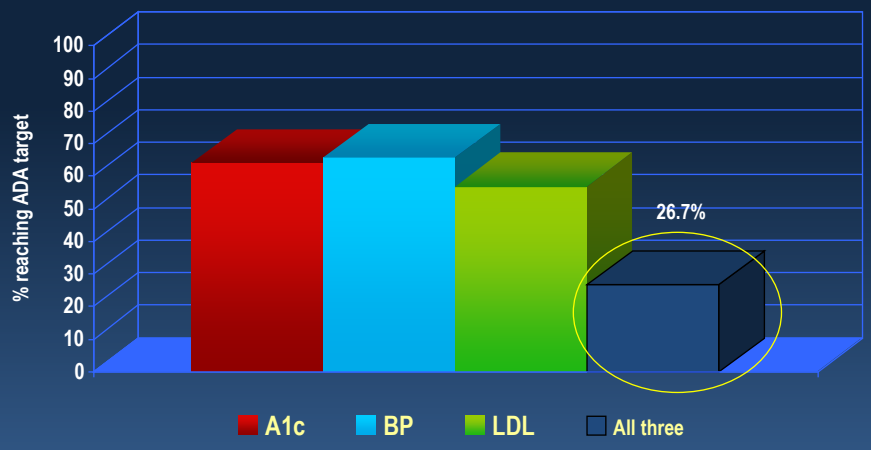
Lecture 1: 8:15 – 9:15 a.m. CDT

William Polonsky, PhD, CDCES, Presents:

Understanding and Addressing Problematic Adherence to Oral and Injectable Cardiometabolic Medications

Patients Achieving Targets: 2014



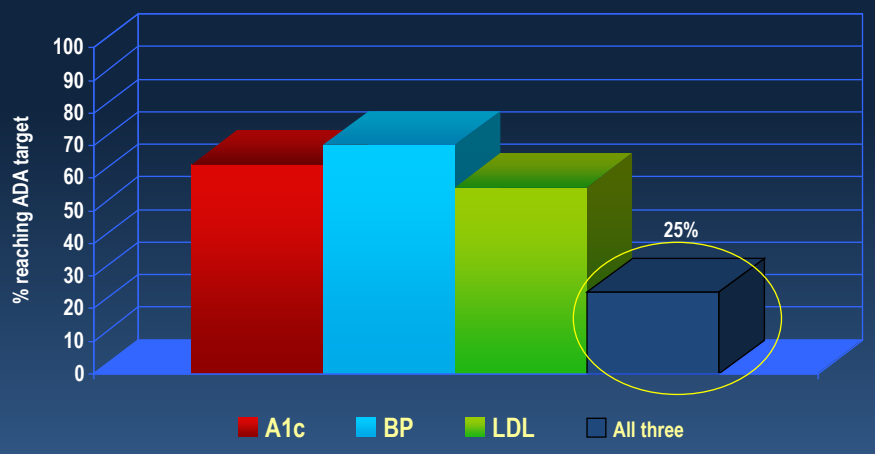
NHANES data: Ali et al, 2014

The Key Behavioral Contributor to Glycemic Control

Outcome: HbA1c (%)	Model 1: all self-care behaviours β	Model 2: all self-care behaviours + covariates β
General diet	0·04	0·06
Specific diet	−0·06	−0·04
Exercise	−0·10[a]	−0·03
SMBG	0·03	−0·002
Medications	−0·14[b]	−0·16[b]

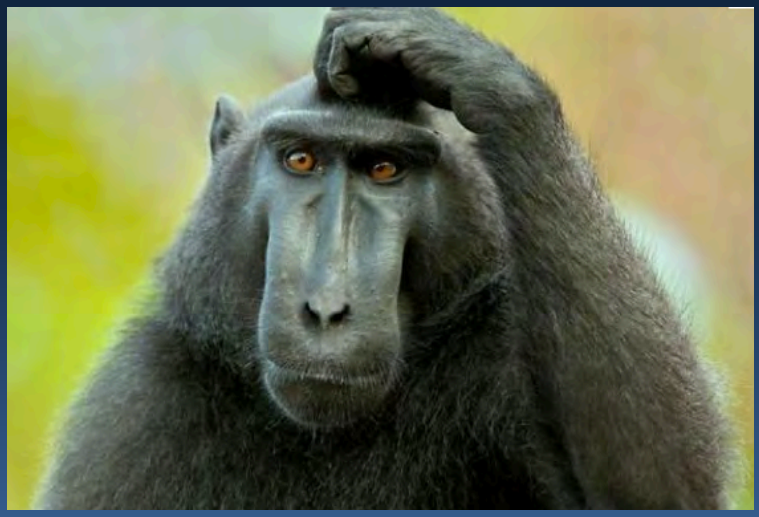
Osborn et al, 2016

Patients Achieving Targets: 2019

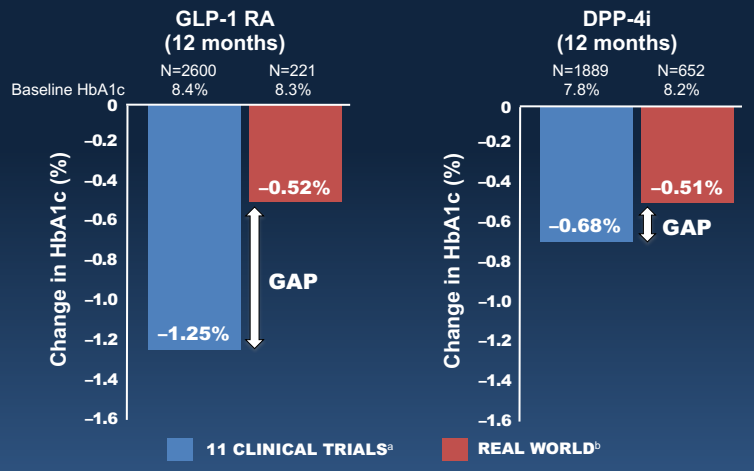


Kazemian et al, 2019

WHY AREN'T WE SEEING DRAMATIC IMPROVEMENTS?

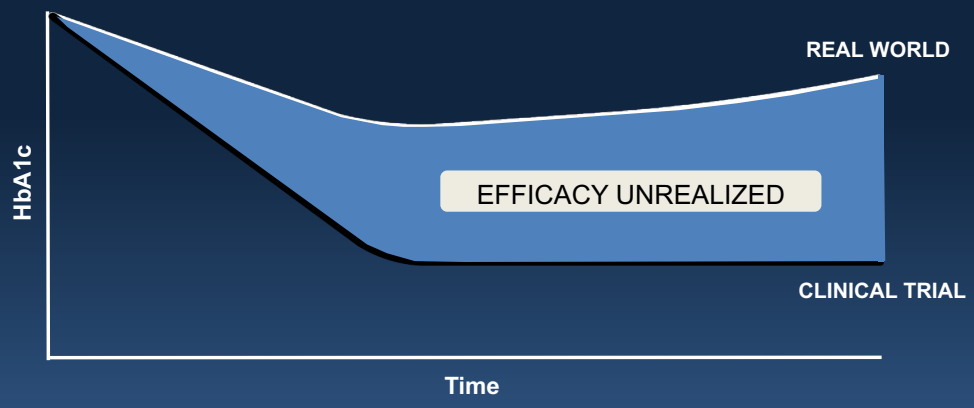


CLINICAL TRIAL RESULTS LOOK GOOD, BUT…

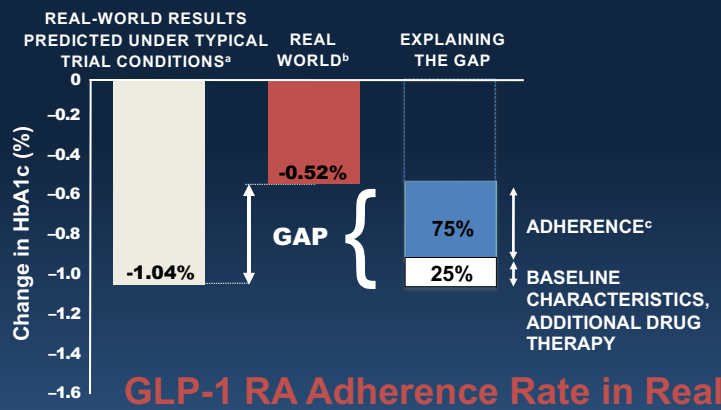


[a]Identified 11 pivotal randomized controlled trials with published change in HbA1c (7 GLP-1 RA [2600 patients] and 4 DPP-4i [1889 patients]).
[b]Optum/Humedica SmartFile database (2007-2014) was used (GLP-1 RA 221 patients; DPP-4i 652 patients). Change in HbA1c measured from drug initiation to 365±90 days later.
Carls et al, 2017

