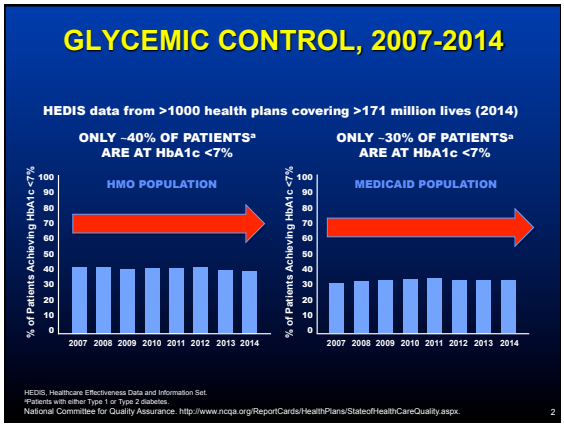
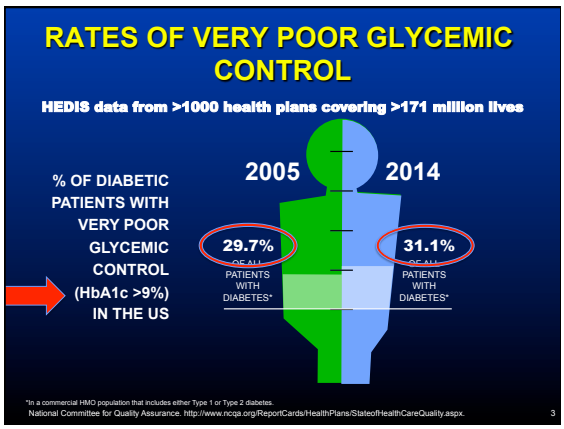
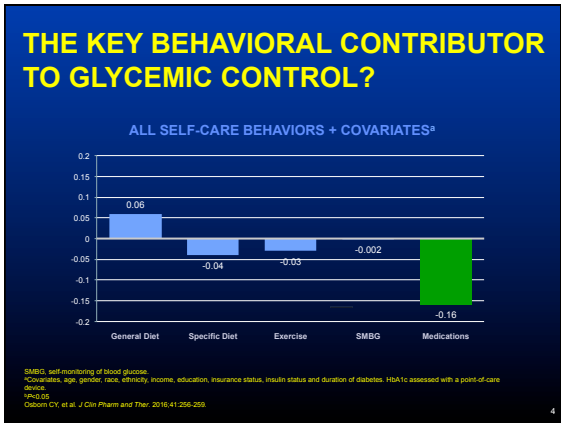
Lecture 1: 8:15 – 9:10 a.m.

William Polonsky, PhD, CDE, Presents:

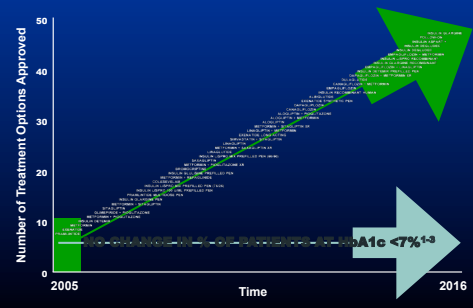
The Efficacy Mirage in Type 2 Diabetes:
Why Do Clinical Trial Results Disappear in Real-World Practice?


GLYCEMIC CONTROL, 2007-2014
HEDIS data from >1000 health plans covering >171 million lives (2014)
ONLY ~40% OF PATIENTS[a] ARE AT HbA1c <7%
HMO POPULATION
ONLY ~30% OF PATIENTS[a] ARE AT HbA1c <7%
MEDICAID POPULATION
% of Patients Achieving HbA1c <7%
2007 2008 2009 2010 2011 2012 2013 2014
HEDIS, Healthcare Effectiveness Data and Information Set.
[a]Patients with either Type 1 or Type 2 diabetes.
National Committee for Quality Assurance. http://www.ncqa.org/ReportCards/HealthPlans/StateofHealthCareQuality.aspx.
2


RATES OF VERY POOR GLYCEMIC CONTROL
HEDIS data from >1000 health plans covering >171 million lives
% OF DIABETIC PATIENTS WITH VERY POOR GLYCEMIC CONTROL (HbA1c >9%) IN THE US
2005
2014
29.7%
31.1%
PATIENTS WITH DIABETES*
*In a commercial HMO population that includes either Type 1 or Type 2 diabetes.
National Committee for Quality Assurance. http://www.ncqa.org/ReportCards/HealthPlans/StateofHealthCareQuality.aspx.
3


THE KEY BEHAVIORAL CONTRIBUTOR TO GLYCEMIC CONTROL?
ALL SELF-CARE BEHAVIORS + COVARIATES[a]
0.06
-0.04
-0.03
-0.002
-0.16
General Diet
Specific Diet
Exercise
SMBG
Medications
SMBG, self-monitoring of blood glucose.
[a]Covariates, age, gender, race, ethnicity, income, education, insurance status, insulin status and duration of diabetes. HbA1c assessed with a point-of-care device.
[b]P<0.05
Osborn CY, et al. J Clin Pharm and Ther. 2016;41:256-259.
4

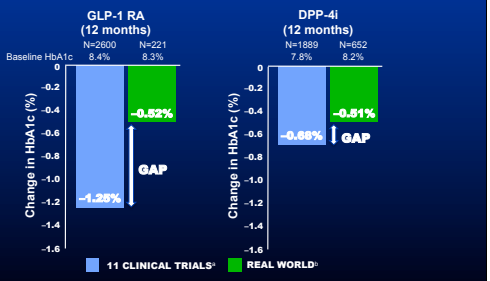
MANY NEW T2D MEDICATION OPTIONS OVER THE LAST DECADE



Type 2 diabetes U.S. drug approvals: 2005-2015. Food and Drug Administration website. https://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

6

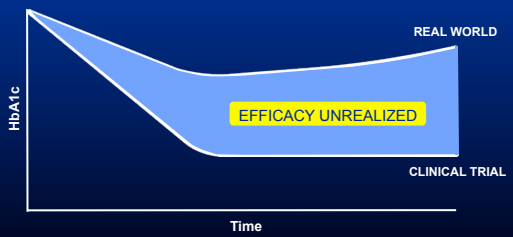
CLINICAL TRIAL RESULTS LOOK GOOD, BUT…



a
b
drug initiation to 365±90 days later.
Carls et al, 2017

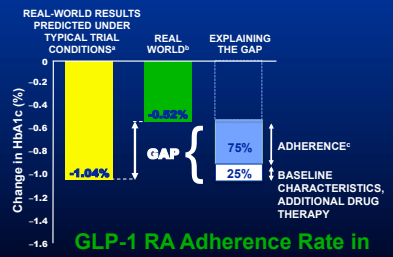
8

THE EFFICACY MIRAGE



9

POOR ADHERENCE IS THE KEY



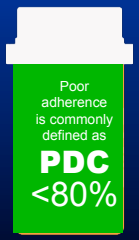
GLP-1 RA Adherence Rate in Real World = 29%

RCT, randomized clinical trial.
[a]Linear regression model fitted to estimate the change in HbA1c 1 year after initiating GLP-1 RA or DPP-4i based on baseline and treatment characteristics. [b]Optum/Humedica SmartFile database (2007-2014) was used (GLP-1 RA 221 patients; DPP-4i 652 patients). Change in HbA1c measured from drug initiation to 365±90 days later. [c]Medical adherence classified as poorly adherent if percentage of days covered (PDC) <80%.

Carls GS et al. 76th ADA Scientific Sessions. June 10–14, 2016. New Orleans, LA. Poster 117-LB.

10

DEFINING POOR ADHERENCE

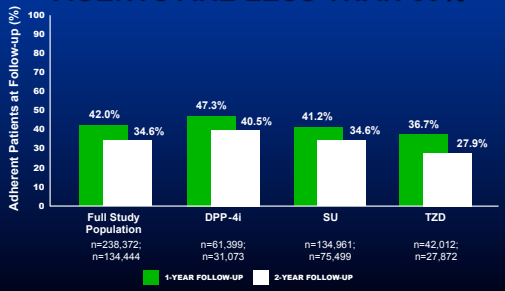


- Proportion of days covered
- Typically measured after first refill
- PDC doesn't account for
  - Prescriptions that are never filled at all[1]
  - What the patient actually takes

PDC, proportion of days covered.
1. Fischer MA et al. *J Gen Intern Med.* 2010;25:284-290.

11

ADHERENCE RATES FOR ORAL AGENTS ARE LESS THAN 50%

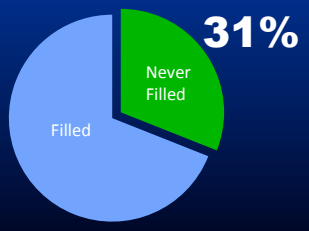


PDC, proportion of days covered; SU, sulfonylurea; TZD, thiazolidinedione.
A retrospective claims analysis of 238,372 patients with T2D with at least 1 prescription claim for a DPP-4i, SU, or TZD from January 1, 2009 to January 31, 2012. Adherence defined as PDC ≥0.8.
Farr AM et al. *Adv Ther.* 2014;31:1287-1305.

12

TRACKING NEW E-PRESCRIPTIONS FOR DIABETES MEDICATIONS

AMONG 75,589 INSURED PATIENTS IN THE FIRST YEAR OF A COMMUNITY-BASED E-PRESCRIBING INITIATIVE

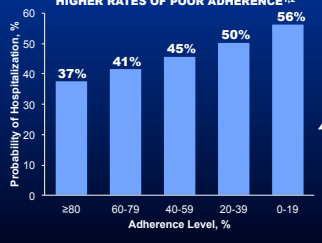


Fischer MA et al. *J Gen Intern Med*. 2010;25:284-290.

13

CLINICAL IMPACT OF POOR ADHERENCE

HOSPITALIZATION RISK INCREASES WITH HIGHER RATES OF POOR ADHERENCE[1,2]



39%
increased risk of all-cause mortality due to poor adherence to oral hypoglycemics[2]

Poor adherence defined as PDC <0.8

Data was provided by a large, Medicare supplemental (MarketScan) database from July 1, 2009 to June 30, 2014. There were 123,235 patients with T2D aged ≥65 who received glucose-lowering agents. Comparisons between adherent (defined as PDC ≥80%) and poorly adherent (PDC <80%) were all statistically significant at $P<0.001$.

1. Boye KS et al. 76th ADA Scientific Sessions. June 10–14, 2016. Poster 1221-P.
2. Ho PM et al. *Arch Intern Med*. 2006;166:1836-1841.

14

INTERVENTION STRATEGIES TO ADDRESS MEDICATION ADHERENCE

- Written medication instructions
- Enhancing HCP adherence skills
- Goal setting
- Stimuli/prompts to take medications
- Enhancing support from significant others
- Special packaging of medications
- Self-monitoring of medication adherence
- Habit analysis and intervention

Conn and Rupar, 2017

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INTERVENTION STRATEGIES TO ADDRESS MEDICATION ADHERENCE

- Medication side effect management
- Feedback about medication adherence
- Medication calendars
- Enhancing patient self-management skills
- Providing consequences/rewards for adherence
- Motivational interviewing
- Stress management

Conn and Rupar, 2017

16

EFFECTIVENESS OF CURRENT INTERVENTION STRATEGIES

Review of 771 RCTs indicate that effects are modest (Cohen's d):

- Overall: 0.29
- Behavioral strategies: 0.33
- Addressing habits: 0.37
- No behavioral strategies: 0.28

"Much room remains for improvement."

Conn and Ruppar, 2017

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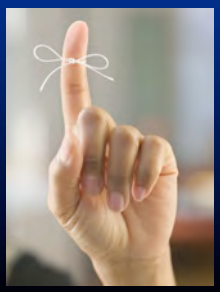
THE PRESUMED PROBLEM: FORGETFUL/DISORGANIZED



19

Gadkari and McHorney BMC Health Services Research 2012, 12:98
http://www.biomedcentral.com/1472-6963/12/98

BMC Health Services Research

RESEARCH ARTICLE Open Access

Unintentional non-adherence to chronic prescription medications: How unintentional is it really?

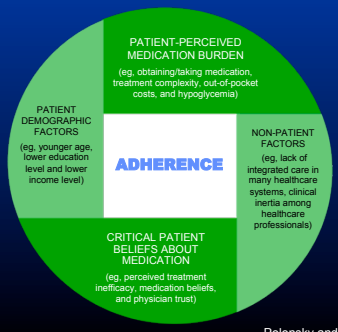
Abhijit S Gadkari* and Colleen A McHorney

"Patient' s medication beliefs, especially perceived need for medication and perceived medication affordability, were strong predictors of unintentional non-adherence."

Gadkari and McHorney, 2012

21

MAJOR CONTRIBUTORS



Polonsky and Henry, 2016

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THE NEW ENGLAND JOURNAL of MEDICINE

MEDICINE AND SOCIETY

Debra Malina, Ph.D., Editor

Beyond Belief — How People Feel about Taking Medications for Heart Disease

Lisa Rosenbaum, M.D.

"It's our job to help patients live as long as possible free of CVD complications. Although most patients share that goal, we don't always see the same pathways to get there.
I want to believe that if patients knew what I know, they would take their medicine. What I've learned is that if I felt what they feel, I'd understand why they don't."

Rosenbaum, 2015

23

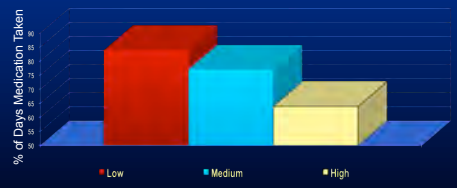
PERCEIVED TREATMENT INEFFICACY

Lack of tangible benefits contributes to discouragement and poor adherence

1. Polonsky WH. *J Diabetes*. 2015;7:777-778. **2.** Polonsky WH, Skinner TC. *Clin Diabetes*. 2010;28(2):89-92.

25

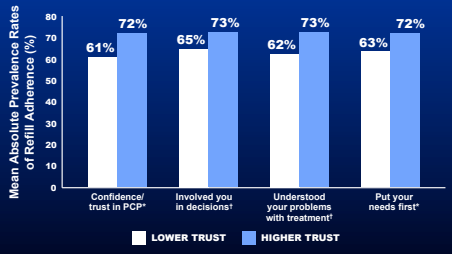
CO-PAYS AND ORAL MEDICATIONS



Colombi AM, et al. *J Occup Environ Med*. 2008;50:535-541

27

LACK OF PHYSICIAN TRUST



Differences in prevalence of poor refill adherence for any cardiometabolic medication in a cohort of 9377 patients with diabetes. Respondents were classified as poorly adherent when they had no medication supply for >20% of the observation time.

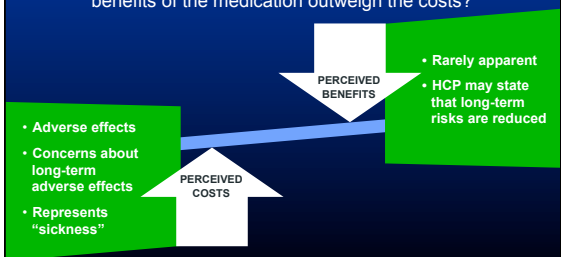
*Trust is defined using 2 items from the Trust in Physicians Scale (TIPS) modified to match the 4-point Consumer Assessment of Healthcare Providers and Systems (CAHPS) scale options during the preceding 12 months. †Shared decision-making was determined using 2 items from the Interpersonal Processes of Care (IPC) instrument during the preceding 12 months.

Ratanawongsa N et al. *JAMA Intern Med*. 2013;173:210-218.

28

MEDICATION BELIEFS

Perceived worthwhileness: Does the patient believe the benefits of the medication outweigh the costs?



Polonsky WH. *J Diabetes*. 2015;7:777-778.

29

MEDICATION BELIEFS

ROY

Takes 2 oral medications for T2D and basal insulin; his last HbA1c was 6.8%

WHO IS DOING <u>BETTER</u> WITH HIS DIABETES?

SAM

Doesn't take any medications for T2D; his last HbA1c was 9.1%

ROY. How healthy you are, and your risk of complications, is <u>not</u> determined by how much medication you take.
It is your metabolic results that matter.
Even if you are not taking pills or insulin, high blood sugars will likely lead to future problems.

Polonsky WH. *J Diabetes*. 2015;7:777-778.

WHY DO PATIENTS FEEL THIS WAY?

- Threatening patients with medication
  - *"If you can't make some positive changes, then we'll have no choice but to put you on more medication, and perhaps even start insulin."*
- Underlying messages
  - More medication should be avoided at all costs
  - You have failed
  - You are to be punished

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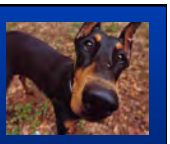
SO WHAT TO DO?



1. Ask correctly
   - *"Any problems taking those medications?"*

   vs.
   - *"What's one thing about taking your medications that's been challenging?"*

35

SO WHAT TO DO?

