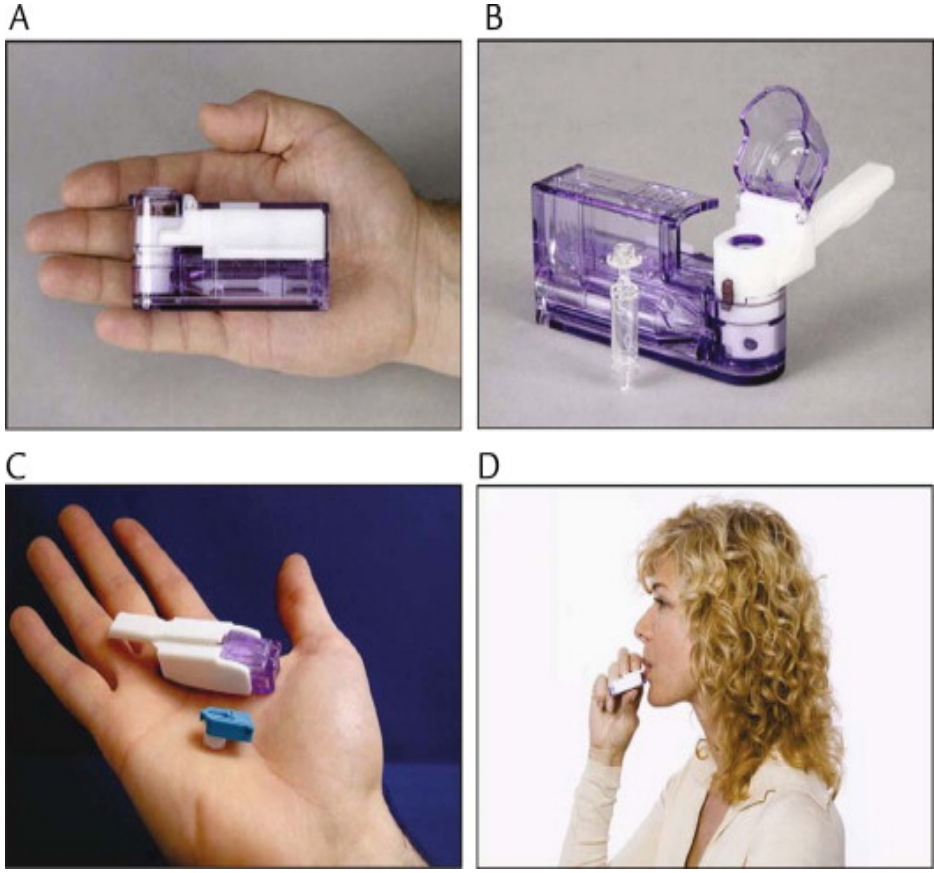
Biosimilar medications are "highly similar" to an already FDA-approved biological product.

The FDA determined that Basaglar was sufficiently similar to Glargine to justify approval based on the safety and effectiveness of Glargine as well as certain Basaglar-specific data.

Basaglar was approved in Europe as a biosimilar last year. The FDA is calling the product a "follow-on" biologic rather than a biosimilar.