THE EFFICACY MIRAGE



POOR ADHERENCE IS THE KEY



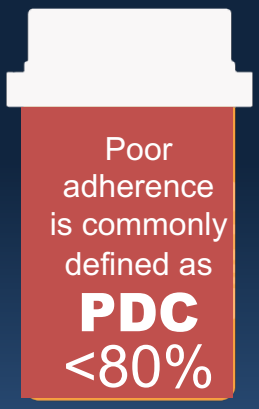
GLP-1 RA Adherence Rate in Real World = 29%

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.

DEFINING POOR ADHERENCE

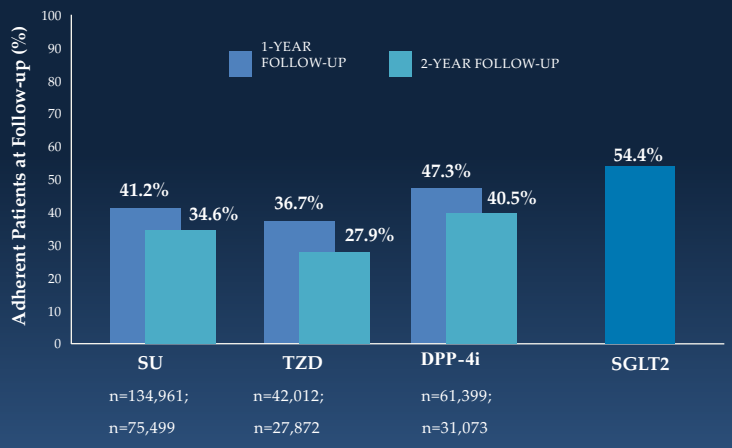


- Proportion of days covered
- Typically measured after first refill
- PDC doesn't account for
  - Prescriptions that are never filled at all1[1]
  - What the patient actually takes

PDC, proportion of days covered.

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

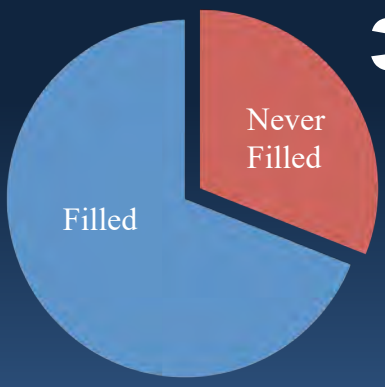
Adherence Rates for T2D Agents



PDC, proportion of days covered; SU, sulfonylurea; TZD, thiazolidinedione.
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.
Symphony PTD Data Set; Nov 2016 – Sep 2017 - Baseline characteristics of the total cohort (N=6,086,767, No of Claims=62,224,558)

TRACKING NEW E-PRESCRIPTIONS FOR DIABETES MEDICATIONS

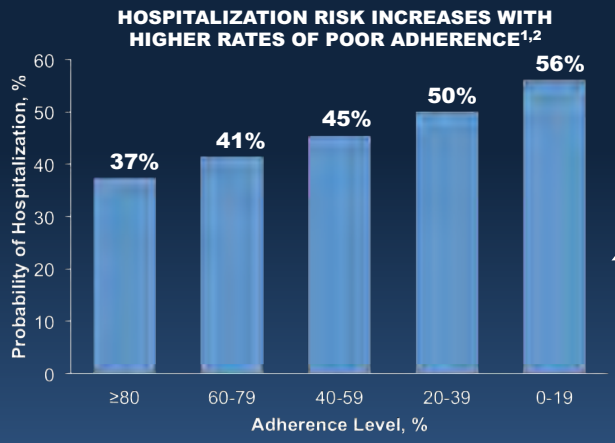
AMONG 75,589 INSURED PATIENTS IN THE FIRST YEAR OF A COMMUNITY-BASED E-PRESCRIBING INITIATIVE



31%

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

IMPACT OF POOR ADHERENCE



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]

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.

73%

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

Poor adherence defined as PDC <0.8

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

INTERVENTION STRATEGIES TO ADDRESS MEDICATION ADHERENCE

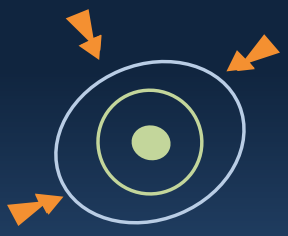
- Medication side effect management
- Feedback about medication adherence
- Medication calendars
- Enhancing patient self-management skills
- Providing consequences/rewards for adherence
- Motivational interviewing
- Stress management

Conn and Rupar, 2017

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

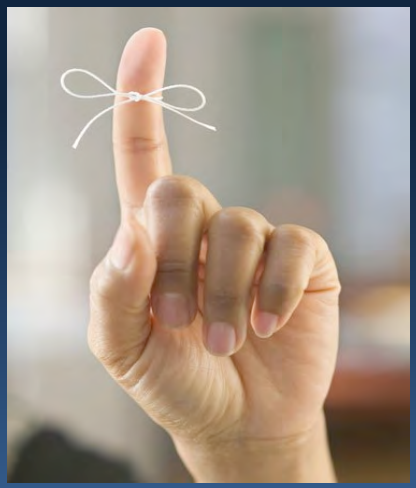


"Much room remains for improvement."

Conn and Ruppar, 2017

WHAT ARE WE MISSING?

THE PROBLEM: FORGETFULNESS?



THE SOLUTION: ADDRESS FORGETFULNESS?

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

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

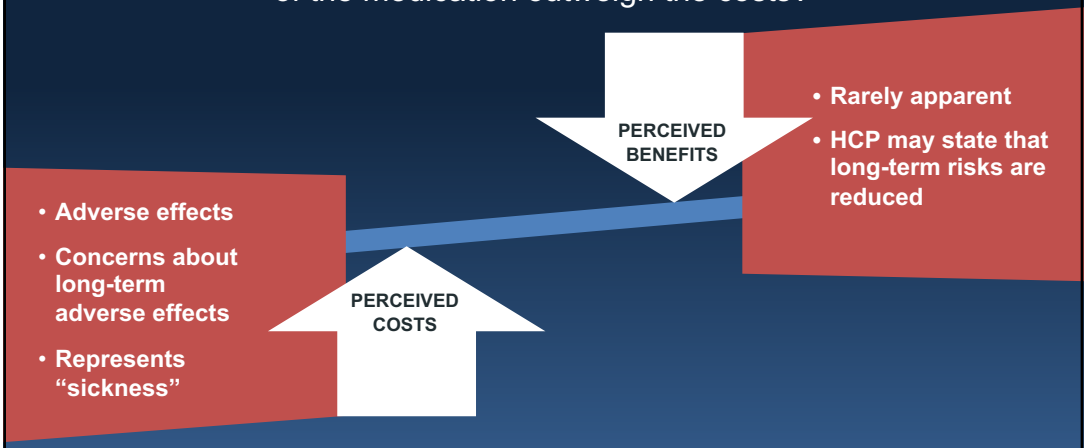
Lisa Rosenbaum, M.D.