1. Ask correctly
2. Forgetfulness
   - "Aside from forgetting, what else is tough about taking your meds?"
   - Anchoring strategies

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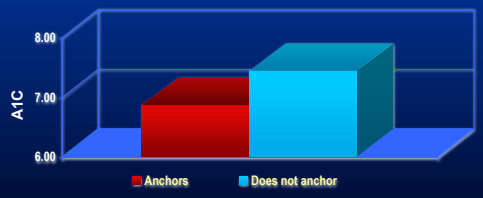
Anchoring Medication to Daily Events



"A daily event (a meal, TV show, bedtime, brushing my teeth) reminds me."

Littenberg B, et al. *BMC Fam Prac.* 2006;7:1.

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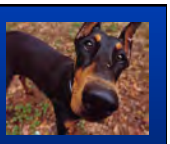
SO WHAT TO DO?



1. Ask correctly
2. Forgetfulness
3. Treatment complexity
   - Simplify if possible
   - Provide additional details as needed

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SO WHAT TO DO?

1. Ask correctly
2. Forgetfulness
3. Treatment complexity
4. Patient-provider trust
   - Listen, listen, listen

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SO WHAT TO DO?

1. Ask correctly
2. Forgetfulness
3. Treatment complexity
4. Patient-provider trust
5. Talk about beliefs about diabetes and medications

40

Challenging Harmful Beliefs

1. Taking your medications is one of the most powerful things you can do to positively affect your health
2. Your medications are working even if you can't feel it
3. Needing more medication isn't your fault
4. More medication doesn't mean you are sicker, less medication doesn't mean you are healthier

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CONCLUSIONS

Poor medication adherence:

- **… explains a great deal of the lack of glycemic progress over the past decade**
- **… is commonly an *attitudinal* issue, not just a behavioral issue.**
- **… is best addressed by considering the patient's perspective, and encouraging a two-way conversation about the perceived pro's and con's of the medication.**

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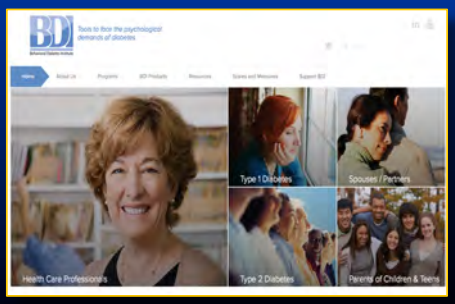
Thanks for Listening!



www.behavioraldiabetes.org

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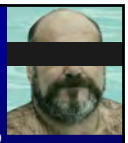
Lecture 2: 11:30 – 12:30 p.m.

Ian Blumer, MD, FRCPC, Presents:

Which One, and When? Oral Medications for the Treatment of Type 2 Diabetes and Their Cardiovascular Affects

Which One, and When? Oral Medications for the Treatment of Type 2 Diabetes and Their Cardiovascular Effects

Case 1: Edward



- 62 year old centrally obese male (BMI 42) with with a 15-year history of type 2 diabetes also with dyslipidemia, HTN, ED, OSA, bladder cancer and CAD
- Family Hx: 3 brothers with type 2 diabetes (1 deceased/CAD)
- Notes: No home glucose monitoring data (He does not bring his meter to clinic as he "forgets" it every time)
  - Diabetes Meds: Metformin 500mg BID, glipizide 20mg BID, sitagliptin 50 mg BID, empagliflozin 10 mg QD , and glargine 100 units QHS started 6 months ago
  - Current A1c 10.5% (9.6% 1 year ago, 10.1% 2 years ago)
  - Creatinine 1.4 mg/dl, eGFR 50
  - LDL 92 mg/dl, Triglycerides 356 mg/dl, HDL 22 mg/dl

What is the most likely reason why Edward has not achieved his A1c goal?

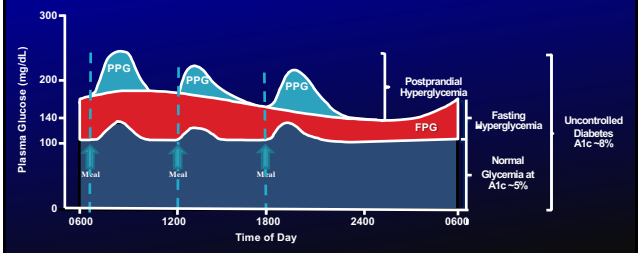
A	He needs prandial insulin
B	He needs a GLP-1 RA
C	He is very ignorant about what to eat regarding his diabetes
D	His diabetes regimen is too complicated
E	He is most likely poorly adherent with his medications

Glycemic Target Goals for Patients with Type 2 Diabetes

Treatment Goal	ADA	AACE
HbA_{1C} (%)	< 7	≤ 6.5
FPG (mg/dL)	80-130	<110
Preprandial glucose (mg/dL)	80–130	< 110
Postprandial glucose (mg/dL)	< 180*	< 140**

* Peak PPG; ** 2 Hr PPG
American Diabetes Association. *Diabetes Care*. 2015: 38(suppl 1):S33-S40.
Handelsman, Y., et al. (2015). Endocr Pract 21(0): 1-87.

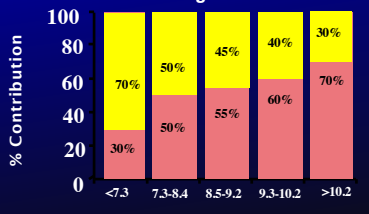
24-hour Glucose Profile in Patients with T2D: Both Fasting and Postprandial Glucose Contribute to the A1c



A1c=glycated hemoglobin; FPG=fasting plasma glucose; PPG=postprandial glucose.
Adapted from Ridde MC. *Diabetes Care*. 1990;13(6):676-686. Material from this publication has been used with the permission of American Diabetes Association. Copyright and all rights reserved.

Fasting vs Postprandial Glucose: Relationship to A1C Level

FPG contribution to HbA1c is greater when HbA1c is higher
PPG contribution to HbA1c is greater when HbA1c is lower

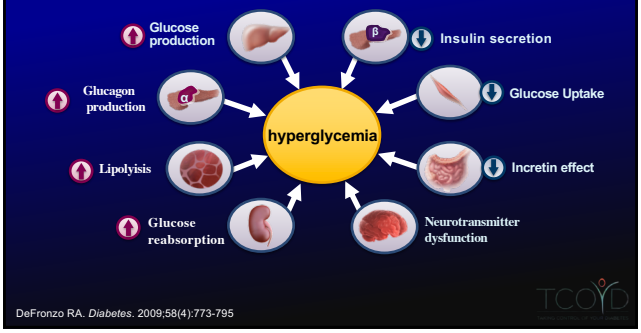


Inflection point Is ~ 8.4%

Postprandial Plasma Glucose (PPG)
Fasting Plasma Glucose (FPG)

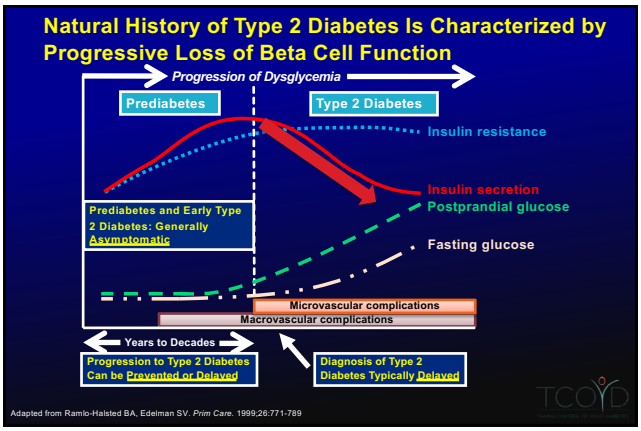
Monnier L et al. *Diabetes Care*. 2003;26(3):881-885.

Multiple Defects Contribute to the Pathophysiology of Type 2 Diabetes Necessitating Targeted Therapy



DeFronzo RA. *Diabetes*. 2009;58(4):773-795

Natural History of Type 2 Diabetes Is Characterized by Progressive Loss of Beta Cell Function



Adapted from Ramlo-Halsted BA, Edelman SV. *Prim Care*. 1999;26:771-789

9 FDA-Approved Classes of Oral Medications for Type 2 Diabetes

- Metformin (first line therapy unless contraindicated)
- Sulfonylureas, meglitinides
- Glitazones (pioglitazone, rosiglitazone)
- DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)
- SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin , ertugliflozin)
- Bile acid sequestrant (colesevelam)*
- Dopamine receptor agonists (bromocriptine meslate)*
- Alpha glucosidase inhibitors (acarbose, miglitol)*

** not discussed in detail in this presentation*

http://www.fda.gov/drugs

Clinical Treatment Pearls

- Always confirm as best you can if the patient is adherent with his/her medications (check refill history)
- The higher the baseline A1c, the greater the fall in A1c with any therapeutic intervention
- Adding diabetes medication instead of switching is the rule rather than the exception
- Always address the ABCs (A1c and Aspirin {81mg if over 50 y/o}, BP {<140/90 mm/Hg} and Cholesterol {LDL<100mg/dl or <70 if CAD present})
- Spending time with the patient and his support person to explain why you are starting a new medication and what benefits it will have over the long term, as well as answering any concerns will improve adherence

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

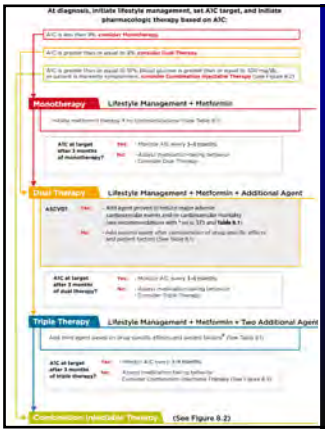
Edelman SV (TCOYDtv). 3 September 2015. Get Type 2 Diabetes and Live Longer Because of it (video)

Case 2: Collin

- 52 year old centrally obese male
- 1-year history of type 2 diabetes, diagnosed with dyslipidemia and HTN
- Family History: Both Parents had type 2 diabetes, HTN and CAD
- Notes: BMI 37 (1yr ago it was 34, 2 yrs ago it was 31)
  - Diabetes therapy included only Metformin 1000 mg BID
  - Current A1c 8.5% (7.6% 6 months ago, 7.1% at diagnosis)
  - Creatinine 1.3 mg/dl, eGFR 65
  - LDL 112 mg/dl, Triglycerides 256 mg/dl, HDL 29 mg/dl

What class of agent would you add to Collin's current regimen (no one right or wrong answer)?

A	Sulfonylurea
B	DPP-4 inhibitor (sita-, saxa-, lina- or alogliptin)
C	SGLT-2 inhibitor (cana-, empa-, ertu- or dapagliflozin)
D	Basal insulin given once a day
E	GLP-1 RA (liraglutide, exenatide, dulaglutide, semaglutide)
F	Thiazolidinedione (pioglitizone)



ADA Antihyperglycemic therapy in type 2 diabetes: General recommendations

- If no atherosclerotic cardiovascular disease (ASCVD), consider combination of metformin with any one of six treatment options (SFU, TZD, DPP-4 inh, SGLT-2 inh, GLP-1 RA, basal insulin).
- If patients has ASCVD, second agent with evidence of CV risk reduction should be added (after consideration of drug-specific and patient factors).

American Diabetes Association. 8. Pharmacologic approached to glycemic treatment: Standards of Medical Care in Diabetes - 2018. *Diabetes Care* 2018;41(Suppl. 1):S73-S85

Summary Of ADA Algorithm

- Step 1: start with metformin unless contraindicated
- Step 2: Use any other option for diabetes available in the entire universe
- Step 3: Use any other option for diabetes available in the entire universe except what you used in steps 1 and 2
- Step 4: Use any other option for diabetes available in the entire universe except what you used in steps 1, 2 and 3

Is this helpful?

Must Individualize Therapy

American Diabetes Association Dia Care 2017;39:S52-S59

Option #1: Metformin (new info)

MOA	* Reduces hepatic glucose output
Benefits	* Significant A1c reductions (~1 to 1.5%) * Favorable to neutral effects on body weight * No hypoglycemia * Generic (low cost)
Concerns	*GI side effects (often dose-related), sustained release formulations may help * Contraindicated in chronic renal insufficiency see below * Potential for lactic acidosis (rare)
Clinical Pearls	*Start with low dose and up-titrate dose to improve GI tolerance or use long acting release formulation *eGFR <60 to ≥45 OK to use/monitor kidneys *eGFR <45 to ≥30 OK to use 50% maximum dose/ monitor kidney function every 3 months If you stop metformin, substitute with a different agent *Check B-12 levels

Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 13th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

Diabetes Care. 2011 Jun; 34(6): 1431–1437.

Option #2: Insulin Secretagogues (sulfonylureas / meglitinides)

Mechanism of Action	* Stimulate the pancreas to secrete insulin
Benefits	* A1c reductions (~1.0 to1.5%) * Quickly lower glucose/A1c * Generic (very low cost, pennies per day)
Concerns	* High 2ndary failure rate, however when you st… them the patient's A1c typically goes up. · Weight gain *Increase risk of hypoglycemia (elderly, CRI, CAD)
Clinical Pearls	*Use shorter-acting SFU (e.g., glipizide) to reduce hypoglycemia risk *May be more effective in lower doses as an 'add-on' medication (combination therapy)

Imp.

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

	Generic Name	Trade Name
Glinides	Nateglinide Repaglinide	Starlix Prandin
Sulfonylureas	Glimepiride Glipizide Glipizide (extended release) Glyburide	Amaryl Glucotrol Glucotrol XL DiaBeta, Micronase Glynase PressTab

Physicians' desk reference (68th ed.). (2014). Montvale, NJ: Physicians' Desk Reference.

Option #3: Glitazones (pio-, rosiglitazone)

(New info in red)

Mechanism of Action	* Reduce insulin resistance
Benefits	* No hypoglycemia * Durable glycemic control * Positive effect on lipids (↑ HDL-C, converts small dense to large buoyant LDL-C)
Concerns	* Weight gain * Edema (precipitating CHF) · Bone fractures primarily in caucasion women · Risk of bladder cancer has been disproven
Clinical Pearls	* Effective in prediabetes, best used early in the natural history (balance with potential side effects) * Be cautious in combo with insulin (fluid retention)

New

Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014. http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm

Case 3: Jamie

- 42 year old African American obese male
- Type 2 diabetes diagnosed at age 35
- PMH: HTN, dyslipidemia
- FH: T2DM, early CAD
- A1c 8.3% on maximum doses of metformin and SFU
  No home glucose monitoring data; "forgets" his meter and log book when he comes to clinic
- Creatinine 1.4 mg/dl, eGFR 55, BMI 36
- BP normally above 140/90 mmHg; on no HTN meds

What therapeutic intervention would you change/initiate if you were evaluating Jamie once you have confirmed he is adherent with his medications?

A	Initiate basal insulin therapy
B	Add a DPP4 inhibitor
C	Add a SGLT2 inhibitor
D	Add a GLP1-RA
E	Intensify lifestyle modification and education

Case 3: Jamie (continued)

- Treatment History
  - A DPP-4 inhibitor was added to his regimen
  - He was sent to a CDE with his wife
  - Follow up was arranged for one month instead of the usual 3 to 4 months
- Jamie did well without weight gain or hypoglycemia
- The A1c fell to 7.4%
- His PCP eventually started an ACE inhibitor to get his BP below 140/90 mm/Hg and a statin to get his LDL <100 mg/dl
- It took almost 12 months to get his A1c, BP and lipids at goal as he was resistant to starting new medications.

Option #4: DPP-4 Inhibitors

Mechanism of Action	* Inhibit the enzyme, DPP-4, that normally inactivates GLP-1 and other incretins within minutes
Benefits	* Once daily oral administration * Virtually no side effects * Can be added to any diabetes drug except GLP-1 RAs * A1c reduction ~ 0.5-1% range (depends on baseline A1c)
Concerns	* Dose adjustment with renal insufficiency (only for sita-,saxa-and alogliptin), not for linagliptin * Rare reports of hypersensitivity skin reactions * No association or signal for pancreatitis and pancreatic cancer (2013 FDA hearing on pancreatic cancer and incretins)
Clinical Pearls	* Efficacy of the DPP-4 inhibitors is similar * All DPP-4 inhibitors come in combination pill with metformin (Alo- is combined with Pio- and Lina- is combined with empagliflozin)

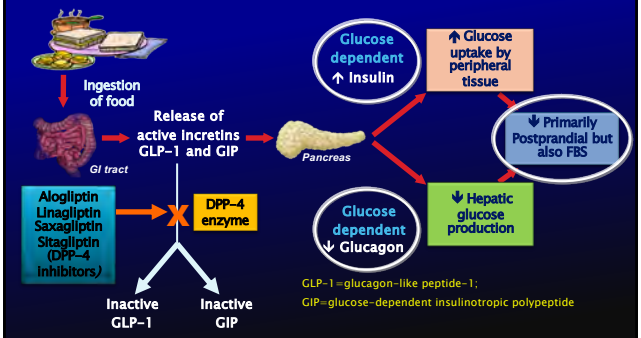
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

Generic and Trade Names

	Generic Name	Trade Name
DPP4-Inhibitors	Alogliptin	Nesina
	Linagliptin	Tradjenta
	Saxagliptin	Onglyza
	Sitagliptin	Januvia

Physicians' desk reference (68th ed.). (2014). Montvale, NJ: Physicians' Desk Reference.