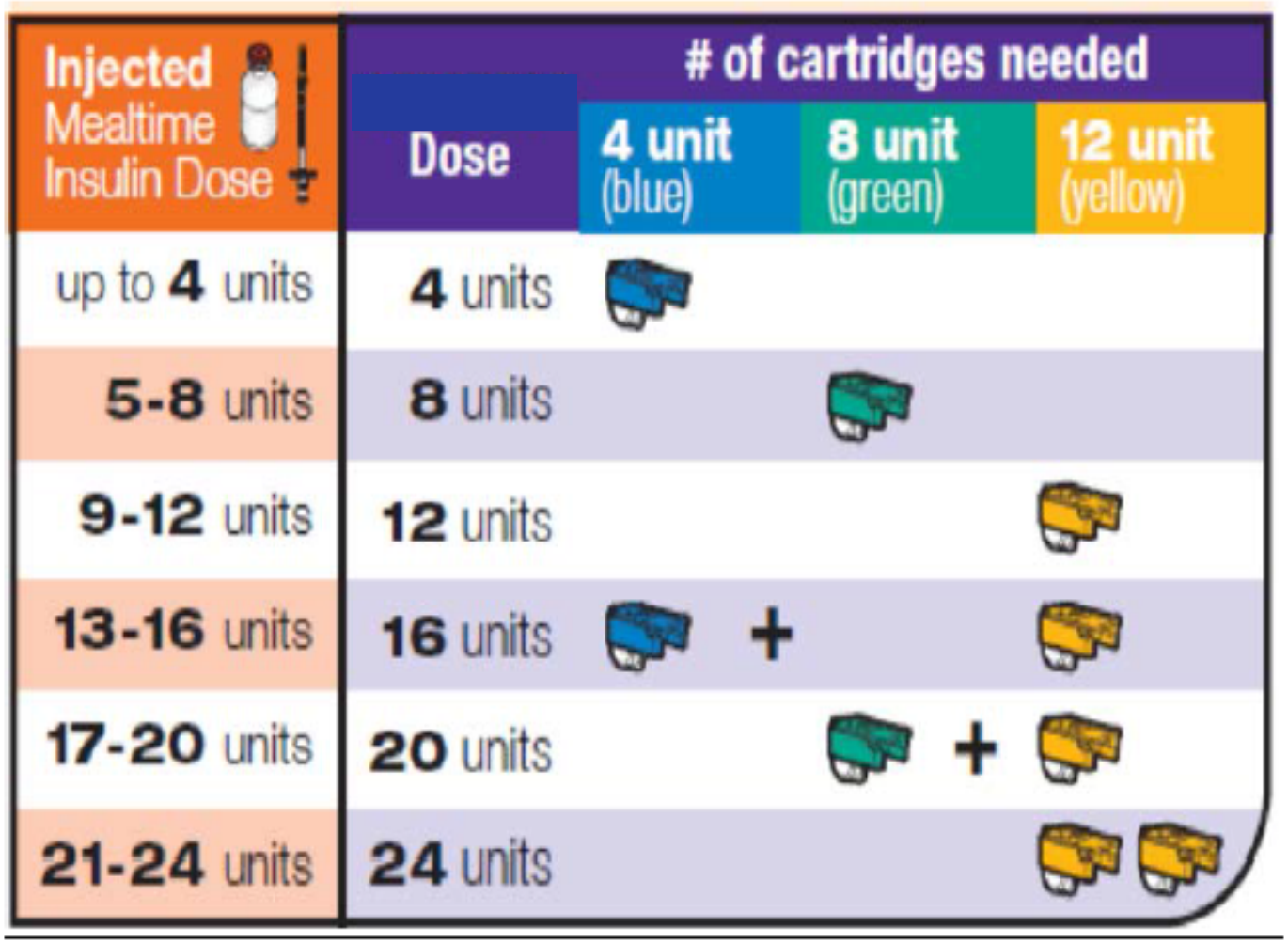
Inhaled Insulin

- A rapid-acting insulin that is inhaled instead of injected.
- This inhaled insulin uses the pocket-sized *Dreamboat* inhaler. The insulin is powdered and encased in a matrix of FDKP, a material that dissolves almost instantly, releasing the insulin, when its inhaled. This delivery system helps insulin enter the bloodstream nearly as fast as an injection.



- Patients with obstructive lung disease should not use inhaled insulin, and acute bronchospasm is a potential side effect.
- Patients with cancer are also warned not to take the drug.

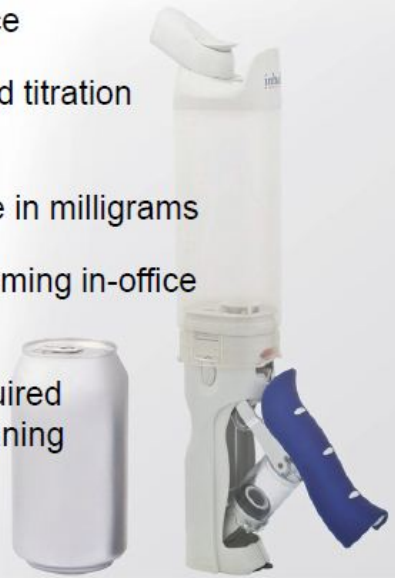
Inhaled Insulin Dosing



Afrezza® Delivers a Distinctly Different Patient Experience than the Previous Inhaled Insulin