"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

MEDICATION BELIEFS

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



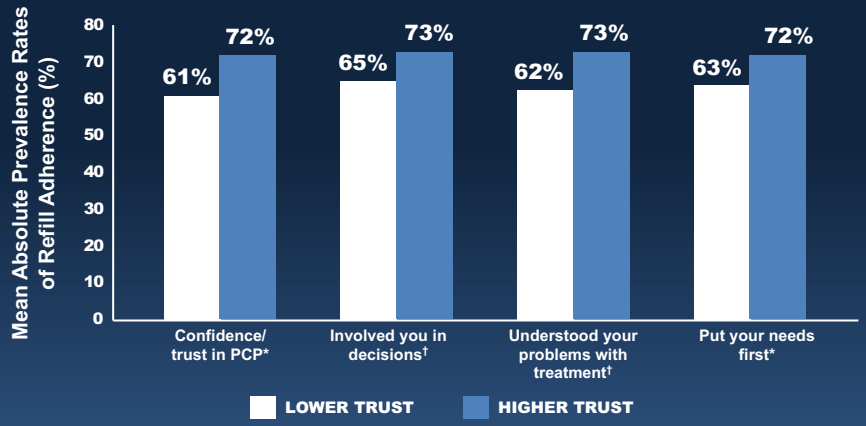
Polonsky WH. *J Diabetes*. 2015;7:777-778.

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.

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.

Association Between Primary Care Practitioner Empathy and Risk of Cardiovascular Events and All-Cause Mortality Among Patients With Type 2 Diabetes: A Population-Based Prospective Cohort Study

Hajira Dambha-Miller, MRCGP, PhD[1,3]
Adina L. Feldman, PhD[2]
Ann Louise Kinmonth, FRCGP,

ABSTRACT

PURPOSE To examine the association between primary care practitioner (physician and nurse) empathy and incidence of cardiovascular disease (CVD) events and all-cause mortality among patients with type 2 diabetes.

Dambha-Miller et al, 2019

Assessing Your HCPs' Empathy

How good was your HCP at:

1. making you feel at ease
2. letting you tell your story
3. really listening
4. being interested in you as a whole person
5. fully understanding your concerns
6. showing care and compassion
7. being positive
8. explaining things clearly
9. helping you to take control
10. making a plan of action with you

Dambha-Miller et al, 2019

HCP Empathy and Mortality Outcomes

- 10-year follow up of patients with newly diagnosed T2D:
- "those reporting better experiences of empathy in the first 12 months after diagnosis had a significantly lower risk **(40% to 50%)** of all-cause mortality over the subsequent 10 years vs. those who experienced low practitioner empathy."

Dambha-Miller et al, 2019

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

SO WHAT TO DO?

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?"***

SO WHAT TO DO?

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

SO WHAT TO DO?

1. Ask correctly
2. Forgetfulness
3. Patient-provider trust and collaboration
   - Listen, listen, listen

SO WHAT TO DO?

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

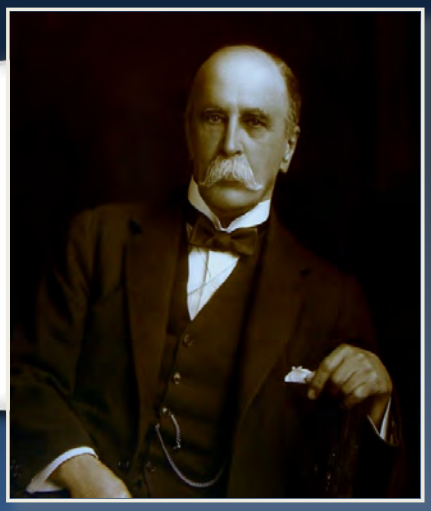
Challenging Harmful Beliefs

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
5. Emphasize the potential long-term gains

Diabetes and Your Health

"To live a long and healthy life, develop a chronic disease and take care of it."

- *Sir William Osler*

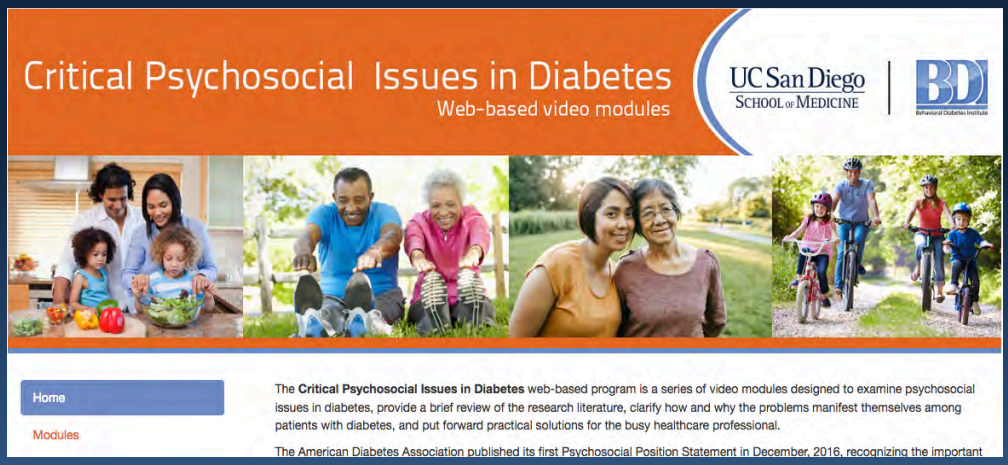


CONCLUSIONS

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.**

Thanks for Listening!



www.behavioraldiabetes.org

Lecture 2: 9:15 – 10:30 a.m. CDT

Jeremy H. Pettus, MD, Presents:

A Focus on Time in Range,
Unmet Needs and Modern Management of Type 1 Diabetes

To Be Discussed…

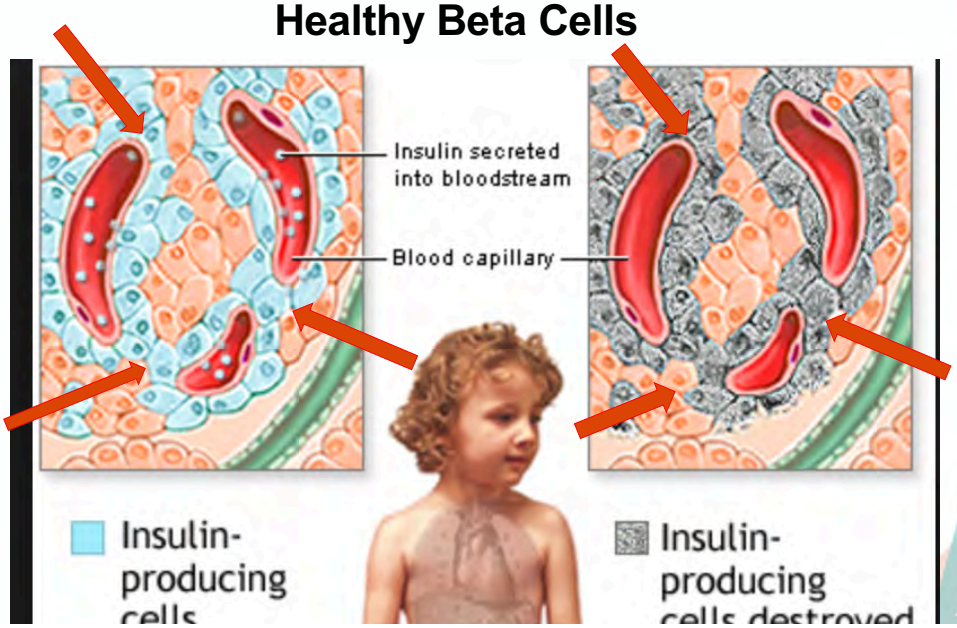
- Incidence and pathophysiology
- Demographics of T1D in the U.S.
- A1c and time in range (TIR)
- Overview of pumps and CGM devices
- Interpreting CGM downloads in ~ 30 secs.
- Identifying and addressing common problems
- New insulin and glucagon formulations
- Advances in hybrid and closed AP

Prevalence of T1D Is Increasing!