Mechanism of Action of DPP-4 Inhibitors



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

Combination Pills With A DPP-4 Inhibitor

Generic Name	Trade Name	Daily Dose Range (mg)	Recommended Frequency
Sitagliptin/metformin	Janumet	50/500, 50/1000	Twice with meals
Saxagliptin/metforminER	Kombiglyze XR	5/500, 2.5/1000, 5/1000	Once daily with evening meal
Linagliptin/metformin	Jentadueto	2.5/500, 2.5/850, 2.5/1000	Twice with meals
Linagliptin/empagliflozin	Glyxambi	5/10, 5/25	Once daily
Dapagliflozin/saxagliptin	Qtern	10 mg/5mg	Once daily
Alogliptin/pioglitazone	Oseni	25/15, 25/30, 25/45, 12.5/15, 12.5/30, 12.5/45	Once
Alogliptin/metformin	Kazano	12.5/500, 12.5 mg/1000	Twice with meals
Ertugliflozin/sitagliptin	Steglujan	5/100, 15, 100	Once daily

Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 13th Edition. Professional Communications, Inc., Greenwich, CT. 528 pages, 2017.

Comparison of DPP-4 Inhibitors

EFFICACY VERY SIMILAR

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin
Usage and Indications	* Use with diet and exercise to improve glycemic control in type 2 diabetes * Combination studies with SFUs, MET, pioglitazone and Insulin			
Dosage Administration	Once daily, with or without food Tablets: 25mg 12.5mg (CrCl <50), & 6.25mg (CrCl <30)	Once daily, with or without food Tablets: 5mg No dose adjustment needed for renal function	Once daily, with or without food Tablets: 5mg & 2.5mg (CrCl <50)	Once daily, with or without food Tablets: 100mg, 50mg (CrCl <50), & 25mg (CrCl <30)
Contraindications	Hypersensitivity	Hypersensitivity (i.e., urticaria, angioedema, or bronchial hyperreactivity)	Hypersensitivity	Hypersensitivity (i.e., anaphylaxis or angioedema)
Warnings and precautions	*When used with a SFU or insulin, a lower dose of SFU or insulin may be needed to reduce the risk of hypoglycemia *Post-marketing reports of pancreatitis (D/C if suspect pancreatitis; Use with caution in patients with history of pancreatitis)			

Physicians' desk reference (68th ed.). (2014). Montvale, NJ: Physicians' Desk Reference.

Case 4: Susan

- 58 year old obese female
- Type 2 diabetes diagnosed 10 years ago
- A1c 8.7%, (one year ago it was 8.2%) and adamantly refused any injectable agent
- On max. doses of metformin and a DPP4-inhibitor
- Family History: Type 2 diabetes and obesity (both parents)
- Notes:
  - Very fearful of injections and gaining weight
  - Normal renal function, BMI 31kg/m^2
  - HGM shows FBS (137-221 mg/dl), and a few post dinner values (187 to 265mg/dl)

How would you treat Susan to lower her A1c?

A	Add a SFU
B	Add a TZD
C	Start a SGLT-2 inhibitor (cana-, dapa-,empa-ertugliflozin)
D	Try to convince her to add a GLP-1 receptor agonist (exenatide, liraglutide, dulaglutide, semaglutide)
E	Try to convince her to add a basal insulin at bedtime

Option #5: SGLT-2 Inhibitors

Mechanism of Action	* Reduces renal glucose reabsorption and increases urinary glucose excretion
Benefits	* No hypoglycemia (except when being used with SFU or insulin) • Mean A1c reduction ~ 1% (starting from a baseline A1c of ~8.0%) * Weight loss (2-5% of body weight) and systolic BP reduction (2-6mmHg)
Concerns	* Genital mycotic infections. In women (6 to 12% higher than comparator) and in uncircumcised males (2 to 6% higher than comparator) * Hypotension secondary to volume contraction especially in the elderly, those on loop diuretic use and in patients with reduced renal function. * 4 to 8% elevation in LDL cholesterol (TGs goes down and HDL goes up) * Assess renal function (discussed later) * New label warnings : DKA (discussed later)/bone fractures/risk of amputation DISCUSSED LATER WITH CVOT DATA
Clinical Pearls	• 1st oral medication that leads to statistically significant weight loss • Empa-and canagliflozin showed positive CVD outcome trials(discussed later) * Can be added to any other oral agent or injectable * Tell women to practice good hygiene and look out for yeast infections (may want to suggest to have some anti yeast infection medication at home such as Monostat)

Physicians' desk reference (68th ed.). (2014). Montvale, NJ: Physicians' Desk Reference.

Generic and Trade Names (dose range)

	Generic Name	Trade Name
SGLT-2 Inhibitor	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Invokana Farxiga Jardiance Steglatro

Canagliflozin:
- Suggested starting dose: 100 mg daily before first meal of day (eGFR >45mL/min)
- Increase to 300 mg daily if tolerating 100 mg daily and eGFR > 60 mL/min

Dapagliflozin:
- Starting dose: 5mg daily in morning with or without food (eGFR for both doses > 60)
- Increase to 10 mg daily if tolerating and need additional glycemic control

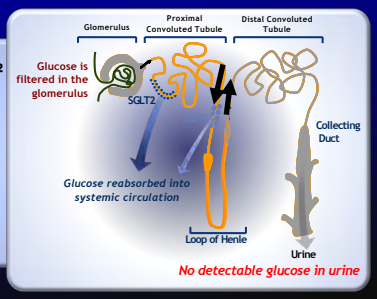
Empagliflozin:
- Starting dose: 10 mg daily in morning with or without food (eGFR>45)
- Increase to 25 mg daily if tolerating and need additional glycemic control (eGFR>45)

Ertugliflozin:
- Starting dose: 5 mg daily in morning with or without food (eGFR for both doses >60)
- Increase to 15 mg daily if tolerating and need additional glycemic control

Physicians' desk reference (68th ed.). (2014). Montvale, NJ: Physicians' Desk Reference.

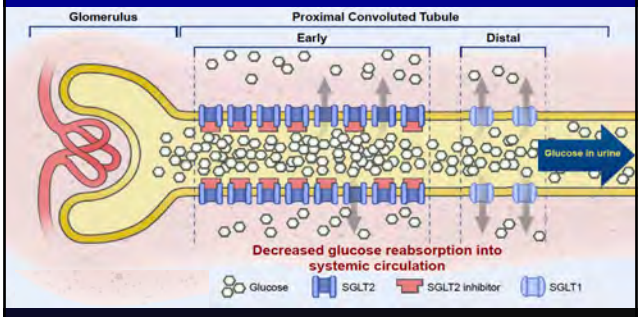
Renal Handling of Glucose in a Non-Diabetic Individual

- 180 g/day/1.73 m² is filtered glucose load[1]
- SGLT–2 transports 90% of filtered glucose out of the tubular lumen[1–4]



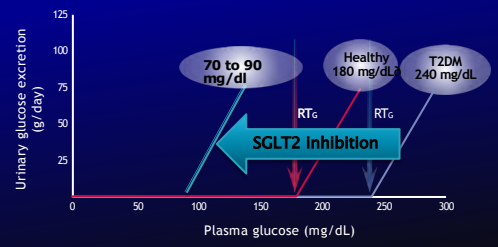
SGLT = sodium-glucose co-transporter.
1. Wright EM et al. *J Intern Med.* 2007;261(1):32-43. 2. Kanai Y et al. *J Clin Invest.* 1994;93(1):397-404. 3. You G et al. *J Biol Chem.* 1995;270(49):29365-29371. 4. Wright EM. *Am J Physiol Renal Physiol.* 2001;280(1):F10-F18.

Reduced Renal Glucose Reabsorption In Type 2 Diabetes With SGLT-2 Inhibition



Adapted with permission from Abdul-Ghani, DeFronzo RA.
1. Cowart SL, Stachura ME. In: Walker HK et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations.* 3rd ed. Boston, MA: Butterworths; 1990:653-657. 2. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract.* 2008;14(6):782-790. 3. Nair S, Wilding JP. *J Clin Endocrinol Metab.* 2010;95(1):34-42. 4. Janssen Pharmaceuticals, Inc.; 2013.

Renal Glucose Reabsorption In Normal, Type 2 DM And With SGLT-2 Inhibition



Adapted with permission from Abdul-Ghani, DeFronzo RA.
T2DM = type 2 diabetes mellitus.
1. Cowart SL, Stachura ME. In: Walker HK et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations.* 3rd ed. Boston, MA: Butterworths; 1990:653-657. 2. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract.* 2008;14(6):782-790. 3. Nair S, Wilding JP. *J Clin Endocrinol Metab.* 2010;95(1):34-42. 4.: Janssen Research & Development LLC. FDA Briefing Document. Endocrinologic and Metabolic Drugs Advisory Committee, 2013.

FDA Drug Safety Communication: the Prescribing Information for ALL SGLT-2 inhibitors was updated to include new Warnings and Precautions for ketoacidosis, urosepsis and pyelonephritis.: December 14, 2015

1. Extremely low incidence
2. Many but not all of the reports for DKA were in patients with LADA
3. Be especially cautious in insulin using patients (since glucagon levels go up with SGLT2s and by lowering the insulin too much an imbalance of glucagon to insulin may occur, leading to DKA)
4. Be especially cautious in women with a history of UTIs, pyelonephritis and/or genital mycotic infections

Brooks M. SGLT2 Inh Diabetes Drugs May Cause Ketoacidosis: FDA. Retrieved from http://www.medscape.com/viewarticle/844754
Erondu N, et al. Diabetes Care September 2015 38:1680-1686; 2015

Case 4: Susan continued

- Low dose SGLT-2 inhibitor was added to her regimen and then titrated to the maximum dose after one month
- A1c dropped to 7.5% (baseline 8.7%) and she lost 15 lbs
- She was more motivated to improve her lifestyle habits and her A1c came down to 7.2% over the next 4 months
- She experienced a yeast infection which was easily treated with a topical antifungal and she did not want to stop the SGLT2 inhibitor
- She also said she had increased urination in the mornings for the first few weeks but that stopped
- LDL went from 100 to 108 mg/dL (8% rise) and her TGs dropped by 25%

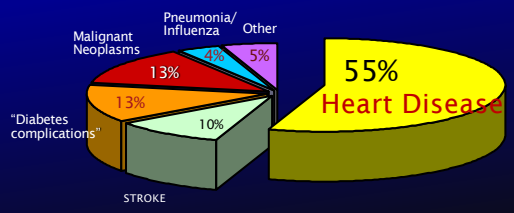
Which of the following statement is true regarding SGLT-2 inhibitors?

A	They are contraindicated with loop diuretics and a history of DKA
B	They should not be used in women or men with a history of UTIs
C	They can be used safely with pioglitazone and GLP-1 RAs
D	They are approved for both type 1 and type 2 diabetes
E	Men who are not circumcised should not use them

What is the most common cause of death in type 2 diabetes?

A	Nephropathy including end stage renal disease requiring dialysis or transplantation
B	Complications from peripheral and autonomic neuropathy
C	Stroke or cardiovascular disease
D	Complications from obesity
E	Peripheral arterial disease

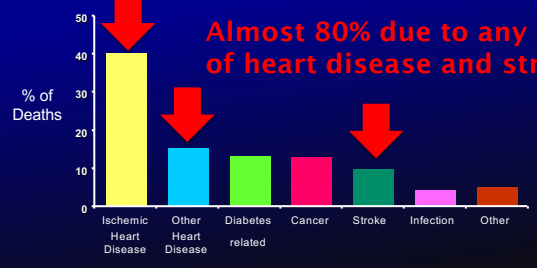
Causes of Mortality in Patients With Diabetes 20 years Ago: The Same Trend Exists Today



http://professional.diabetes.org/?loc=bb-dorg

Diabetes in America.. NIH No. 95-1468. 1995:233-257.

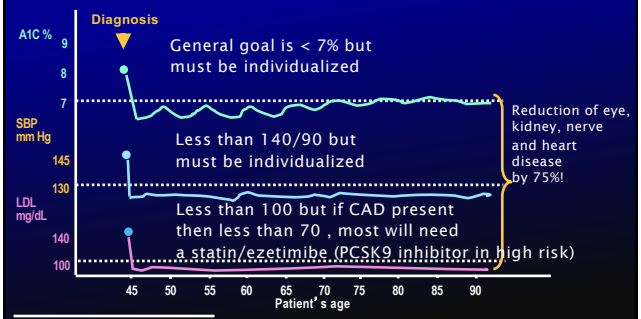
Most Common Causes of Death in People With Type 2 Diabetes: It is not eye, kidney or nerve disease!



http://professional.diabetes.org/?loc=bb-dorg

Geiss LS, et al. In: Diabetes in America, 2nd ed. 1995. Bethesda, MD: National Institutes of Health; 1995:Chapter 11.

Primary Objectives of Effective Management



American Diabetes Association. *Diabetes Care.* 2017;40(suppl 1)

Impact of Intensive Glucose-Lowering Therapy in DM: Summary of Major RCTs

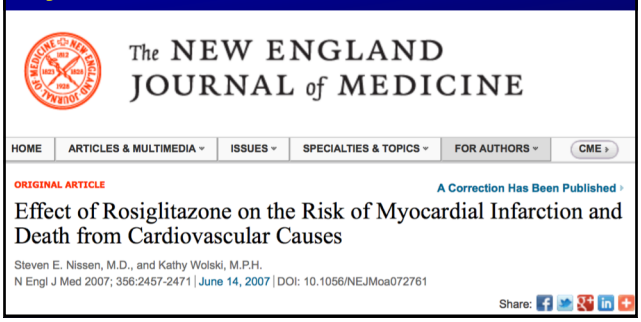
Study	Microvasc		CVD		Mortality	
UKPDS 33 (7.0 vs. 7.9%)	↓	↓	↔	↓	↔	↓
DCCT / EDIC* (7.2 vs. 9.1%)	↓	↓	↔	↓	↔	↓
ACCORD (6.4% vs. 7.5%)	↓		↔		↑	
ADVANCE (6.3% vs. 7.0%)	↓		↔	↔	↔	↔
VADT (6.9% vs. 8.4%)	↓		↔	↓	↔	↔

Courtesy of Silvio Inzucchi MD, Yale University

Adapted: Kendall DM, Bergenstal RM. International Diabetes Center 2009, 2015 UKPDS Group. *Lancet* 1998;352:854; Holman RR. *NEJM* 2008;359:1577; DCCT Group. *NEJM* 1993;329:977; Nathan DM. *NEJM* 2005;353:2643. Gerstein HC. *NEJM* 2008;358:2545; Patel A. *NEJM* 2008;358:2560; Duckworth W. *NEJM* 2009;360:129. (*erratum*:361:1024); DCCT Group. JAMA 2015;313:45; Zoungas S. *NEJM* 2014;371:1392; Hayward RA *NEJM* 2015;372:23

Initial Trial
Long Term F/U
* in T1DM

The Etiology Of The CVOTs: a flawed meta analysis published in the NEJM by Steve Nissen and later discredited



Large Non-Insulin CVOTs in T2DM
DPP-4 Inhibitors

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-i	saxagliptin ✓	alogliptin ✓	sitagliptin ✓	linagliptin	linagliptin
Comparator	placebo NEUTRAL	placebo NEUTRAL	placebo NEUTRAL	sulfonylurea	placebo
N	16,500	5,400	14,000	6,000	8,300
Results	2013	2013	June 2015	2017	2017

Large Non-Insulin CVOTs in T2DM
GLP-1 Receptor Agonists

Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP1-RA	liraglutide ✓	lixisenatide ✓	semaglutide ✓	exenatide LR ✓	dulaglutide
Comparator	placebo POSITIVE	placebo NEUTRAL	placebo POSITIVE	placebo NEUTRAL	placebo
N	9,500	4,000	3,000	7,400	8,300
Results	2016	2015	2016	2018	2019

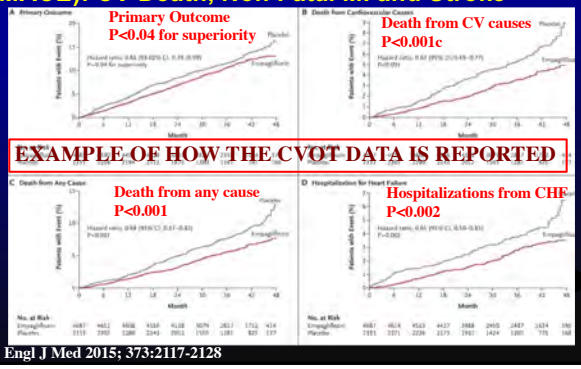
Courtesy of Silvio Inzucchi MD, Yale University

Large Non-Insulin CVOTs in T2DM
SGLT-2 Inhibitors

Study	EMPA-REG	CANVAS	DECLARE	NCT01986881
SGLT-2-i	empagliflozin ✓	canagliflozin ✓	dapagliflozin	ertugliflozin
Comparator	placebo POSITIVE	placebo POSITIVE	placebo	placebo
N	7,000	5,900	22,200	3900
Results	Sept 2015	2017	2019	2020

Courtesy of Silvio Inzucchi MD, Yale University

EMPA-REG CVOT: Primary outcome (3-point MACE): CV Death, Non Fatal MI and Stroke



N Engl J Med 2015; 373:2117-2128

Real-World CV Study on SGLT-2 Inhibitors (CVD reduction may be a class effect?)