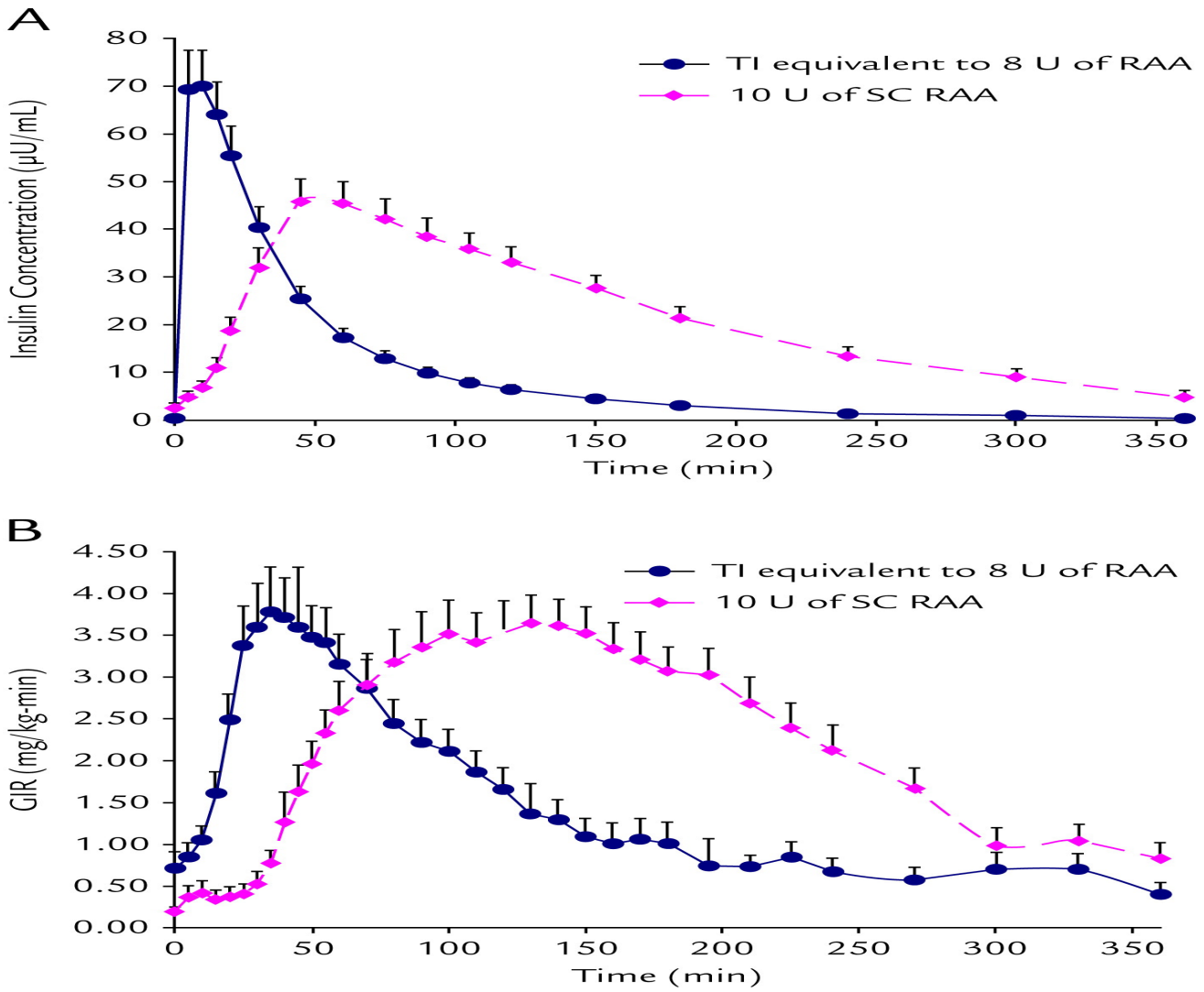
Exubera®

- ✓ Lower bioavailability and slower clearance
- ✓ Large device
- ✓ Complicated titration system
- ✓ Doses were in milligrams
- ✓ Time consuming in-office training
- ✓ Device required weekly cleaning



Afrezza®

- ✓ Higher bioavailability and faster clearance
- ✓ Small device
- ✓ Easy to use
- ✓ Doses equivalent to insulin units
- ✓ Less training required
- ✓ No cleaning requirement