- 40,000 people diagnosed each year in U.S.[2]
- 110 people are diagnosed with T1D each day
- By 2040 there will be 5 million people with T1D

1. T1D Exchange T1D population based on company research
2. www.JDRF.org

Type 1 is an Autoimmune Disease: The Immune System Attacks Healthy Beta Cells



Natural Progression is months to a few years

August 6, 2019

Teplizumab Gets Breakthrough Status for Type 1 Diabetes Prevention

Steve Duffy

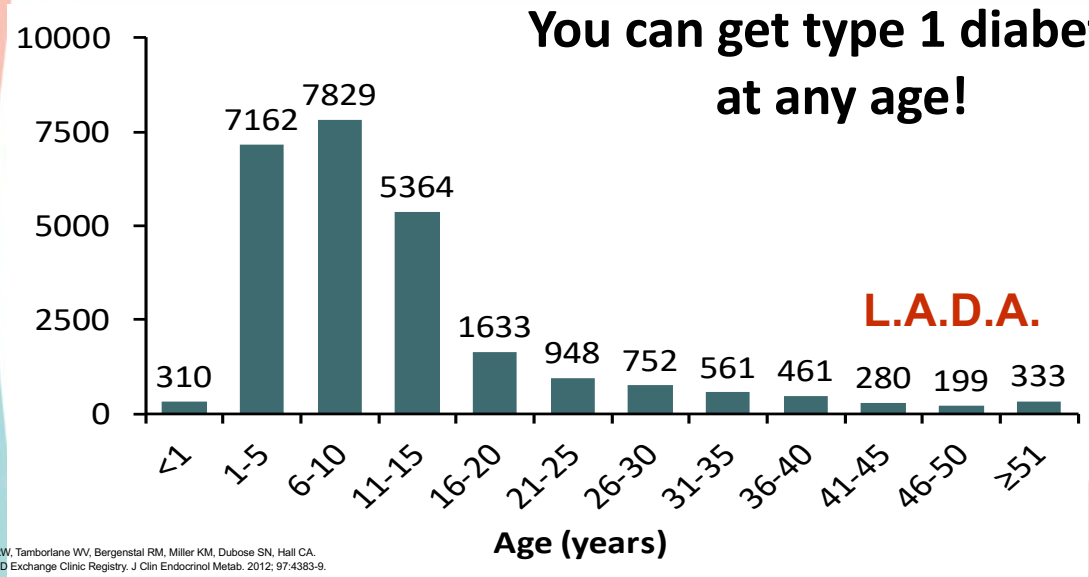
Type 1 Diabetes TrialNet

The Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to teplizumab (PRV-031; Provention Bio), an anti-CD3 monoclonal antibody, for the prevention or delay of clinical type 1 diabetes (T1D) in individuals at risk of developing the disease.

Teplizumab is an investigational anti-CD3 monoclonal antibody

The designation was based on data from a recent

Age at Diagnosis of T1D



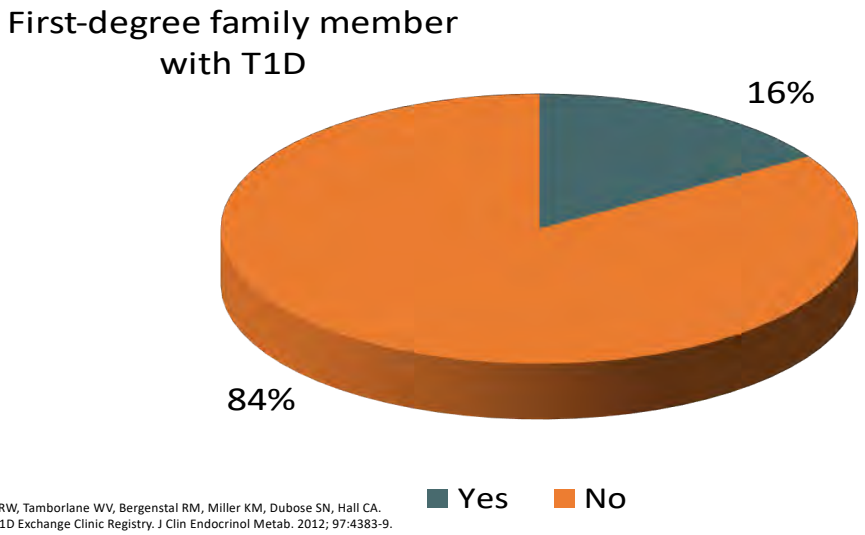
Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

Latent Autoimmune Diabetes in Adults (L.A.D.A.)

- **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)

Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fourth Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2013.
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