CVD-REAL study shows SGLT-2 inhibitors significantly reduced hospitalizations for heart failure and death versus other type-2 diabetes medicines

9 March 2017

- CVD-REAL study assessed data from 300,000+ patients
  - (87% did not have history of CV disease)
- **Reduced rate of hospitalization for heart failure by 39% and all-cause mortality by 51%**

https://doi.org/10.1161/CIRCULATIONAHA.117.029190
Circulation. 2017;CIRCULATIONAHA.117.029190
Originally published May 18, 2017

New FDA Indication for Diabetes Medications

- Diabetes medications FDA approved for CV risk reduction

1. Empagliflozin (based on EMPA-REG data)
   - Reduction in risk of CV death in patients with type 2 diabetes and established CV disease
2. Liraglutide (based on LEADER data)
   - Reduction in risk of major CV events in patients with type 2 diabetes and established CV disease
   - Canagliflozin and semaglutide under review

New FDA Warning for Diabetes Medications

- FDA warning for lower limb amputation
- 2 fold increase in amputation in the CANVAS CVOT trial.
- Relative risk 0.63 (canagliflozin) vs 0.34 (placebo) amputations per 100 patient years
- No increased risk of amputation in the phase 3 clinical trial program (~10,000 patients)

Not All CVOTs Are Created Equal

Important

- Differences in study design: powered for safety or superiority
- Patient characteristics: age, weight, co-morbid complications, presence of CAD
- Comparators may be different
- Weigh gain and hypoglycemia differences
- Time to first event
- Regional differences
- Outcomes differ: overall mortality, non fatal and fatal MI, stroke, etc.
- Adherence may effect results

Gautam Das, Journal of Diabetes Research & Clinical Metabolism 2015, http://www.hoajonline.com/journals/pdf/2050-0866-4-3.pdf

Courtesy of Mikail Kosiborodi MD, Saint Lukes

Key Principles of Management of Type 2 Diabetes

- Glycemic targets & glucose-lowering therapies should be individualized
- Diet, exercise and education are the foundations of therapy
- Unless contraindicated, metformin is optimal 1st line drug
- After metformin, combination therapy with 1-3 other oral and/or injectable agents; minimize side effects
- Many patients over time will require insulin therapy alone or in combination with other agents to maintain glycemic control
- CAD is the most common cause of death and prevention strategies need to be emphasized

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

Lecture 3: 1:15 – 2:15 p.m.

John Anderson, MD, Presents:

Clinical Applications of Injectable Agents: GLP-1 Receptor Agonists, Basal Insulin and More Intensive Regimens

Case 1: Eric

- 47 yr.-old centrally obese (BMI 32) male with a 5 year history of Type 2 diabetes
- Currently on maximum doses of metformin, a SFU, and a DPP-4 inhibitor
- History of dyslipidemia, hypertension and ED
- A1c has ranged from 8.1 to 8.5% over the past 2 years
- He and his wife have seen a dietician and CDE several times

Time	Blood glucose range	Blood glucose average
Pre-Breakfast	166 - 231 mg/dL	(~182 mg/dL)
Pre- Lunch	143 - 197 mg/dL	(~177 mg/dL)
Pre- Dinner	112 - 275 mg/dL	(~213 mg/dL)
Bedtime	159 - 231 mg/dL	(~194 mg/dL)
No reports of hypoglycemia		

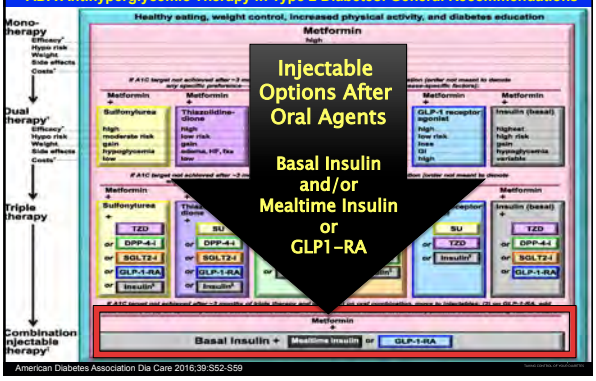
He tests 2 to 4 times a week

Which of the following would you recommend for Eric if he were your patient?

A	Initiate basal insulin
B	Initiate a GLP-1 Receptor Agonist (RA)
C	Initiate a basal bolus insulin regimen
D	Initiate a fixed combination of a basal insulin and a GLP-RA

This exact question will be repeated at the end of the presentation

ADA Antihyperglycemic Therapy in Type 2 Diabetes: General Recommendations



American Diabetes Association Dia Care 2016;39:S52-S59

Basal Insulin vs GLP-1 RA

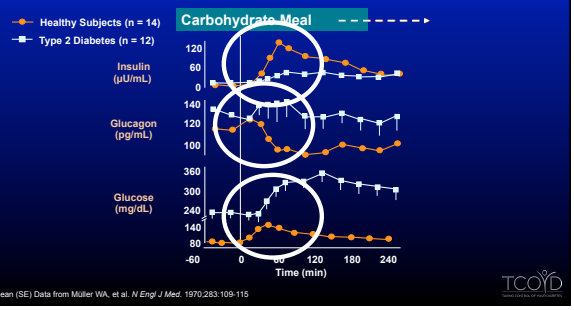
(an incretin hormone)

Insulin: injectable once or twice a day	GLP-1 RA: injectable once a day or once weekly
Need to titrate dose targeting the FBG	Reduced need to titrate dose to BG, but increase dose slowly to avoid GI side effects
Need to institute home glucose monitoring (SMBG)	"No" need for SMBG
Important to have frequent follow up when initiating basal insulin (days to weeks)	Follow up not as crucial
Weight gain	Weight loss
Hypoglycemia	No Hypoglycemia

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

TCOYD

The Pathogenesis of Type 2 Diabetes: Insulin and Glucagon Responses Are Abnormal

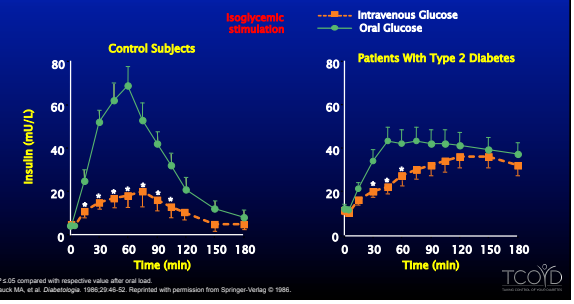


Mean (SE) Data from Müller WA, et al. *N Engl J Med.* 1970;283:109-115

TCOYD

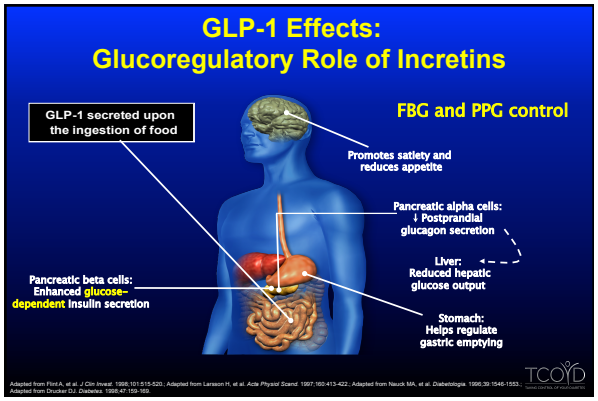
The Incretin Effect and Its Reduction in Type 2 Diabetes

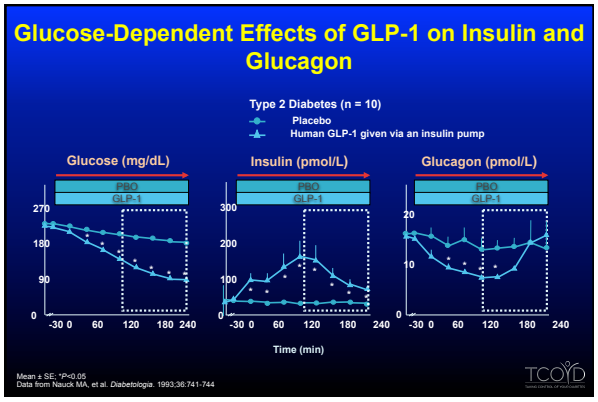
Insulin secretion after oral versus IV glucose

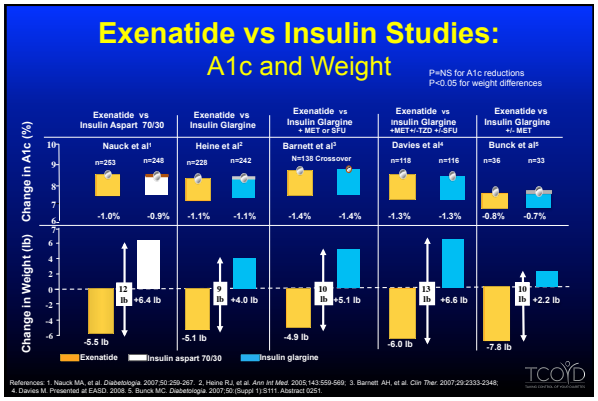


*P ≤ 05 compared with respective value after oral load.
Nauck MA, et al. *Diabetologia.* 1986;29:46-52. Reprinted with permission from Springer-Verlag © 1986.

TCOYD


GLP-1 Effects:
Glucoregulatory Role of Incretins
GLP-1 secreted upon the ingestion of food
FBG and PPG control
Promotes satiety and reduces appetite
Pancreatic alpha cells: ↓ Postprandial glucagon secretion
Liver: Reduced hepatic glucose output
Pancreatic beta cells: Enhanced glucose–dependent insulin secretion
Stomach: Helps regulate gastric emptying
TCOYD


Glucose-Dependent Effects of GLP-1 on Insulin and Glucagon
Type 2 Diabetes (n = 10)
Placebo
Human GLP-1 given via an insulin pump
Glucose (mg/dL)
Insulin (pmol/L)
Glucagon (pmol/L)
PBO
GLP-1
Time (min)
Mean ± SE; *P<0.05
Data from Nauck MA, et al. Diabetologia. 1993;36:741-744
TCOYD


Exenatide Studies:
A1c and Weight
P=NS for A1c reductions
P<0.05 for weight differences
Exenatide vs Insulin Aspart 70/30
Exenatide vs Insulin Glargine
Exenatide vs Insulin Glargine + MET or SFU
Exenatide vs Insulin Glargine +MET+/-TZD +/-SFU
Exenatide vs Insulin Glargine +/- MET
Nauck et al1
Heine et al2
Barnett et al3
Davies et al4
Bunck et al5
Change in A1c (%)
Change in Weight (lb)
-1.0%
-0.9%
-1.1%
-1.1%
-1.4%
-1.4%
-1.3%
-1.3%
-0.8%
-0.7%
-5.5 lb
+6.4 lb
-5.1 lb
+4.0 lb
-4.9 lb
+5.1 lb
-6.0 lb
+6.6 lb
-7.8 lb
+2.2 lb
Exenatide
Insulin aspart 70/30
Insulin glargine
TCOYD

GLP-1 Receptor Agonists

Mechanism of Action	* Mimic the effects of human GLP-1
Benefits	* Significant A1c reductions (1.0 to 2.0%) * Shorter acting GLP-1 RAs have greater effects on PPG * Statistically significant weight loss * No hypoglycemia (due to GLP-1 RA directly) * Once daily and once weekly formulations
Concerns	* GI side effects (typically nausea) * Contraindicated in patients with a personal or family history of MTC or MEN2 * Relative contraindication in patients with a history of pancreatitis (important to know the etiology)
Clinical Pearls	* Ideal choice in obese patients with poor control, especially those on large doses of insulin * "No" need to initiate or increase glucose testing * One of the most powerful agents for type 2 diabetes

Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. Eleventh Edition. Professional Communications, Inc., Greenwich, CT. 285 pages, 2011.

TCOYD

Generic and Trade Names: GLP-1 RAs

	Generic Name	Trade Name
GLP-1 Receptor Agonists	Exenatide	
	Twice-daily	Byetta
	Once-weekly	Bydureon
	Liraglutide	
	Once-daily	Victoza
	Dulaglutide	
	Once-weekly	Trulicity
	Lixisenatide	
	Once-daily	Adlyxin
	Semaglutide	
	Once weekly	Ozempic
Basal Insulin/ GLP-1Receptor Agonist Fixed Combination	Glargine/lixisenatide	Soliqua
	Degludec/liraglutide	Xultophy
	both once-daily	

TCOYD

ITCA 650—Medical Device To Deliver Type 2 Medication

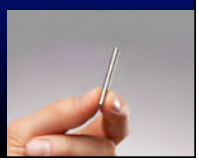
TECHNOLOGY

- Previously-approved subdermal delivery system; short office proceedure
- Small micropump
  - maintains stability at temps ≈37°C
  - maintains stability for ≥ 12 months

\+

MEDICATION: EXENATIDE

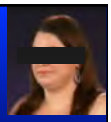
- Previously-approved GLP-1 therapeutic which demonstrates:
  - glycemic control
  - weight loss
  - safety



Not yet approved by the FDA

Case 2: Megan

- Megan is a 39 year old female with a 4 year history of type 2 diabetes
- On maximal doses of metformin, SFU, and a DPP-4 inhibitor
- She adamantly does not want to take insulin
- PMH: dyslipidemia, hypertension OSA, PCOS and overweight (BMI=29)
- eGFR 75 ml/min
- Her A1c for the past 18 months has been ~8.5%



FBS (mg/dl)	PPG (mg/dl)
Mean 191	Mean 265

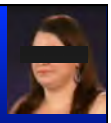
What would you recommend now for Megan?

A	Start a SGLT2 inhibitor
B	Try to convince her to start basal insulin
C	Start a GLP-1 RA and discontinue the DPP-4 inhibitor
D	Start a fixed combination of a basal insulin and a GLP-RA

Case 2: Megan (continued)

- She agreed to start a GLP1-RA (exenatide [once-weekly], liraglutide, dulaglutide, semaglutide or lixisenatide).
- If prescribing once-weekly GLP-1 RA, inform patient that it may take several weeks to reach equilibration and, with once-weekly exenatide, skin nodules may occur.
- She experienced no nausea or hypoglycemia. Over the next three months she lost 14 pounds and her A1c fell from 8.6% to 7.3%.

What should be this patient's A1c goal?



Before GLP-1*

FBS (mg/dl)	PPG (mg/dl)
Average 191	Average 265

After GLP-1*

FBS (mg/dl)	PPG (mg/dl)
Average 131	Average 167

* Increased frequency of SMBG testing not a requirement with GLP-1 receptor agonists

Fixed Combinations Of Basal Insulin and GLP- Receptor Agonist

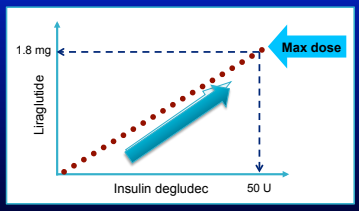
Insulin degludec/liraglutide: Xultophy
Insulin glargine/lixisenatide: Soliqua

- 1 dose step (unit) has 1 unit insulin degludec and 0.036 mg of liraglutide (max. dose is 50 iDeg/1.8mg lira)
- Injected once daily at same time each day with or without food

- 1 dose step (unit) has 1 unit insulin glargine and 0.33 mcg lixisenatide (max. dose is 60 iGlar/ 20 mcg lixi)
- Injected once daily within one hour prior to the first meal of the day

Lancet Diabetes Endocrinol. 2014 Nov;2(11):856-8. 2017 PDR PIs

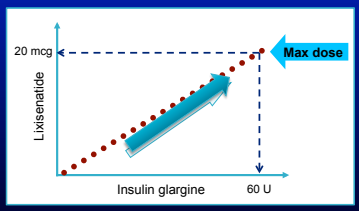
Fixed-Ratio Combination of Insulin Degludec and Liraglutide (Xultophy)



One dose step = 1 U insulin degludec and 0.036 mg liraglutide

Buse JB, et al. *Diabetes Care.* 2014; 37:2926-33.