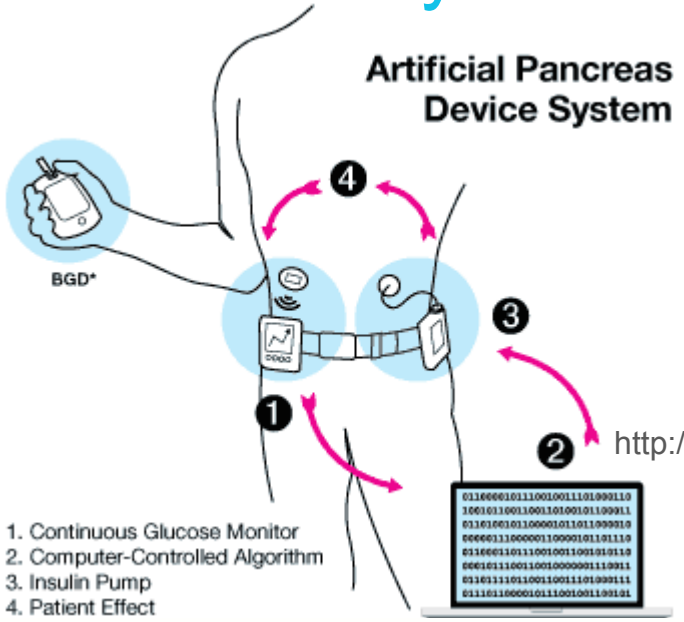
Pharmacokinetic/pharmacodynamic profile of Technosphere inhaled insulin (TI) versus a Rapid Acting Analog (RAA)

Tricia Santos Cavaiola, Steven Edelman,
Inhaled Insulin: A Breath of Fresh Air? A Review of Inhaled Insulin
Clinical Therapeutics, Volume 36, Issue 8, 2014, 1275–1289

Continuous subcutaneous Insulin Infusion (CSII) Pump

Closed Loop Insulin Delivery

http://www.diabetes.co.uk



http://www.fda.gov/

First Generation

1 **Very-Low-Glucose Insulin Off Pump**
Pump shuts off when user not responding to low-glucose alarm

2 **Hypoglycemia Minimizer**
Predictive hypo-glycemia causes alarms, followed by reduction or cessation of insulin delivery before blood glucose gets low

3 **Hypoglycemia/ Hyperglycemia Minimizer**
Same product as #2 but with added feature allowing in-sulin dosing above high threshold (e.g. 200 mg/dL)

Second Generation

4 **Automated Basal/Hybrid Closed Loop**
Closed loop at all times with meal-time manual-assist bolusing