Family History of T1D

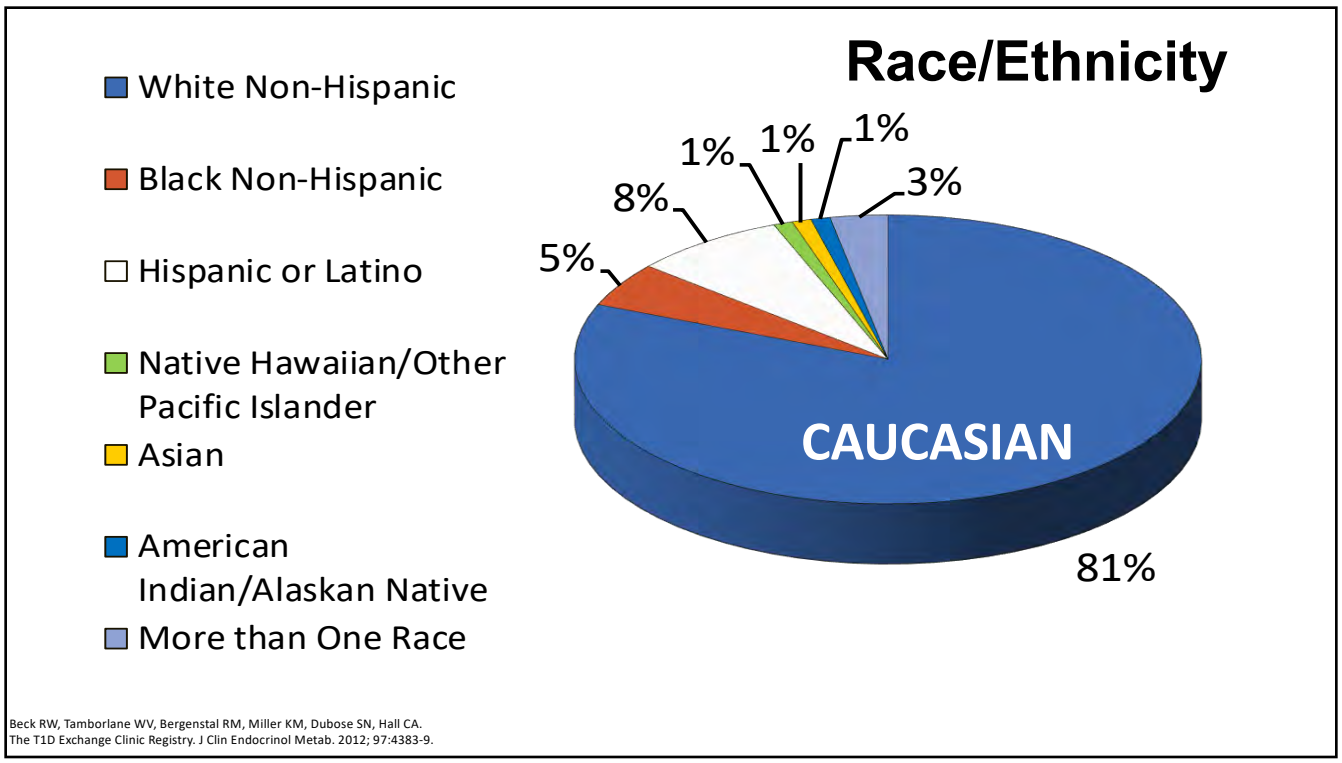


Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

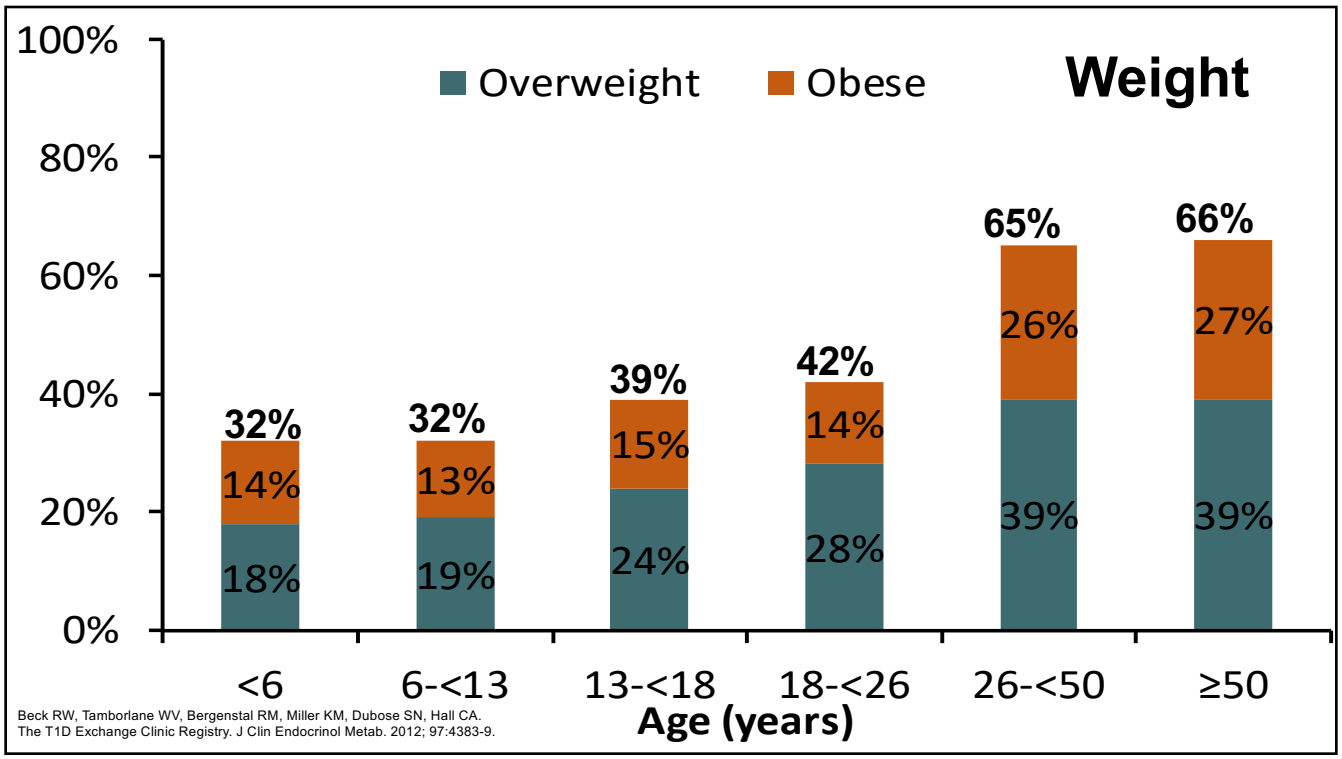
Risk of Developing Type 1 vs Type 2

General Population	**0.3%**	**8-11%**
If you have a sibling with T1D	4%	**~30%**
If your mother has T1D	2-3%	**~30%**
If your father has T1D	**6-8%**	**~30%**
If you have an identical twin with T1D	**~50%**	100%

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

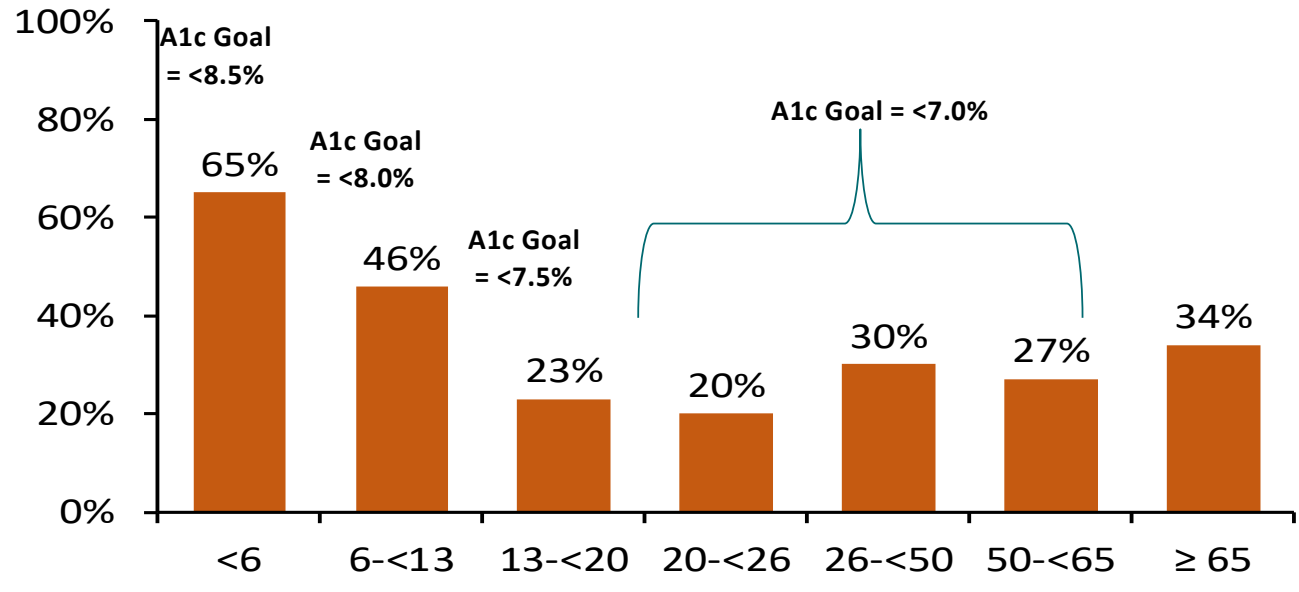


Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.