Fixed-Ratio Combination of Insulin Glargine and Lixisenatide (Soliqua)



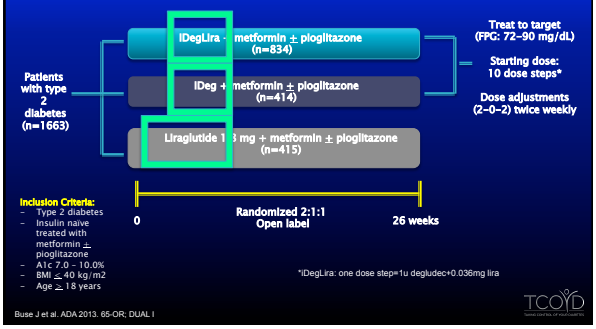
One dose step = 1 U insulin glargine and 0.33 mcg lixisenatide

Buse JB, et al. *Diabetes Care.* 2014; 37:2926-33.

Insulin Degludec/Liraglutide vs. Insulin Glargine/Lixisenatide

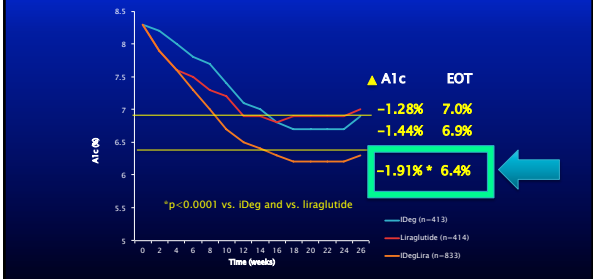
Pen dose steps (units): insulin degludec + liraglutide (Xultophy)	Pen dose steps (units): insulin glargine + lixisenatide (Soliqua)
10 dose steps=10 units insulin degludec +0.36 mgs of liraglutide 50 dose steps=50 units insulin degludec +1.8 mgs of liraglutide	15 dose steps=15 units insulin glargine + 5 mcg of lixisenatide 30 dose steps=30 units insulin glargine + 10 mcg of lixisenatide 60 dose steps=60 units insulin glargine + 20 mcg of lixisenatide
Starting dose: **16 dose steps which has 16 units insulin degludec + 0.58 mgs of liraglutide**	Starting dose: **If glargine U-100 dose is <30, start at 15 dose steps which has 15u glargine + 5mcg lixi** **If glargine U-100 dose is >30, start at 30 dose steps which has 30u glargine + 10 mcg lixi**
Titrate according to FBG, as if you were using basal insulin alone, generally 2 dose steps at a time, usually every 3-4 days	Titrate according to FBG, as if you were using basal insulin alone, generally 2-4 dose steps at a time, usually weekly
Maximum dose is 50 units of insulin degludec and 1.8 mgs of liraglutide	Maximum dose is 60 units of insulin glargine and 20 mcgs of lixisenatide

Insulin Degludec/Liraglutide in Type 2 Diabetes: Phase 3 Trial



Buse J et al. ADA 2013. 65-OR; DUAL I

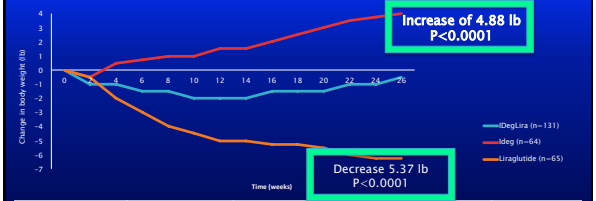
A1c 8.3% to 6.4% with Insulin Degludec/Liraglutide



Mean values (+SEM) based on FAS and LOCF imputed data; EOT = end of trial; p-values are from an ANCOVA ADA/EASD A1c target < 7.0%; AACE A1c target < 6.5%

Buse J et al. ADA 2013. 65-OR

Body Weight and Hypoglycemia



	iDegLira Rate (episodes/PYE)	IDeg Rate (episodes/PYE)	Lira Rate (episodes/PYE)	iDegLira vs. IDeg RR Estimate (95% CI)	iDegLira vs. Lira RR Estimate (95% CI)
Hypoglycemia	1.80	2.57	0.22	0.68 (0.53; 0.87)*	7.61 (5.17; 11.21)**

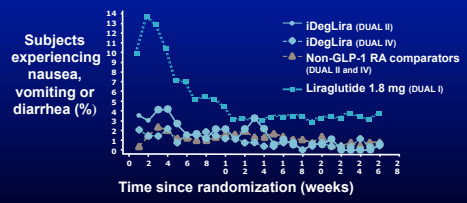
Mean weight values (±SEM) based on FAS and LOCF imputed; estimated treatment difference and p-values are from an ANCOVA analysis
Hypoglycemia: PG <56 mg/dL and/or requiring assistance, PYE: Patient years exposure; RR: Rate ratio: iDegLira/Comparator; p<0.05 two-sided. *p=0.002; **p<0.0001

Buse J et al. ADA 2013, 65-OR

DUAL VII – Open-label trial comparing iDeg/Lira to basal-bolus insulin therapy (glargine + aspart) for 26 weeks

- iDeg/lira was non-inferior to basal-bolus for glycemic control
  - Mean A1c reduction from 8.2 to 6.7% in both groups
- iDeg/lira was associated with:
  - Lower insulin doses (40.1 units for iDeg/Lira group compared to 84.6 units in basal-bolus)
  - Less hypoglycemia: 89% less severe or symptomatic confirmed hypoglycemia compared to basal-bolus
  - Mean weight loss (0.9kg) versus weight gain (2.6kg) with basal-bolus

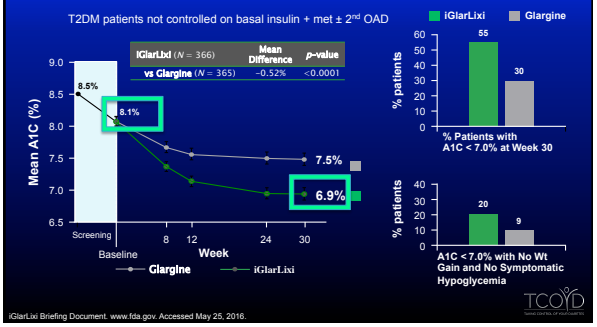
Gastrointestinal Side Effects
Post hoc analysis: Gradual Titration Helps



p=non-significant for odds of experiencing gastrointestinal side effects for subjects on iDegLira versus non-GLP-1 RA comparator

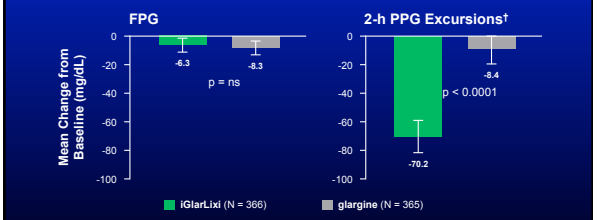
Aroda *et al. Diabetes* 2015;64 (Suppl. 1):A235; abstract 1009-P

Efficacy of Fixed-Ratio iGlarLixi in T2DM Patients Not Controlled on Basal Insulin



iGlarLixi Briefing Document. www.fda.gov. Accessed May 25, 2016.

Fixed-Ratio iGlarLixi in T2DM Patients Not Controlled on Basal Insulin: Glucose and Weight Effects



Mean weight change:
iGlarLixi -0.7 kg; glargine 0.7 kg
iGlarLixi vs glargine -1.40 kg (p < 0.0001)

†PPG changes are mean for all 3 meals. 30 week study. Glargine run-in to bring glucose to 140 or less.
iGlarLixi Briefing Document. www.fda.gov. Accessed May 25, 2016.

Summary: Benefits for Combining GLP-1 Receptor Agonists and Basal Insulin Analogs

- Combined glycemic effects of GLP-1RA and basal insulin provides greater glycemic efficacy than either of its component parts.
- Dose related adverse effects of each component (nausea and weight gain) are minimized.
- No increased risk of hypoglycemia in the setting of improved glycemic control as compared to basal insulin alone.
- In the setting of inadequate control on basal insulin, adding a GLP-1RA is associated with greater benefits (weight loss and minimal hypo) than adding prandial insulin.

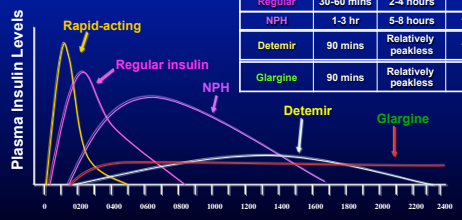
Generic and Trade Names: Insulin

	Generic Name	Trade Name
Fast-Acting Insulin	regular U-500 regular aspart faster acting aspart glulisine lispro (U-100 and U-200) inhaled insulin	Humulin R, Novolin R Humulin R U-500 NovoLog Fiasp Apidra Humalog Afrezza
Basal Insulin	intermediate-acting: NPH long-acting: detemir glargine (U-100) glargine (U-300) degludec (U-100/200) follow-on biologic glargine (U-300)	 Humulin N Novolin NPH Levemir Lantus Toujeo Tresiba Basaglar

TCOYD

Time Action Profiles: Traditional Insulins

Insulin	Onset	Peak	Duration
Rapid-acting	10-15 mins	60-90 mins	4-5 hr
Regular	30-60 mins	2-4 hours	5-8 hr
NPH	1-3 hr	5-8 hours	12-18 hr
Detemir	90 mins	Relatively peakless	12-24 hr
Glargine	90 mins	Relatively peakless	24 hr



Inhaled insulin: peak by 10-15 min, duration of 2-3 hrs Faster-acting aspart: onset faster, duration shorter, than rapid-acting

Lepore M et al. Diabetes. 2000;49:21 42-21 48; Howey DC et al. Diabetes. 1994;43:396-402; Plank J et al. Diabetes Care. 2005;28:1107-112.; Willitt SD et al. Insulin Therapy. Marcel Dekker, Inc.:2002:73-85.

TCOYD

Shortcomings of Traditional Basal Insulins Include:

- 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

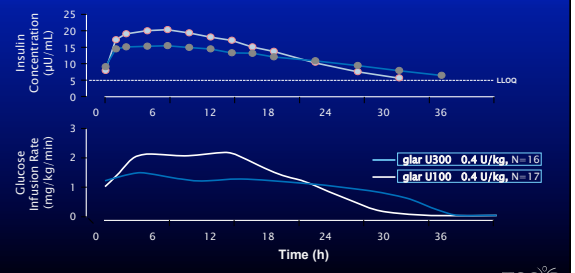
Two New Basal Insulins Recently Added To Our List Of Options

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

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

PK/PD Profile with Glar U300 vs Glar U100

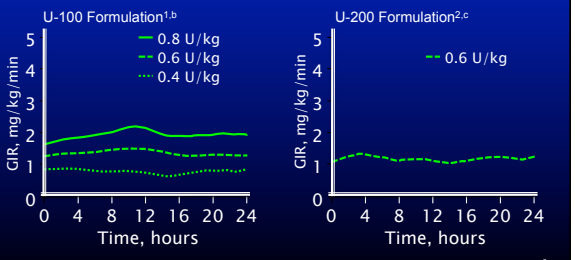
U300 glargine (Toujeo) has a more even and prolonged PK/PD profile; glucose control well beyond 24 hrs.



Glargine u300 less potent than glargine u100; may need 13 to 17% more than previous dose of glargine u100 (Lantus)

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

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;14:944-9501
2. Heise T, et al. *Diabetes*. 2012;61(suppl 1):A91 [abstract 349-OR].

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

Case 3: Jennifer

- A 56 year-old female diagnosed with type 2 diabetes 6 years ago
- Currently on maximum doses of 3 oral agents: metformin 1000 mg BID, glipizide 20 mg BID and linagliptin 5 mg QD
- "Refused" to start insulin for years (afraid of weight gain), but a few months ago did try 10 units of glargine in the morning. After 3 months on 10 units she felt it "did not work" and she stopped it.
- A1c > 8.5% for the past 2 years
- Current SMBG (mg/dl) below:

	Pre-Breakfast	Pre-Lunch	Pre-Dinner	Bedtime
Monday	211	----	----	185
Tuesday	247	----	174	----
Wednesday	181	----	----	196
Thursday	226	----	179	----

Which of the following is the single most likely explanation for her failure with basal insulin:

A	Patient fear of Insulin
B	Health care provider inertia
C	Inadequate titration of the glargine U-100
D	Glargine U-100 should have been given at bedtime

Initiating Insulin Therapy in Type 2 Diabetes: General Concepts

Don't wait forever.
Address patient concerns/fears.
Consider combination therapy with oral agents.

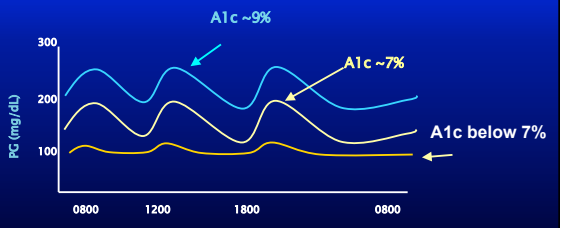
Start with basal insulin.
Titrating the dose is essential (self titration can work well).

Use a fast-acting analog at meal time when indicated.
(may only needed to be given with the largest meal)

Self-monitoring of blood glucose (SMBG) is an important tool in motivating patients and in guiding dose adjustments.

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

First Goal: Correct Fasting Hyperglycemia



Second Goal: Control postprandial hyperglycemia if A1c still >7% (or above individual goal)

Adapted with permission from Cefalu WT. In: Leahy J, Cefalu W, eds. Insulin Therapy. New York: Marcel Dekker; 2002:1-11.

TCOYD

Adding Basal Insulin to Oral Agents An Effective Strategy to Initiate Insulin Therapy

- Only 1 injection per day is typically required
- No need for mixing different types of insulin
- Convenience (usually given at night or first thing in the morning)
- Slow, safe, and simple titration
- Low dosage compared to a full insulin regimen
- Limited weight gain – especially compared to insulin only regimens
- Effective improvement in glycemic control by suppressing hepatic glucose production

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

TCOYD

Case 4: Rick

- 61 yr.-old overweight (BMI 30, 220lbs) male
- Type 2 diabetes diagnosed 9 years ago
- History of CAD s/p MI 2 years ago
- Treated for 2 years with diet and exercise alone even though his A1c was above 9.5% ("did not want to take medications")
- Eventually started on metformin, sequentially followed by a sulfonylurea and a DPP-4 inhibitor (100mg sitagliptin), and his A1c fell from 9.9% to 7.9%
- It took two years (6 clinic visits) to initiate these 3 meds and get his A1c down

What should be this patient's A1c goal?

TCOYD

Case 4: Rick (continued)

- eGFR 45 ml/min, normal LFTs
- PMH: HTN, dyslipidemia, OSA, CAD, pancreatitis, ED
- Other meds: ACE inhibitor, clopidogrel, atorvastatin, HCTZ and tadalafil, carvedilol, and several vitamin supplements
- Loves to eat at fast food restaurants
- Asked to test once a day at different times

Time	Blood glucose range	Blood glucose average
Pre-Breakfast	148 – 229 mg/dL	(~175 mg/dL)
Pre- Lunch	111 – 182 mg/dL	(~147 mg/dL)
Pre- Dinner	91 – 155 mg/dL	(~139 mg/dL)
Bedtime	148 – 231 mg/dL	(~184 mg/dL)
No reports of hypoglycemia		

Which of the following would you suggest for Rick if he were your patient?

A	Work on lifestyle and no medication addition
B	Initiate basal insulin
C	Start a GLP-1 RA and stop his DPP-4 inhibitor
D	Start a SGLT-2 Inhibitor

Case 4 : Rick (continued)

- Insulin degludec U-200 was added at night (20 units) and titrated up to 120 units over the next 10 weeks
- He was asked to test 2x/day (pre-breakfast and bedtime)
- It is important to make sure the patient is not going to bed high

Pre-Breakfast	82 – 155 mg/dL	(~122 mg/dL)
Pre- Lunch	----	----
Pre- Dinner	----	----
Bedtime	128 – 183 mg/dL	(~155 mg/dL)

- A1c dropped to 7.1%, no hypoglycemia. Gained 2 lbs in 3 months
- Oral agents can be continued unless hypoglycemia occurs during the day, in which case the sulfonylurea should be reduced or withdrawn

Appropriate Self-Titration is Critical to the Success of Insulin Therapy

- An ADA/EASD consensus algorithm for the initiation and adjustment of basal insulin:

Start with a long-acting basal insulin

Initiate at 10 units/day or 0.2 units/kg/day

Check fasting glucose daily and increase dose by:

2 units every 3 days until fasting in target range (70 – 130 mg/dL)

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.
Nathan et al. Diabetes Care. 2009;32:193-203.