5 **Fully Automated Insulin Closed Loop**
Manual meal-time bolus eliminated

Third Generation

6 **Fully Automated Multihormone Closed Loop**

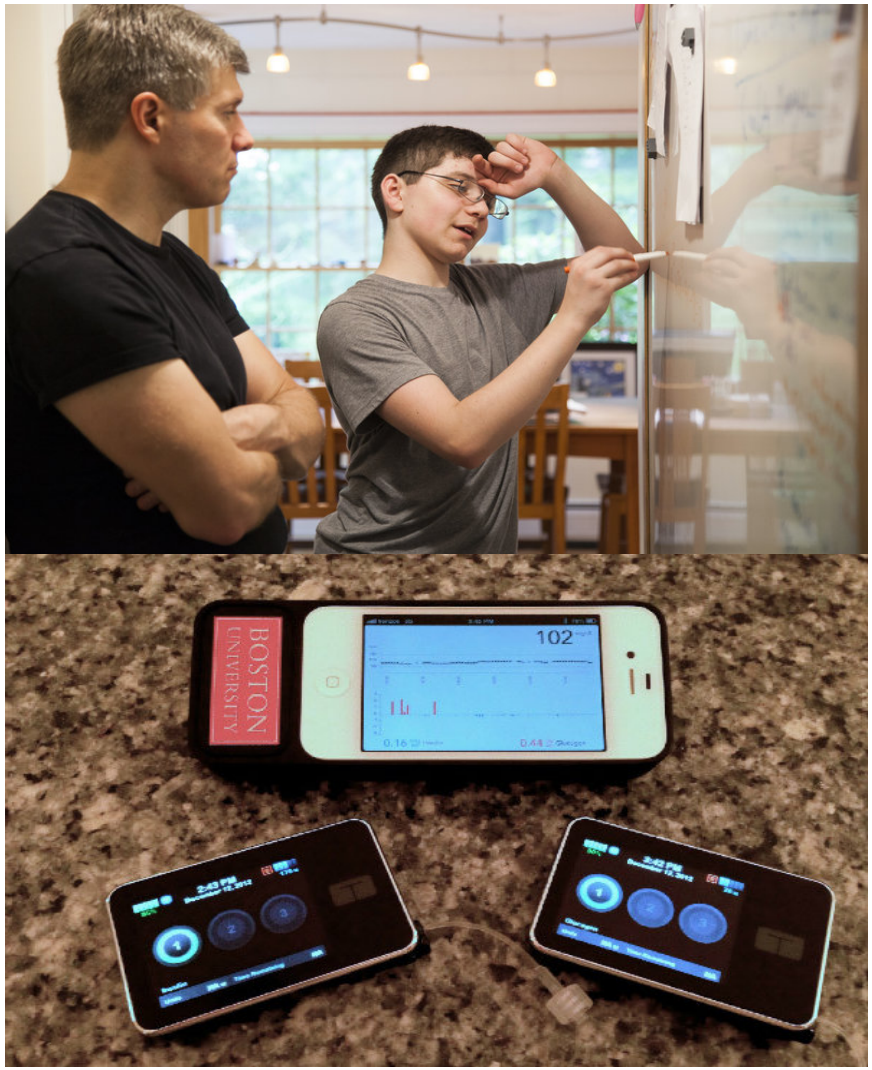
Artificial Pancreas

This version of the artificial pancreas, consisting of a continuous glucose monitor, smartphone, and two pumps, was tested in the Beacon Hill study.

Two Pumps
Participants wear one pump containing insulin (which lowers blood glucose) and another with glucagon (which raises it). The pumps deliver the medications following commands from the smartphone's artificial-pancreas app.

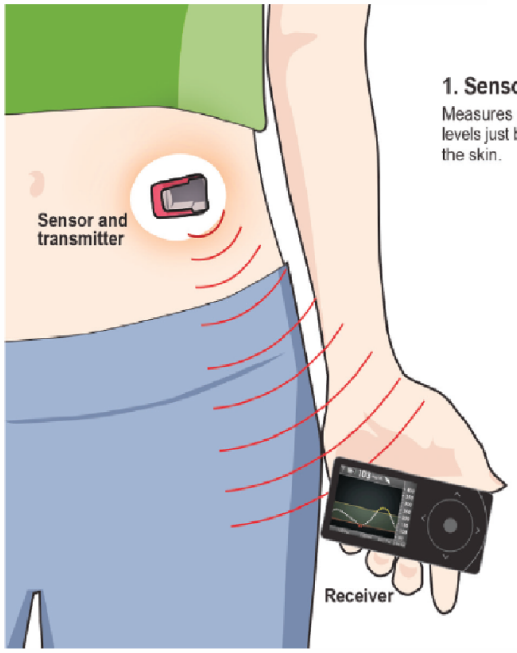
Continuous Glucose Monitor
This device checks glucose levels just under the skin every few minutes and beams the information to the smartphone.

Smartphone
The smartphone contains the artificial-pancreas app. The app uses glucose measurements from the CGM to calculate how much insulin or glucagon to give the user. The smartphone wirelessly sends this information to the two pumps.



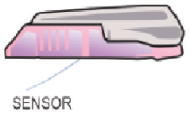
http://www.diabetesforecast.org/2014/mar/images/v67n03_p42.jpg

Continuous Glucose Monitoring Systems (CGMS)