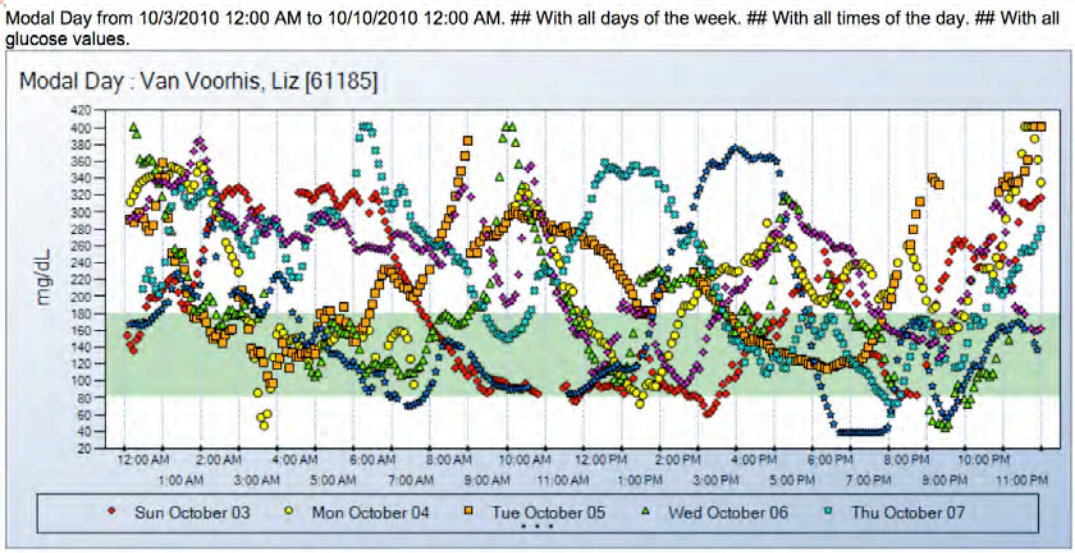
Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

Only ~30% Of Type 1s Reach ADA Goal Of An A1c Less Than 7%

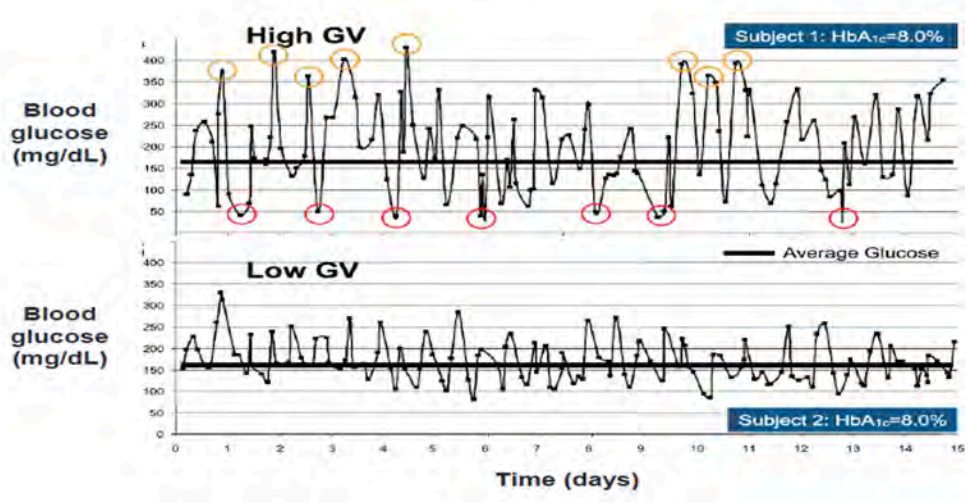


Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

This is Type 1 Diabetes for a lot of Patients



These Patients Have the Same A1c



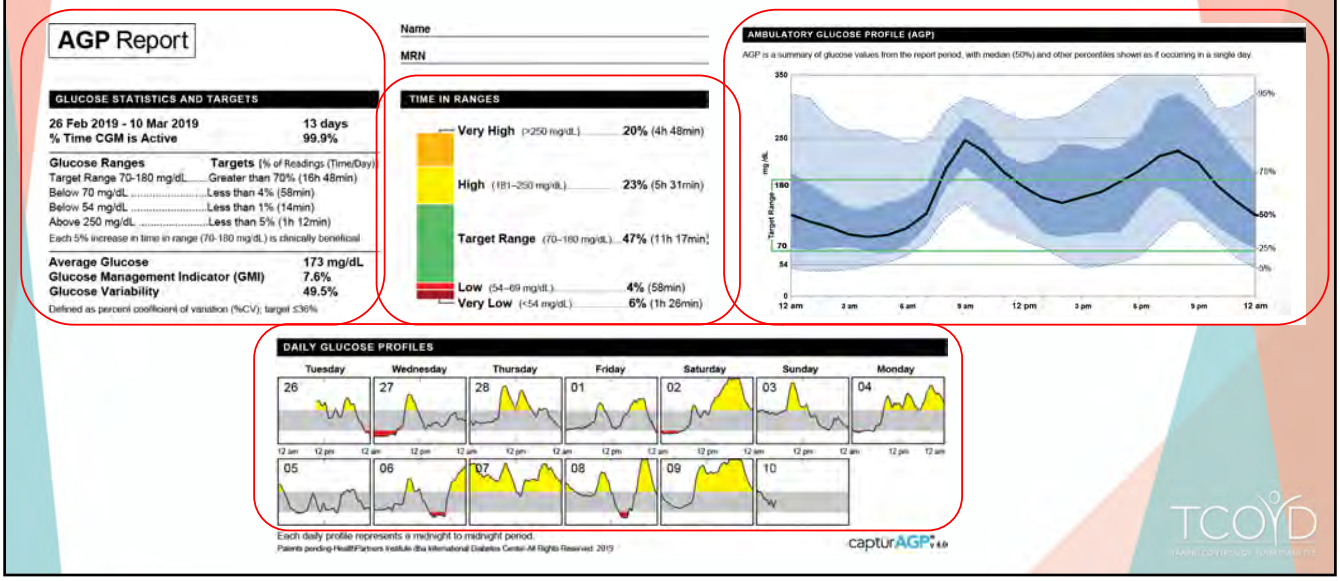
GV, glycemic variability

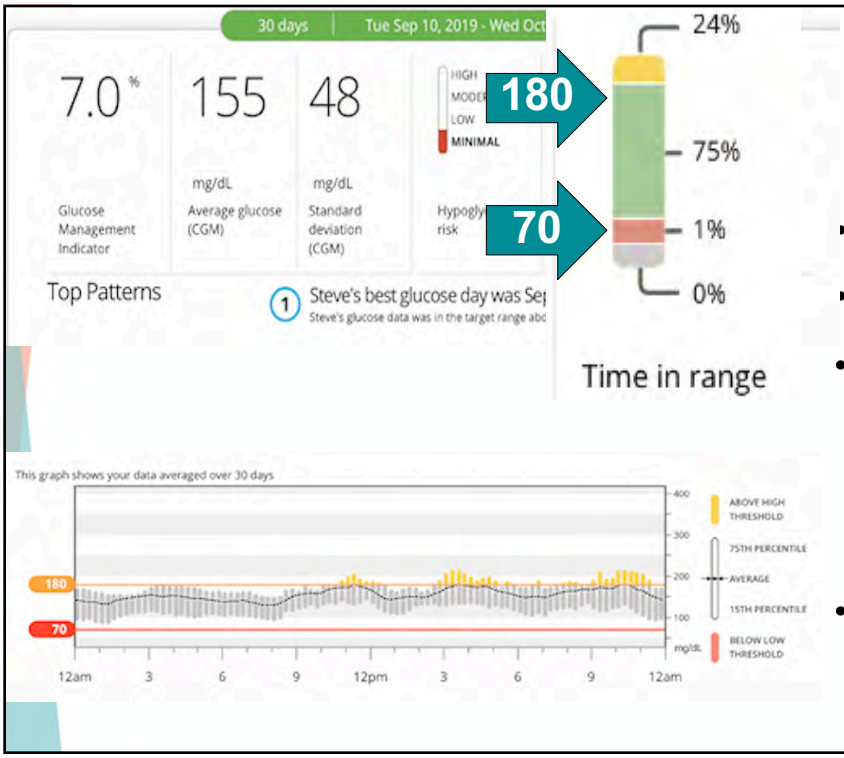
1. Kovatchev B et all. Diabetes Care. 2016;39:502-510; 2. Suh S et al. Diabetes Metab J. 2015;39:273-282; 3. Bergenstal RM. Diabetes Care. 2015;38:1615-1621; 4. Beck RW et al. Diabetes Care. 2019;42:400-405