Simple Daily Self-Titration Option*
(much easier to follow by the patient than the 3 day titration)

Increase by **1 to 2 Units** every **1** day until FPG ≤ 120 mg/dL

EXAMPLE
Less than 100: decrease by 2 units

Between 100 and 150: no change

Over 150: increase by 2 units

The goal can be individualized

* A 3-4 day titration schedule is more appropriate for the new longer-acting basal insulins (U300 glargine and degludec)

Dosage was not increased that week if there were any episodes of documented hypoglycemia (<72 mg/dL) during the preceding week. FPG, fasting plasma glucose.

Gerstein HC et al. Diabet Med. 2006;23:736-742.

Second Pitfall In Initiating/Titrating Basal Insulin
(First one is too slow titration after starting)

Not Paying Attention To Bedtime Glucose Value

1. Ask the patient to do paired testing (test at bedtime and again the next morning).
2. If the bedtime BG is high, it needs to be addressed by either lifestyle modification including reduced caloric consumption and/or post dinner exercise.
3. Other options include prandial insulin or a GLP-1 RA.

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

Clinical Pearls: Combination Therapy with Basal Insulin

-1-	Start with 10 to 20 units (based on FBS, weight)
-2-	The key to success is frequent follow up after initiation to avoid "failure" (most patients will need 40 to 70 units/day)
-3-	Have the patient follow a self-titration regimen and return to clinic or follow up in some other manner (phone, fax, email, telehealth, etc.) relatively soon
-4-	You can usually limit SMBG to only once a day in the morning but check at bedtime once in awhile to make sure the pt. does not need pre dinner fast acting insulin.

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

Case 5: Angela

- 65 year old female on triple oral agent therapy (SFU ,met, DPP-4 inhibitor) was started on 10 units of insulin glargine (U-100) qAM in July 2011
  - FPG ~ 220 mg/dL, A1c 8.5 %, wt = 176 lb
- Insulin glargine (U-100) was titrated to 45u qAM from July 2011 to November 2011
  - FPG 78-132 mg/dL, A1c = 7.4%, wt = 181 lbs, eEGR 62
- Patient was asked to test more frequently than usual for 3 to 4 days before meals and bedtime (pattern testing)

	July 2011	November 2011
A1c (%)	8.5	7.4
FPG (mg/dL)	~220	78 - 132

Case 4: Angela (cont)

- 65 year old woman on glargine (U-100) and 3 oral agents: SMBG data

	Pre-Breakfast	Pre-Lunch	Pre-Dinner	Bedtime
Monday	101	124	----	185
Tuesday	132	146	109	214
Wednesday	98	111	89	229
Thursday	78	----	121	201

---- = did not test

Which of the following would you recommend for Angela at this point?

	Pre-Breakfast	Pre-Lunch	Pre-Dinner	Bedtime
Monday	101	124	----	185
Tuesday	132	146	109	214
Wednesday	98	111	89	229
Thursday	78	----	121	201

A	Increase basal insulin
B	Switch to premix insulin at dinner
C	Intensify regimen by adding rapid acting insulin at dinner
D	SGLT-2 inhibitor

Case 5: Angela (cont)

- Dinnertime bolus added:
  - Patient was started on 5 units of rapid-acting insulin analog at dinnertime and titrated up to 15 units over a few weeks based on the bedtime blood glucose levels (initial dose can be ~10% of the total basal dose). Options include lispro, aspart, glulisine, and inhaled Insulin
  - The basal insulin dose (glargine [U-100] 45 units) was titrated downward to 40 units on initiation of rapid-acting insulin based on the patient's near normal fasting blood glucose levels in order to avoid nocturnal/fasting hypoglycemia

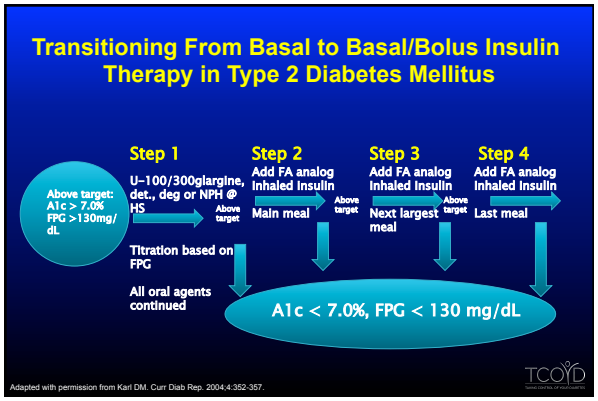
Nathan DM et al. Diabetologia 2008;51:8-11.
Raccah D et al. Diabetes Metab Res Rev. 2007;23:257-264.

Case 5: Angela (cont)

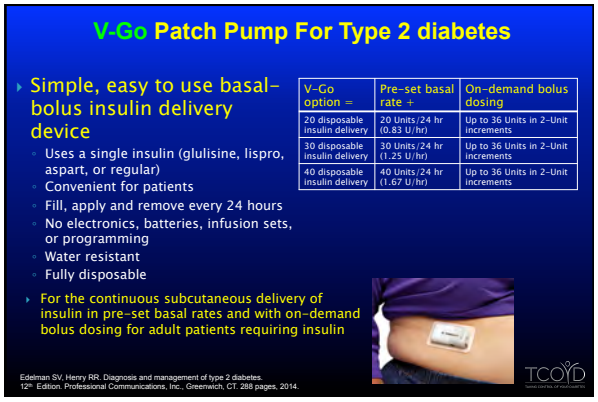
- SMBG values on glargine (U-100) 40 units at bedtime; lispro 15 units pre-dinner

	Pre-Breakfast	Pre-Lunch	Pre-Dinner	Bedtime
Wednesday	88	----	----	136
Thursday	131	----	143	188
Friday	98	122	----	121
Saturday	112	----	134	169

- A1c fell from 7.4% to 6.8%.
- Angela experienced occasional mild hypoglycemia.


Transitioning From Basal to Basal/Bolus Insulin Therapy in Type 2 Diabetes Mellitus
Above target: A1c > 7.0% FPG >130mg/dL
Step 1
U-100/300glargine, det., deg or NPH @ HS
Above target
Titration based on FPG
All oral agents continued
Step 2
Add FA analog Inhaled Insulin
Main meal
Above target
Step 3
Add FA analog Inhaled Insulin
Next largest meal
Above target
Step 4
Add FA analog Inhaled Insulin
Last meal
A1c < 7.0%, FPG < 130 mg/dL
Adapted with permission from Karl DM. Curr Diab Rep. 2004;4:352-357.


Memoir & Kwikpen
NovoPen Echo & FlexTouch
SoloStar
Convenient
Discreet
Protect insulin from light, heat and agitation


V-Go Patch Pump For Type 2 diabetes
Simple, easy to use basal-bolus insulin delivery device
Uses a single insulin (glulisine, lispro, aspart, or regular)
Convenient for patients
Fill, apply and remove every 24 hours
No electronics, batteries, infusion sets, or programming
Water resistant
Fully disposable
V-Go option = | Pre-set basal rate + | On-demand bolus dosing
20 disposable insulin delivery | 20 Units/24 hr (0.83 U/hr) | Up to 36 Units in 2-Unit increments
30 disposable insulin delivery | 30 Units/24 hr (1.25 U/hr) | Up to 36 Units in 2-Unit increments
40 disposable insulin delivery | 40 Units/24 hr (1.67 U/hr) | Up to 36 Units in 2-Unit increments
For the continuous subcutaneous delivery of insulin in pre-set basal rates and with on-demand bolus dosing for adult patients requiring insulin
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

Calibra Finesse Patch Pump For Type 2 diabetes

- Simple, easy to use *bolus only* delivery device
  - Holds 200 units
  - Delivers 2 units at a time (button)
  - Fill, apply and remove in 3 days
  - No electronics, batteries, infusion sets, or programming
  - Fully disposable
  - Not available as yet
- For for giving a *bolus* of subcutaneous delivery of rapid acting insulin for type 1 and type 2 diabetes

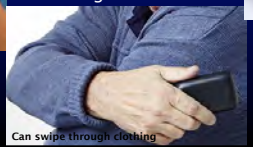
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

T:flex Holds 480 Units Of Insulin

FreeStyle Libre Flash

Continuous Measurement, Intermittent Sensing

Sensor goes on easily
No calibration
Swipe to get a reading
Has trend arrows
Water resistant
Lasts 10 days
No alerts or alarms
No sharing feature



Can swipe through clothing

swipe

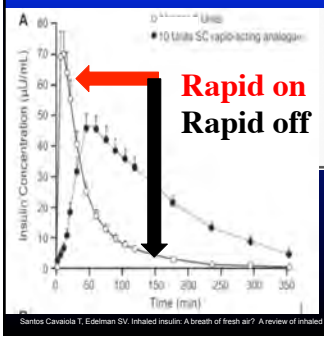
Shortcomings of Existing Bolus Insulins Include

- Not rapid enough:
  - Leading to mismatch between peak postprandial glucose and peak insulin action
  - Need to take up to ½ hour before eating
- Lasts too long…leading to delayed hypoglycemia
- Inconsistent action leading to inconsistent blood glucose levels

Boss, A.; Ellerman, WY; Ellerman, K. Drug Development Research 69:138–142 (2008)

TCOYD

Inhaled Insulin



4, 8, 12 unit Insulin cartridges

- 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)

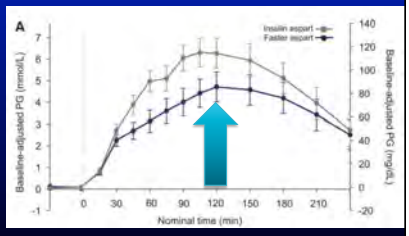
TCOYD

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-acting aspart

Statistically significant greater glucose lowering at 1 and 2 hours with faster-acting aspart.



Bode et al DTT Vol 19 2017

TCOYD

Case 1: Eric (Follow up!)

- 47 yr.-old centrally obese (BMI 32) male with a 5 year history of Type 2 diabetes
- Currently on maximum doses of metformin, a SFU, and a DPP4 inhibitor
- History of dyslipidemia, hypertension and ED
- A1c has ranged from 8.1 to 8.5% over the past 2 years
- He and his wife have seen a dietician and CDE several times

Time	Blood glucose range	Blood glucose average
Pre-Breakfast	166 - 231 mg/dL	(~182 mg/dL)
Pre- Lunch	143 - 197 mg/dL	(~177 mg/dL)
Pre- Dinner	112 - 275 mg/dL	(~213 mg/dL)
Bedtime	159 - 231 mg/dL	(~194 mg/dL)
No reports of hypoglycemia		

He tests 2 to 4 times a week

Which of the following would you recommend for Eric if he were your patient?

A	Initiate basal insulin
B	Initiate a GLP-1 RA; stop DPP-4 inhibitor
C	Initiate a basal bolus insulin regimen
D	Initiate a fixed combination of a basal insulin and a GLP-RA; stop DPP-4 inhibitor

Summary

- GLP-1 agonists represent a tremendous advance in the treatment of type 2 because of glucose lowering in addition to weight loss and reducing the risk of hypoglycemia
- Combination therapy (adding basal insulin to daytime OHAs) is safe, effective and easy to implement
- The fixed combination of basal insulin and a GLP-1 RA has clinical advantages in terms of efficacy, reduced side effects and ease of use
- The Basal Bolus approach in type 2 diabetes does not need to be four injections per day
- Patient and clinical inertia are serious problems
- Adherence and persistence needs to be addressed at every visit

Lecture 4: 2:15 – 3:15 p.m.

Steven V. Edelman, MD, Presents:

Cutting-Edge Strategies for the Treatment of People with Type 1 Diabetes

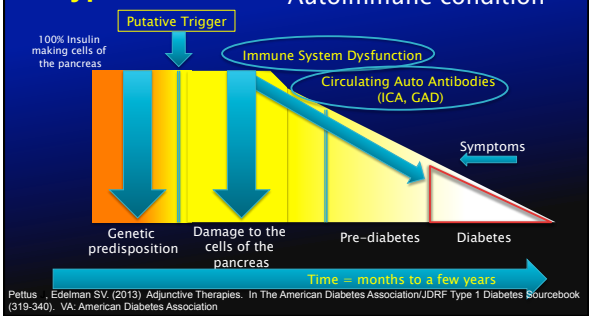
It is all about "Time In Range": Keeping the glucose levels between 70 and 180 mg/dl

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

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

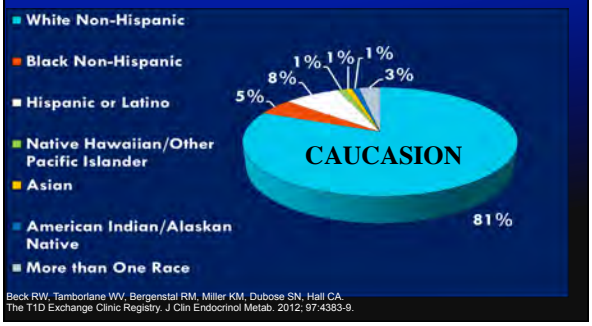
Natural History and Cause of Type 1 Diabetes

Autoimmune condition



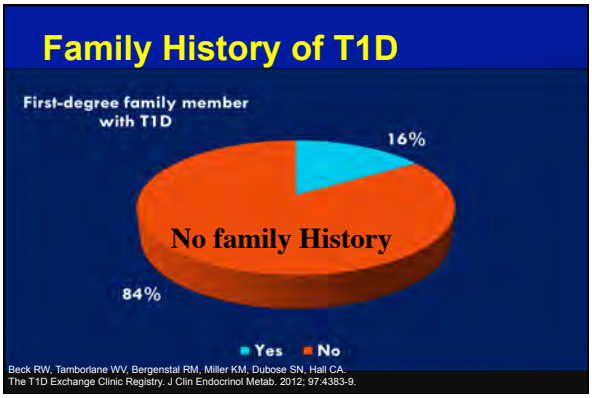
Pettus , Edelman SV. (2013) Adjunctive Therapies. In The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook (319-340). VA: American Diabetes Association

Race/Ethnicity



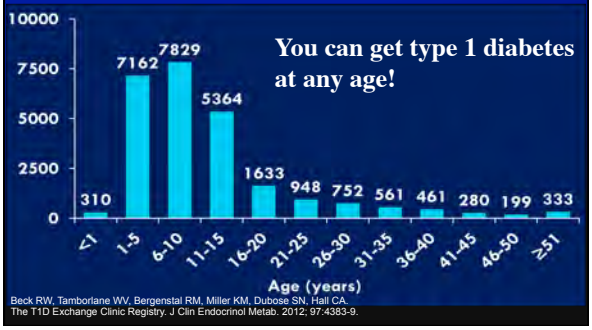
Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

Family History of T1D



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.

Age at Diagnosis of T1D



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.

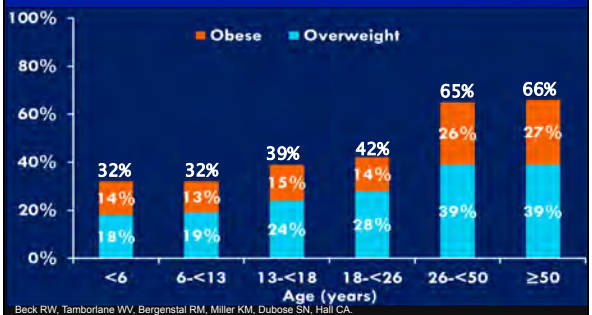
Latent Autoimmune Diabetes in Adults (LADA)

- 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

Fourth Edition Professional Communications Inc., Greenwich, CT. 844 pages, 2013. Communications, Inc., Greenwich, CT. 288 pages, 2014.