TRANSMITTER

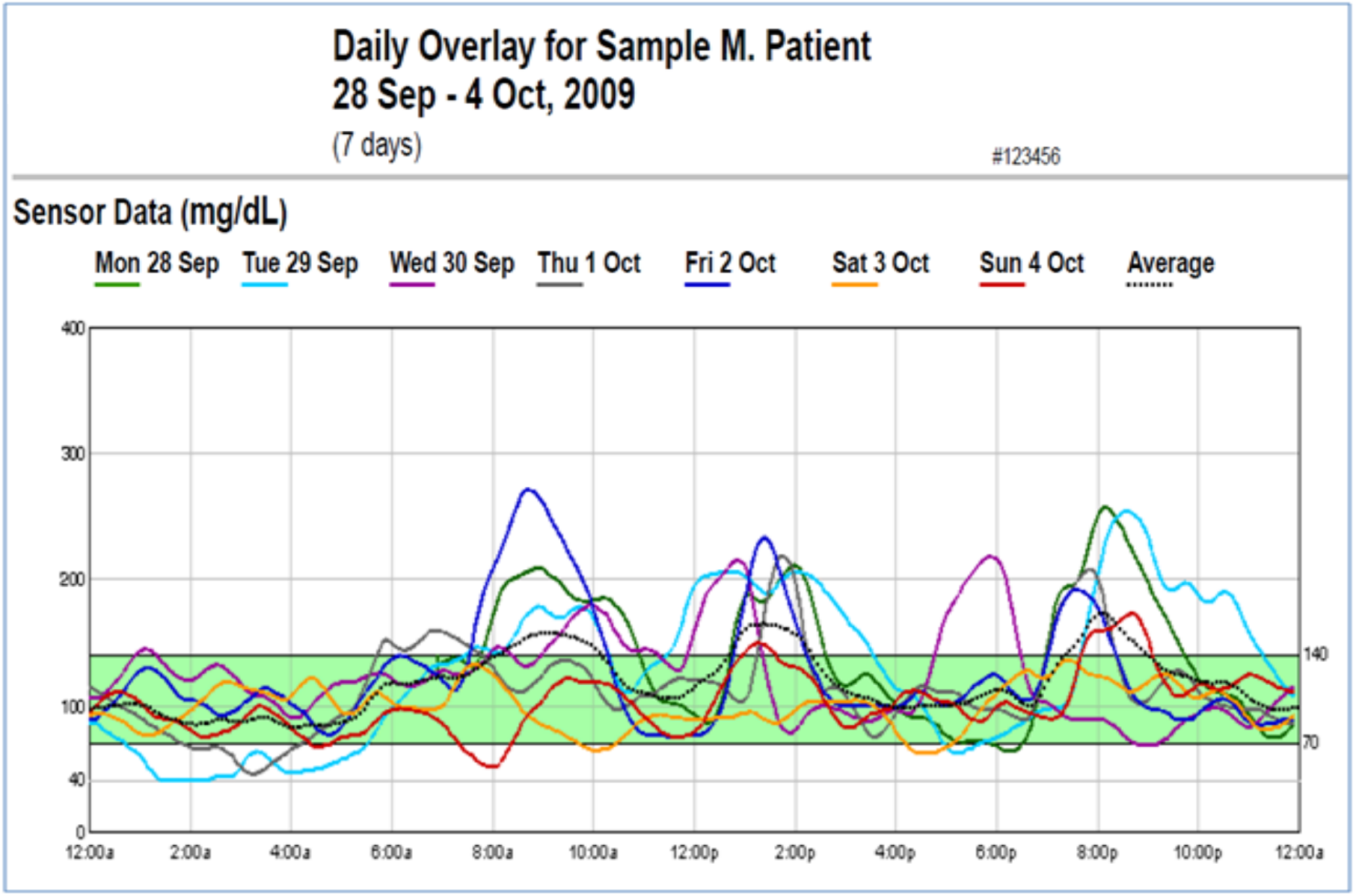
1. Sensor
Measures glucose levels just below the skin.



2. Transmitter
A transmitter fits onto the sensor and sends data wirelessly to a receiver.

3. Receiver
The receiver, about the size of a cell phone, fits in a pocket or purse. It can be programmed to alert you when glucose gets too high or too low, even during sleep.

CGMS report


Daily Overlay for Sample M. Patient
28 Sep - 4 Oct, 2009
(7 days)
#123456
Sensor Data (mg/dL)
Mon 28 Sep
Tue 29 Sep
Wed 30 Sep
Thu 1 Oct
Fri 2 Oct
Sat 3 Oct
Sun 4 Oct
Average
400
300
200
100
40
0
140
70
12:00a
2:00a
4:00a
6:00a
8:00a
10:00a
12:00p
2:00p
4:00p
6:00p
8:00p
10:00p
12:00a