Provider CGM Overview

1. Review CGM download **together** with the patient, explain what you are observing
2. Look at average glucose and predicted A1c
3. Look at time in range and start with time hypoglycemic (goal < 5%)
4. Look at total time in ideal range (goal > 70%)
5. Look at 24 hour day to see when highs and lows occur
6. Look at individual days to tease out those problem areas
7. Review **alert settings** on the CGM. Especially if the significant other looks exhausted and has alarm PTSD

Ambulatory Glucose Profile (AGP): One Report to Rule Them All

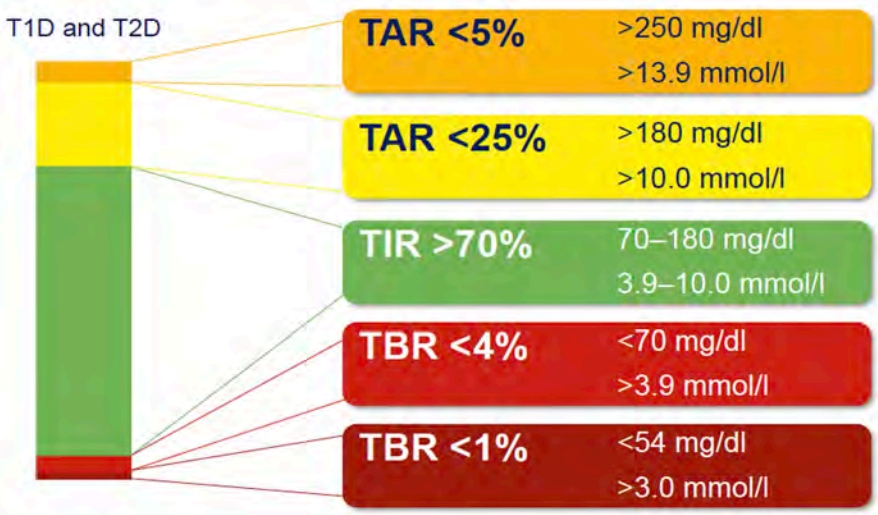




The CGM Report
Getting Oriented

- **Mean glucose value**
- **Standard deviation (SD)**
- **Time in range (70-180 mg/dl)**
  - **Time >180 mg/dl**
  - **Time <70 mg/dl**
- **24-hour multiday profile**

CGM TIR Targets for Most with T1D and T2D

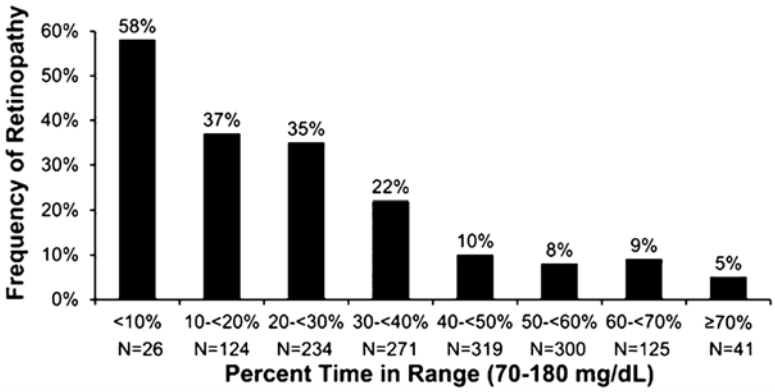


High risk individuals (with complications or comorbidities & pregnancy) have different targets

Battelino T, Danne T, Bergenstal RM, et al. Diabetes Care 2019;42:1593-1603

Improved TIR is Associated with Lower Microvascular Disease

- Beck 2019 – Looked back at DCCT data for mean TIR of 7-point profiles (n=1440, 32,528 fingerstick glucose)

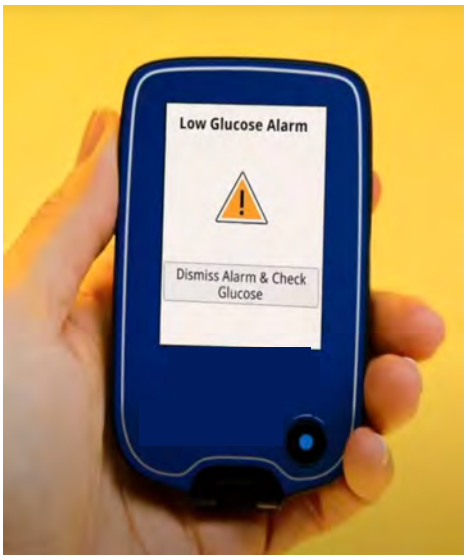


DCCT = Diabetes Control and Complications Trial

Available CGM Systems

Options to Connect Directly to Smart Phone/Smart Watch

- Last 10 days
- No calibration
- No finger sticks
- Predictive low alert
- Medicare approved



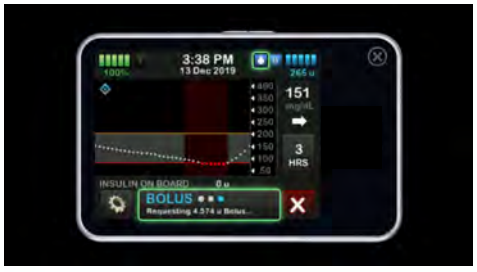
CGM System

- Requires calibration
- Predictive low alerts
- Requires high alerts
- 6-day wear
- Need to confirm with fingerstick when dosing insulin
- No sharing capabilities

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

Available CGM + Pump Systems

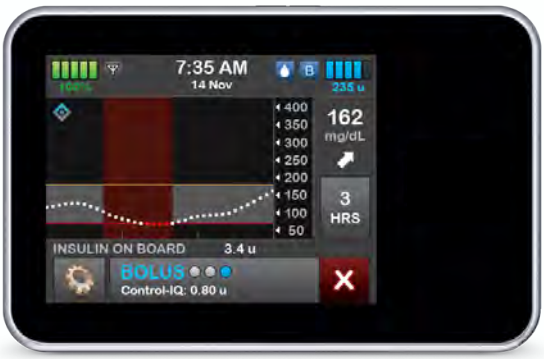
How Does Control IQ Keep You in Range?



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 31, 2019 VOL. 381 NO. 18

Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes



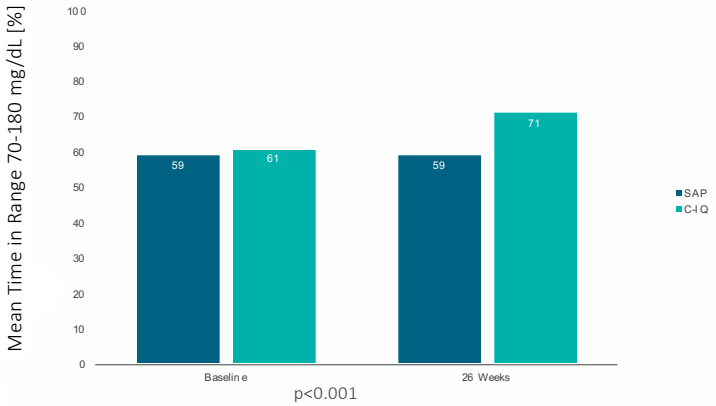
Improved "Time in Range"