Overweight / Obese



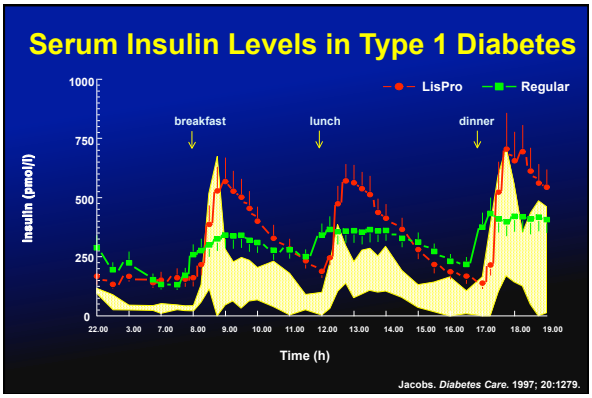
Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

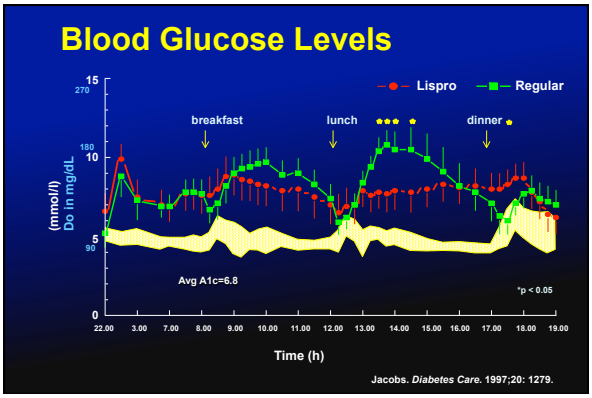
Case 1: Phil

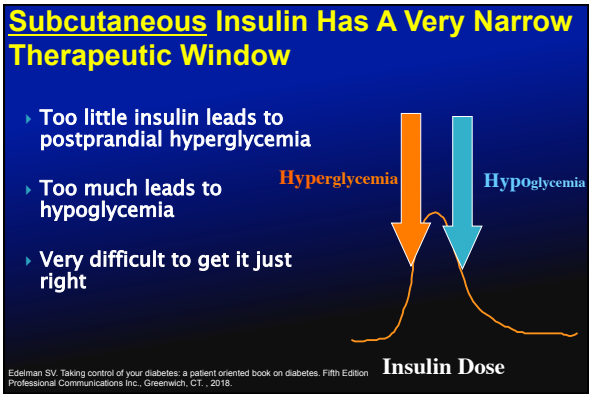
- 46 year old male with the diagnosis of type 1 diabetes at age 6 (Classic presentation of DKA)
- He has been on an insulin pump for many years
- Over the last 8 years he has developed central obesity and his insulin requirements doubled
- He also developed high blood pressure and dyslipidemia (triglycerides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

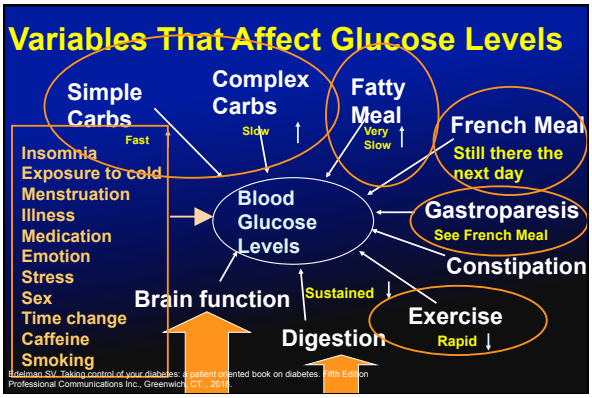
What is the most likely explanation of why Phil's insulin requirements doubled later in life?

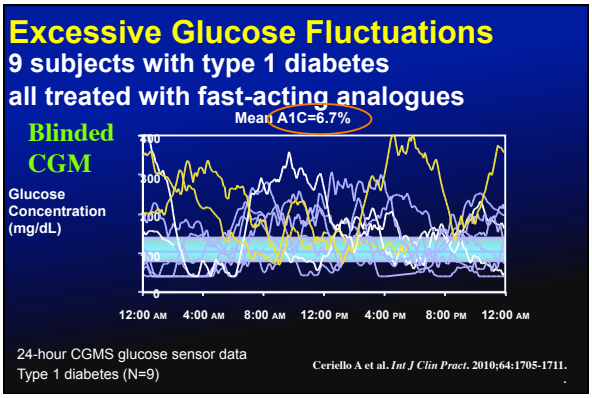
A	He developed central obesity
B	He has both type 1 and type 2 diabetes
C	His A1c kept rising
D	The insulin he was receiving by mail was denatured and lost potency

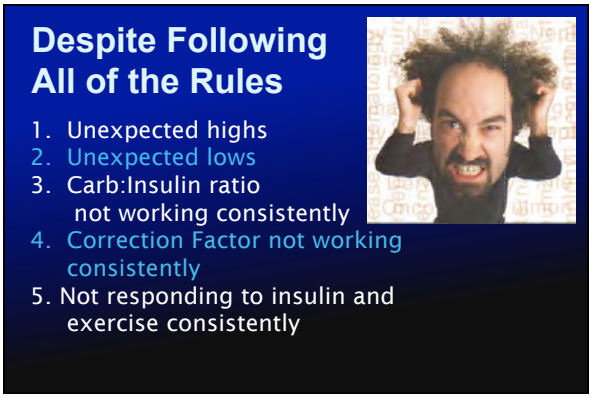

Serum Insulin Levels in Type 1 Diabetes
LisPro
Regular
breakfast
lunch
dinner
Insulin (pmol/l)
1000
750
500
250
0
22.00 3.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00
Time (h)
Jacobs. Diabetes Care. 1997; 20:1279.

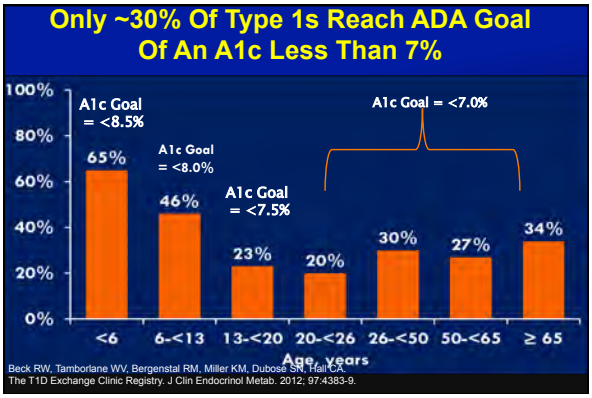

Blood Glucose Levels
Lispro
Regular
breakfast
lunch
dinner
(mmol/l)
Do in mg/dL
15
270
10
180
5
90
0
Avg A1c=6.8
*p < 0.05
22.00 3.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00
Time (h)
Jacobs. Diabetes Care. 1997;20: 1279.

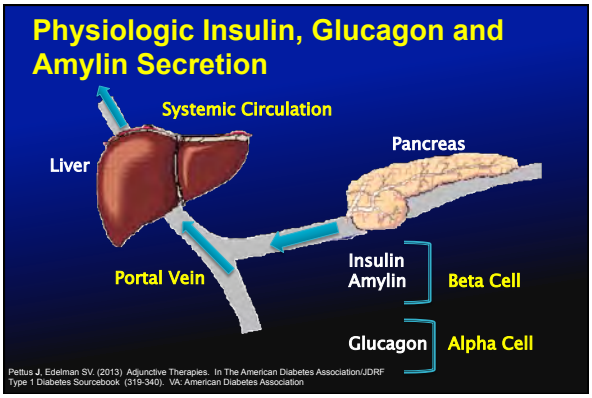

Subcutaneous Insulin Has A Very Narrow Therapeutic Window
Too little insulin leads to postprandial hyperglycemia
Too much leads to hypoglycemia
Very difficult to get it just right
Hyperglycemia
Hypoglycemia
Insulin Dose
Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT. , 2018.

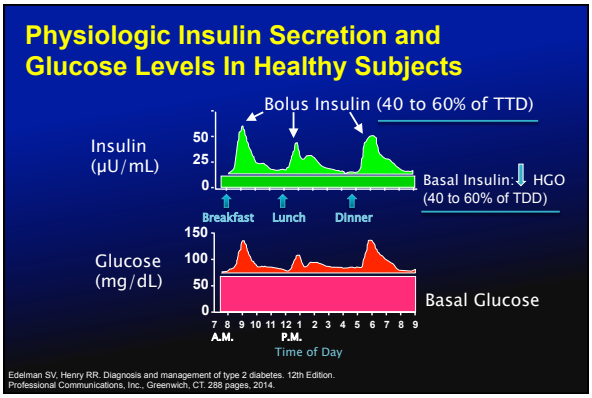

Variables That Affect Glucose Levels
Simple Carbs
Fast
Complex Carbs
Slow
Fatty Meal
Very Slow
French Meal
Still there the next day
Insomnia
Exposure to cold
Menstruation
Illness
Medication
Emotion
Stress
Sex
Time change
Caffeine
Smoking
Blood Glucose Levels
Gastroparesis
See French Meal
Constipation
Brain function
Sustained
Exercise
Rapid
Digestion
Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fifth Edition Professional Communications Inc., Greenwich, CT. , 2013.


Excessive Glucose Fluctuations
9 subjects with type 1 diabetes
all treated with fast-acting analogues
Mean A1C=6.7%
Blinded CGM
Glucose Concentration (mg/dL)
300
200
70
0
12:00 AM
4:00 AM
8:00 AM
12:00 PM
4:00 PM
8:00 PM
12:00 AM
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


Only ~30% Of Type 1s Reach ADA Goal Of An A1c Less Than 7%
100%
80%
60%
40%
20%
0%
A1c Goal = <8.5%
A1c Goal = <8.0%
A1c Goal = <7.5%
A1c Goal = <7.0%
65%
46%
23%
20%
30%
27%
34%
<6
6-<13
13-<20
20-<26
26-<50
50-<65
≥ 65
Age, years
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.


Physiologic Insulin, Glucagon and Amylin Secretion
Systemic Circulation
Liver
Pancreas
Portal Vein
Insulin
Amylin
Beta Cell
Glucagon
Alpha Cell
Pettus J, Edelman SV. (2013) Adjunctive Therapies. In The American Diabetes Association/JDRF
Type 1 Diabetes Sourcebook (319-340). VA: American Diabetes Association

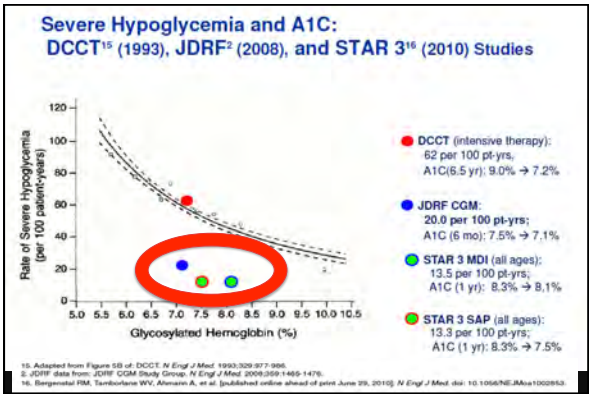

Physiologic Insulin Secretion and Glucose Levels In Healthy Subjects
Bolus Insulin (40 to 60% of TTD)
Insulin (μU/mL)
50
25
0
Basal Insulin: HGO (40 to 60% of TDD)
Breakfast
Lunch
Dinner
Glucose (mg/dL)
150
100
50
0
Basal Glucose
7 8 9 10 11 12 1 2 3 4 5 6 7 8 9
A.M.
P.M.
Time of Day
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition.
Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

Case 2: Tom

- 36 year old male with type 1 diabetes for 20 years
- He is on a basal bolus regimen (20 units of insulin glargine at bedtime and 16 to 22 units of fast acting meal and correction boluses throughout the day.
- His correction factor is 1:40 (goal of 125) and his insulin to carbohydrate ratio is 1:12
- A1c is 7.1%,, however his glucose values bounce from high to low and he is very frustrated.
- He tests his glucose value 6 to 8 times a day
- He tried to be as consistent as possible with his diet and exercise
- His wife is very supportive and he is motivated to do well

What therapeutic intervention do you think is the most important to help Tom with his glucose control ?

A	Put Tom on an insulin pump
B	Put Tom on a continuous glucose monitor
C	Split his dose of insulin glargine so that he takes 10 units BID
D	Send Tom to a diabetes education class



530G/630G/670G (Enlite/ Gardian)

G5 & G6

Continuous Glucose Monitoring Devices Currently Available in the United States

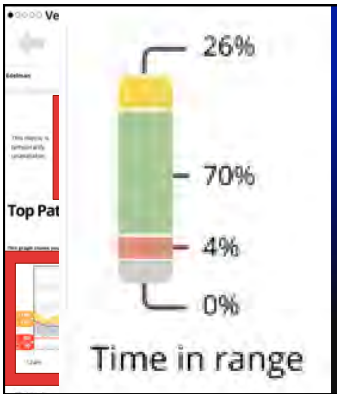
G5 & G6 Platinum

630G/670G Enlite/ Gardian

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

Herrmann K, Frias JP, Edelman SV, Lutz K, Shan K, Chen S, Maggs D, Kolterman OG. Pramlintide improved measures of glycemic control and body weight in patients with type 1 diabetes mellitus undergoing continuous subcutaneous insulin infusion therapy. *Postgraduate Medicine*. 123(3), 2013.



Smart Phone Clarity App

Mean glucose value

Standard Deviation

Time in Range

24 hour multiday profile

How Do Patients (n=300) with Type 1 Translate CGM Data Into Diabetes Management Decisions

Mean age was 46 ± 14 years old
Duration of diabetes: 22±14 years
Mean A1C (self reported) was 6.9% ± 0.8%
Minimal hypoglycemia
Insulin delivery:
- 75% used CSII
- 25% used multiple daily injections

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

How much insulin would you give yourself to bring your glucose down from 220mg/dl to around 120 mg/dl if the trend arrow is horizontal?

a. 0.5 units
b. 1–1.5 units
c. 2–2.5 units
d. 3–3.5 units
e. 4–4.5 units
f. 5–5.5 units
g. 6–6.5 units
h. 7–7.5 units
i. 8–8.5 units
j. 9 units

3.0 units

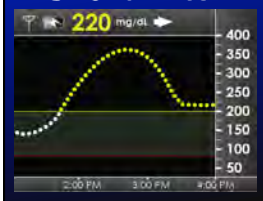
CF~1:30

How much insulin would you give yourself to bring your glucose down from 220 mg/dl to 120mg/dl with two trend arrows straight up?

a. 2–2.5 units
b. 3–3.5 units
c.. 4–4.5 units
d. 5–5.5 units
e. 6–6.5 units

Mean change in Insulin Dose Based on 2 ARROWS UP: Survey of 300 CGM users

3.0 units



6.8 units

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

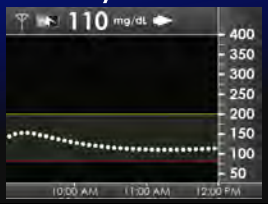
How CGM and Trending Information Can Affect Dosing Decisions

→	**Constant:** Your glucose is steady (not increasing/decreasing more than 1 mg/dL each minute)	3.0 units — No Change in calculation
↗	**Slowly rising:** Your glucose is rising 1-2 mg/dL each minute	
↑	**Rising:** Your glucose is rising 2-3 mg/dL each minute	
↑↑	**Rapidly rising:** Your glucose is rising more than 3 mg/dL each minute	6.8 units — 40% Mean Increase
↘	**Slowly falling:** Your glucose is falling 1-2 mg/dL each minute	
↓	**Falling:** Your glucose is falling 2-3 mg/dL each minute	
↓↓	**Rapidly falling:** Your glucose is falling more than 3 mg/dL each minute	1.5 units — 48% Mean Decrease
no arrow	**No Rate of Change Information:** The receiver cannot always calculate how fast your glucose is rising or falling	

Dose Adjustment At Meal Time (➔)

Assume it is lunch time and your glucose is 110 mg/dl. Your trend graph and trend arrow is flat *(straight across).* You are eating a meal with 50 gram carbohydrates and your usual fat and protein. How much insulin would you take?

a. 1 unit
b. 2 units
c. 3 units
d. 4 units
f. 5 units ← 1:10 CHO
g. more than 5 units



Dose Adjustment At Meal Time (↑↑)

Assume it is lunch time and your glucose is 110 mg/dl. You have 2 trend arrows pointing up. How much additional insulin would you take?

a. Same amount of insulin as with flat trend arrow
b. Same amount of insulin as with ➔ + 1 units
c. Same amount of insulin as with ➔ + 2 units
d. Same amount of insulin as with ➔+ 3 units
e. Same amount of insulin as with ➔+ 4 units
f. Same amount of insulin as with ➔ + 5 units
g. Same amount of insulin as with ➔+ 6 units
h. Same amount of insulin as with ➔ + 7 units
i. Same amount of insulin as with ➔+ 8 units
j. > 8 additional units

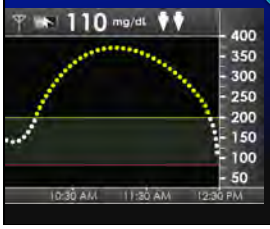
81% mean increase

Example: **5 units** when trend arrow is flat and **9.1 units** with two trend arrow going up

59% said they would allow more time between the meal bolus and eating

Dose Adjustment At Meal Time (⬇⬇)

Assume it is lunch time and your glucose is 110 mg/dl. You have 2 arrows (trend arrows) pointing down. How would this information change your dose?