CGMS report


Dexcom Studio™
File
Tools
Help
Nighttime Range
Target Glucose Range
Dubois, Wil [SM23471048]
Home
Patterns
Hourly Stats
Daily Trends
Distribution
Glucose Trend
Daily Stats
Success Report
A1c Records
Patients
Options
Selected Dates: Tuesday, October 23, 2012 to Monday, October 29, 2012
Print Report
View Report
Tue Oct 23
Wed Oct 24
Thu Oct 25
Fri Oct 26
Sat Oct 27
Sun Oct 28
Mon Oct 29
mg/dL
400
350
300
250
200
150
100
50
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
High
Low
Pattern Insights Summary
Nighttime Lows (0 Found)
No significant patterns detected
Daytime Lows (0 Found)
No significant patterns detected
Nighttime Highs (1 Found)
Most significant pattern of highs found between 11:10 PM and 3:55 AM
Daytime Highs (0 Found)
No significant patterns detected
Statistics
Glucose Average
152 mg/dL
Sensor Usage
7 of 7 Days
Calibrations / day
3.0
Standard Deviation
± 38 mg/dL
70
29
70 % High
29 % Target
1 % Low
Target Range
80 - 130 mg/dL
Nighttime Range
10:00 PM - 6:00 AM
Reading attached Receiver ... Finished
Receiver 'SM23471048' Attached.
1:41 PM
10/29/2012

CGMS (AGP) report

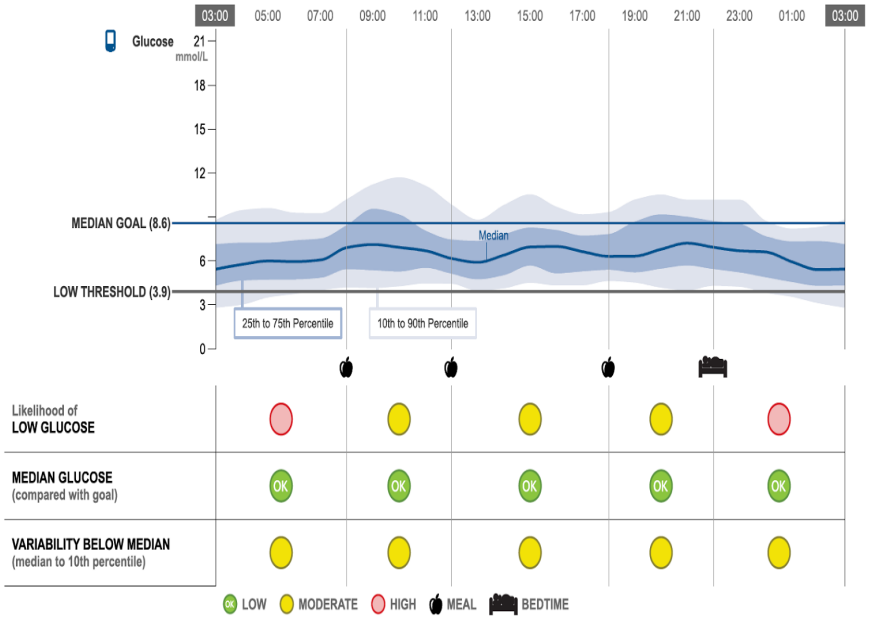
Glucose Pattern Insights

13 September 2014 - 10 October 2014 (28 days)

LOW-GLUCOSE ALLOWANCE SETTING: Medium

MEDIAN GOAL SETTING: 8.6 mmol/L (A1c: 7.0% or 53 mmol/mol)

Estimated A1c 5.8% or 40 mmol/mol



AGP=Ambulatory Glucose Profile

Information on the likelihood of low glucose, the proximity of the median glucose to target, and the degree of variability below the median at various times of day from the glucose pattern insights analysis

Glucose Control Measure	Assessment		
	OK Low	Moderate	High
Likelihood of Low Glucose	Less than 10% likelihood of exceeding the low-glucose allowance*	Between 10% and 50% likelihood of exceeding the low-glucose allowance*	Greater than 50% likelihood of exceeding the low-glucose allowance*
Median Glucose (compared to goal)	Less than goal	Greater than goal	Greater than goal AND More than 20% and 40 mg/dL (2.2 mmol/L) greater than the whole-day median
Variability Below Median (Median to 10th percentile)	Less than 35 mg/dL (1.9 mmol/L)	Between Low and High	Greater than a level that would support achieving the Median Goal without potentially causing low glucose


Thank You!