53% mean decrease

Example: 5 units when trend arrow is flat and 2.4 units with two trend arrows going down

65% said they would take their insulin after the meal

How CGM and Trending Information Can Affect Dosing Decisions

→	**Constant:** Your glucose is steady (not increasing/decreasing more than 1 mg/dL each minute)	5.0 units
↗	**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	9.1 units 81% Mean Increase
↘	**Slowly falling:** Your glucose is falling 1- 2 mg/dL each minute	
↓	**Falling:** Your glucose is falling 2-3 mg/dL each minute	
↓↓	**Rapidly falling:** Your glucose is falling more than 3 mg/dL each minute	2.4 units 53% Mean Decrease
no arrow	**No Rate of Change Information:** The Receiver cannot always calculate how fast your glucose is rising or falling	

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

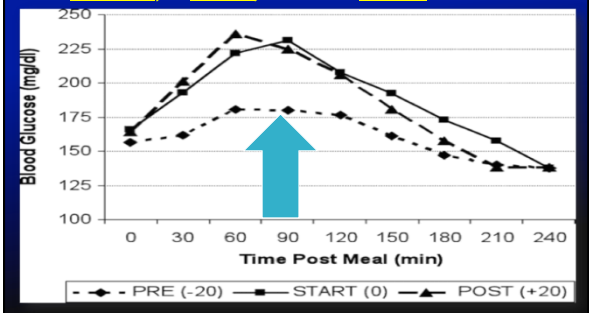
Add 75 mg/dl

Add 100 mg/dl

Wait until trend arrow becomes horizontal

S. Diabetes Technol Ther 2017;11:138–47

Blood glucose after a meal when bolus given 20 minutes BEFORE, at START, or 20 min AFTER the meal



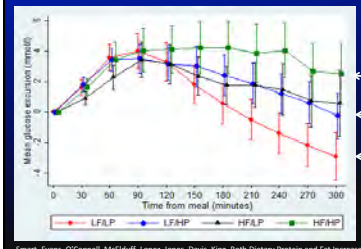
Cobry et al, Diab Tech Therap 2010;12: 173-177

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 avocados?

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

Both Dietary Fat and Protein Increase Postprandial Glucose Concentrations

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

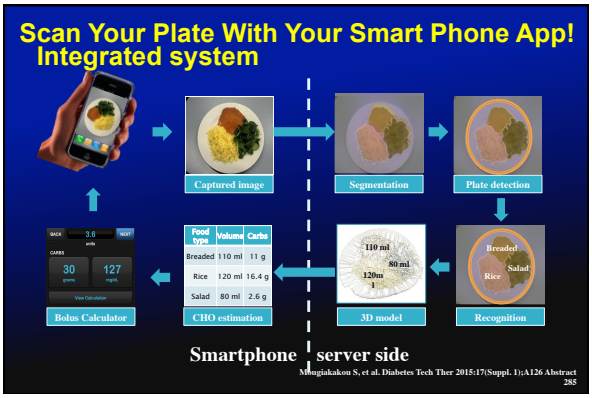


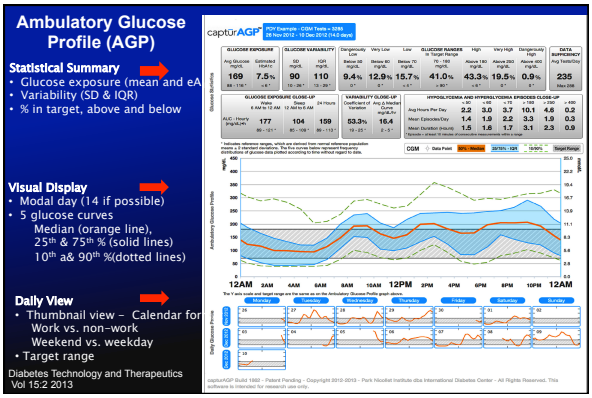
High fat/high protein

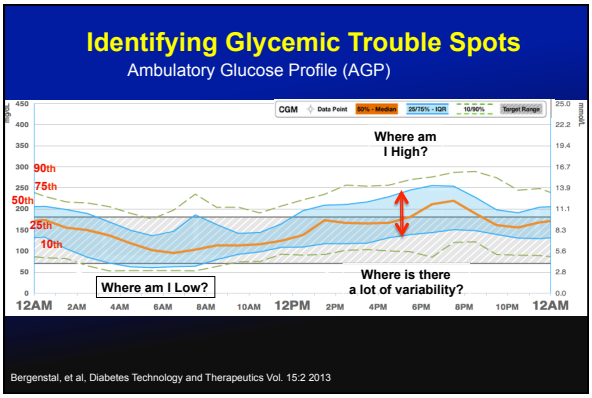
High fat/low protein
Low fat/high protein

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


Scan Your Plate With Your Smart Phone App!
Integrated system
Captured image
Segmentation
Plate detection
Food type
Volume
Carbs
Breaded 110 ml 11 g
Rice 120 ml 16.4 g
Salad 80 ml 2.6 g
110 ml
80 ml
120ml
Breaded
Salad
Rice
Bolus Calculator
CHO estimation
3D model
Recognition
Smartphone
server side
Mougiakakou S, et al. Diabetes Tech Ther 2015:17(Suppl. 1):A126 Abstract 285


Ambulatory Glucose Profile (AGP)
Statistical Summary
• Glucose exposure (mean and eA
• Variability (SD & IQR)
• % in target, above and below
Visual Display
• Modal day (14 if possible)
• 5 glucose curves
Median (orange line),
25th & 75th % (solid lines)
10th a& 90th %(dotted lines)
Daily View
• Thumbnail view – Calendar for
Work vs. non-work
Weekend vs. weekday
• Target range
Diabetes Technology and Therapeutics
Vol 15:2 2013
captürAGP


Identifying Glycemic Trouble Spots
Ambulatory Glucose Profile (AGP)
CGM
Data Point
50% - Median
25/75% - IQR
10/90%
Target Range
Where am
I High?
90th
75th
50th
25th
10th
Where am I Low?
Where is there
a lot of variability?
12AM
2AM
4AM
6AM
8AM
10AM
12PM
2PM
4PM
6PM
8PM
10PM
12AM
Bergenstal, et al. Diabetes Technology and Therapeutics Vol. 15:2 2013

FreeStyle Libre Flash IS or Intermittent Sensing

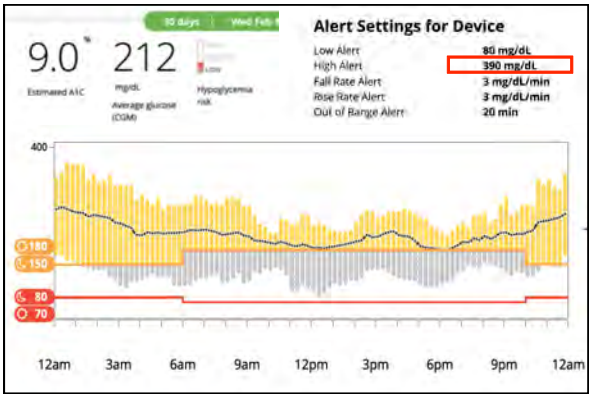
- Goes on easily
- 12 hour warm up time
- Lasts 10 days
- Swipe to get a number
- Has trend arrows
- No calibration
- No alerts or alarms
- No sharing feature

swipe

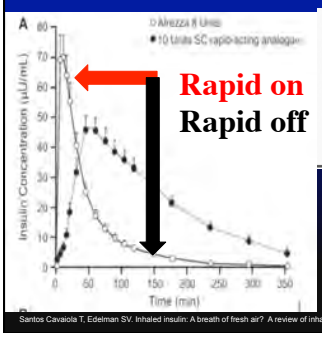
Concerns To Address With CGM

- Alarm fatigue
- High and low alert settings (80 to 180mg/dl)
- High and low snooze alarms (also known as repeat high and low alerts)
- Take advantage of the Share system
- Stacking (taking multiple boluses too close in time

Edelman SV, Hirsch IB, Pettus JH. Practical Management of Type 1 Diabetes. Second Edition. Professional Communications, Inc., Greenwich, CT. 175-209, 2014.



Inhaled Insulin



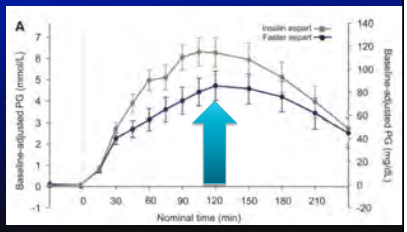
- Better post meal glucose values
- Less delayed hypoglycemia

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

Faster-Acting Aspart or Fiasp

(addition of L-arginine and niacinamide for faster absorption)

2 hour PG levels in T1D onPump therapy after a standardized meal comparing Aspart (Novolog)with Faster Aspart (Fiasp)



Bode et al DTT Vol 19 2017

Newer Insulin Pumps

- Animas Vibe G4 — Discontinued
- Tandem t:slim G5/X2
- Medtronic 630/670G/530G
- OmniPod

Edelman SV. Taking control of your diabetes: A patient oriented book on diabetes. 2nd Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2013.

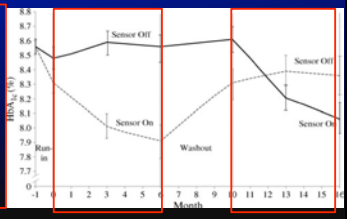
Insulin Pumps: Advantages

- 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 4th edition. 2013 and Walsh JA, Roberts R. Pumping Insulin 5th edition. 2011.

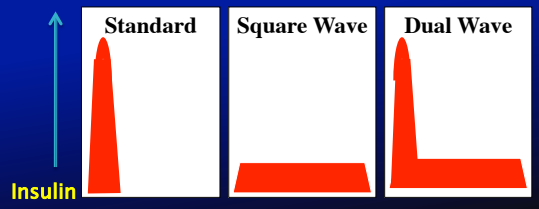
CGM Information Enables Greater Use Of Pump Features, Resulting In A1C Reduction

-Increase in boluses
-Increase use of the bolus calculator
-Increase in use of temporary basal rates
-Increase in temporary suspend
-Reduction in hypoglycemia



SWITCH study: Randomized crossover trial of children and adults (n=153) on CSII with A1C 7.5–9.5%, Diabetologia. 2012; 55(12):3155-62.

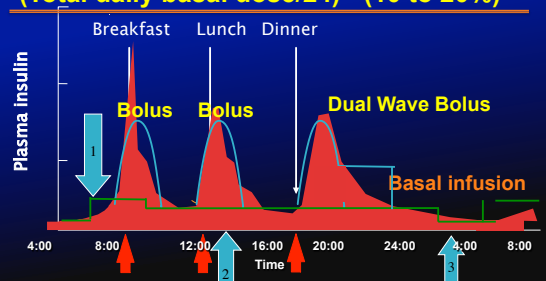
Bolus Options With Pump Therapy



1. Standard: quickly absorbed food
2. Square Wave: gastroparesis, fatty meals, Pramlintide (symlin)
3. Dual Wave: combination of rapid and slowly absorbed meals

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

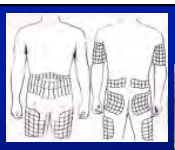
Variable Basal Rate Capability
(Total daily basal dose/24) - (10 to 20%)



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

Infusion Sites

- Infusion sites need to be changed every two to three days
- Quick release catheters
- Auto inserters

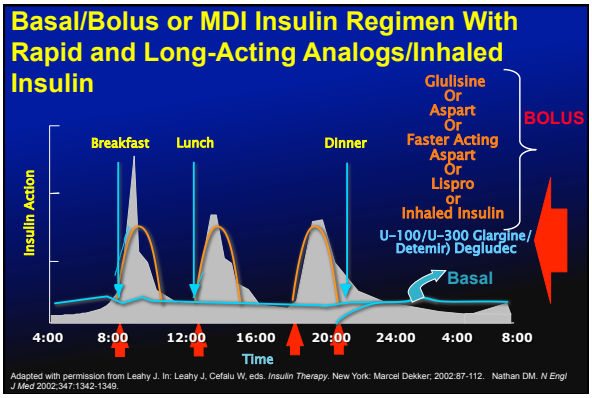


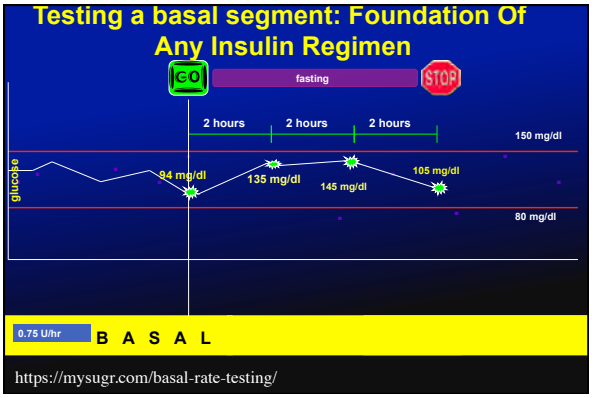

Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fourth Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2013.

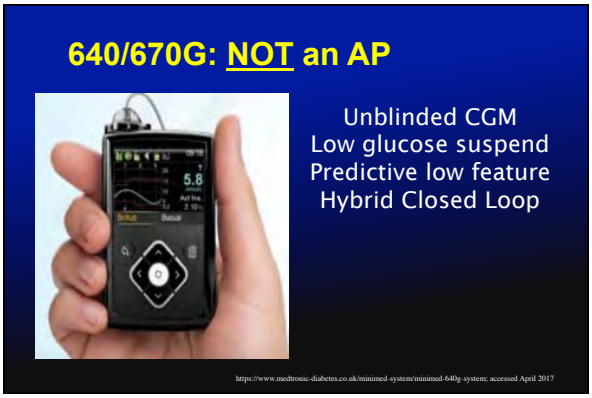
Disadvantages of Pump Therapy

- A disruption in short acting insulin delivery due to a dislodged catheter, blockage, or an empty reservoir can result in a fairly rapid rise in glucose concentration
  - Severe hyperglycemia
  - Ketoacidosis
- Cost of the insulin pumps
  - Pump costs approximately $3,500 to $5,000 (some pumps offer pay as you go options)
  - Monthly cost of $30 to $40 due to batteries, infusion lines, syringes, and adhesive tape
- Minor skin irritation or infections at the insulin pump catheter insertion site
- Very occasional abscess

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

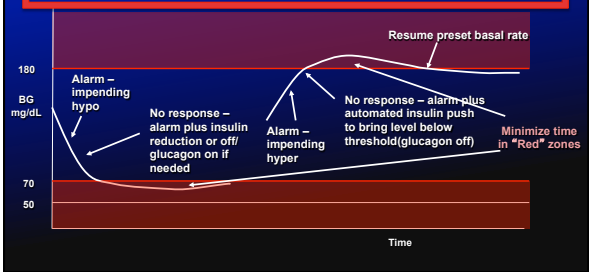

Basal/Bolus or MDI Insulin Regimen With Rapid and Long-Acting Analogs/Inhaled Insulin
Glulisine
Or
Aspart
Or
Faster Acting
Aspart
Or
Lispro
or
Inhaled Insulin
BOLUS
U-100/U-300 Glargine/
Detemir) Degludec
Basal
Breakfast
Lunch
Dinner
Insulin Action
4:00
8:00
12:00
16:00
20:00
24:00
4:00
8:00
Time
Adapted with permission from Leahy J. In: Leahy J, Cefalu W, eds. Insulin Therapy. New York: Marcel Dekker; 2002:87-112. Nathan DM. N Engl J Med 2002;347:1342-1349.


Testing a basal segment: Foundation Of Any Insulin Regimen
GO
fasting
STOP
2 hours
2 hours
2 hours
150 mg/dl
glucose
94 mg/dl
135 mg/dl
145 mg/dl
105 mg/dl
80 mg/dl
0.75 U/hr
B A S A L
https://mysugr.com/basal-rate-testing/

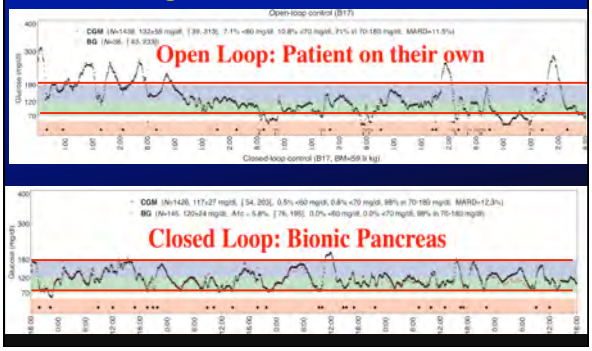

640/670G: NOT an AP
Unblinded CGM
Low glucose suspend
Predictive low feature
Hybrid Closed Loop
https://www.medtronic-diabetes.co.uk/minimed-system/minimed-640g-system; accessed April 2017

An Artificial Pancreas Is Coming Faster Than We Thought Possible

iLet • BigFoot • Tandem • Insulet • Medtronic



CGM Readings On and Off the Bionic Pancreas



Summary/Conclusions

- CGM will bridge the gap until a real cure for type 1 is discovered
- Numerous variables can and will affect the blood glucose levels on a daily basis
- Every day is different for a person with type 1 diabetes
- A glucose value at one point in time has limited value when dosing insulin
- Trend arrows can help PWD make better daily diabetes decisions