Reduced A1c

Reduced Hypoglycemia

Results

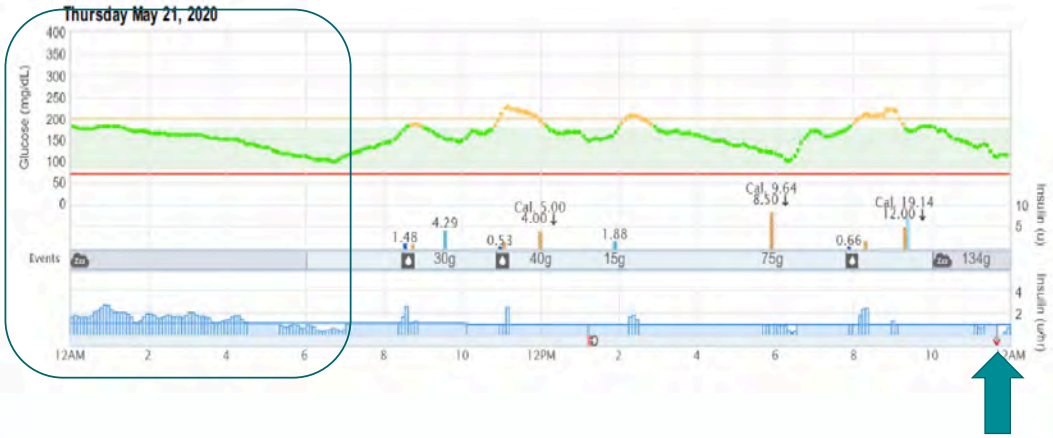
Primary Outcome Time in Range 70-180 mg/dL*



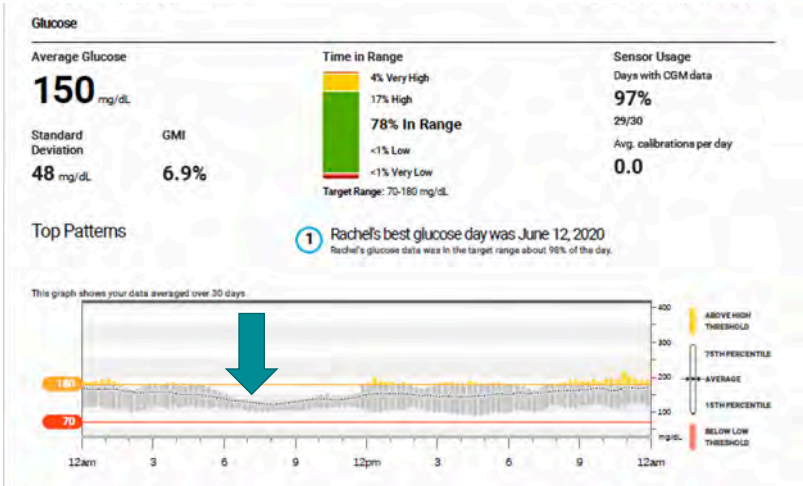
average additional time per day that Control-IQ participants spent in range compared to SAP users*

*As measured by CGM

Basal Rate Modulation Overnight to Improve Control…

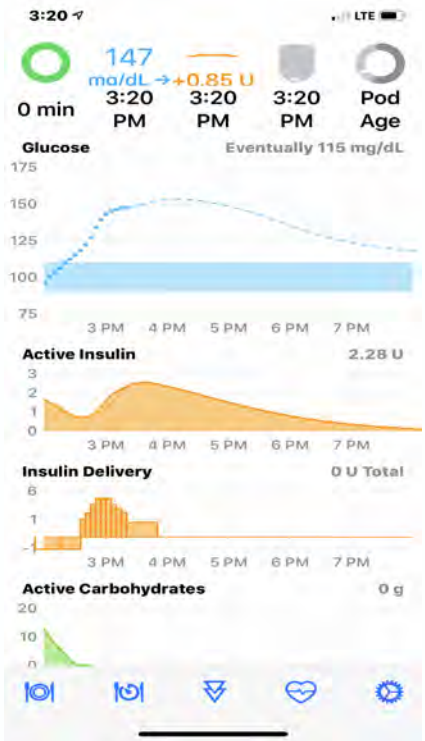


AP Systems Very Effective Overnight



Hybrid-Closed Loop System

- Auto-adjusts basal rate when in auto mode
- Target blood sugar: 120mg/dl
- Mealtime boluses required
- Sensor (needs frequent calibration to stay in auto mode)



DIY Looping Hybrid Closed Loop NOT FDA Approved

- Basal rate modulator
- Communicates with certain CGM devices (no calibration needed)
- Always in auto mode
- Still need to enter carbs and give correction doses

Smart Pens: Same Software Programs as Pumps

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

Example of a Bionic Pancreas

2 ports for insulin and glucagon

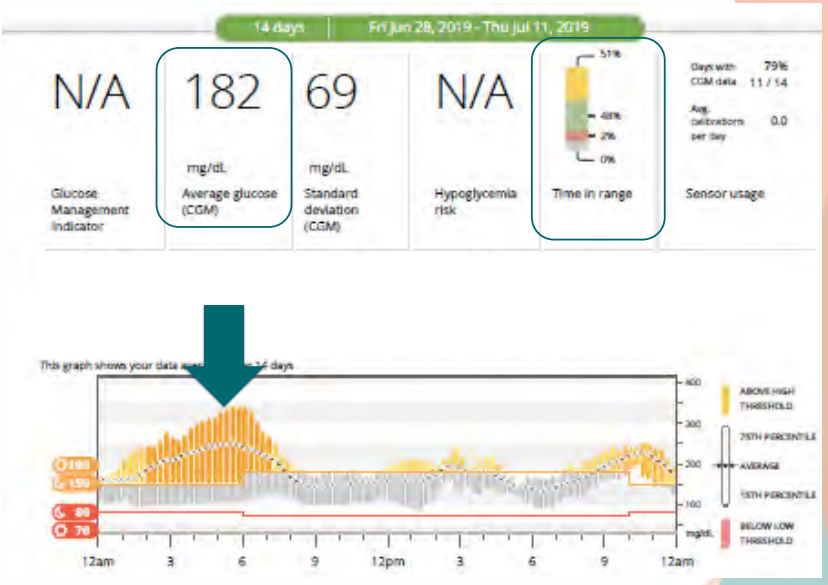
Let's Practice

Example Cases

Case 1: Sam

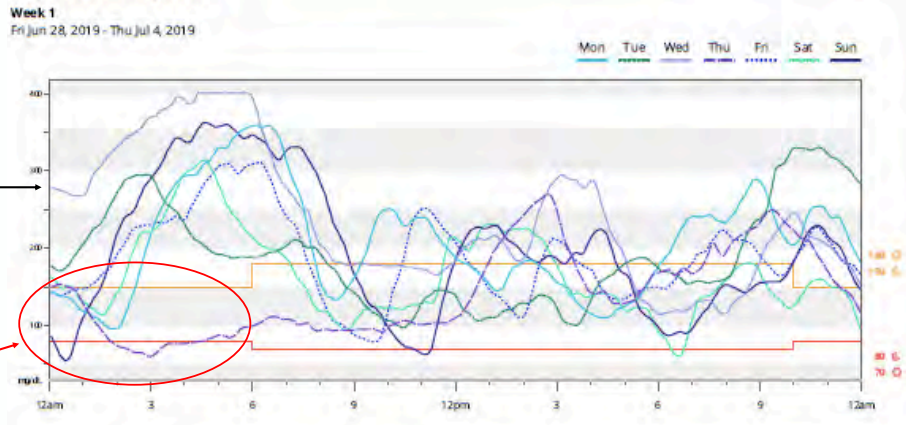
<u>Quick Interpretation</u>

- Adult with T1D
- A1c ~8%
- High variability
- Minimal lows
- Most glycemic burden overnight



Case 1 Cont…

Rises around 1AM without coverage, may be a learned behavior based on experience when no snacking



- To address overnight fall in glucose, we reduced the basal 20%
- Eliminates the need for "mandatory" bedtime snack
- Over time, increased time in range

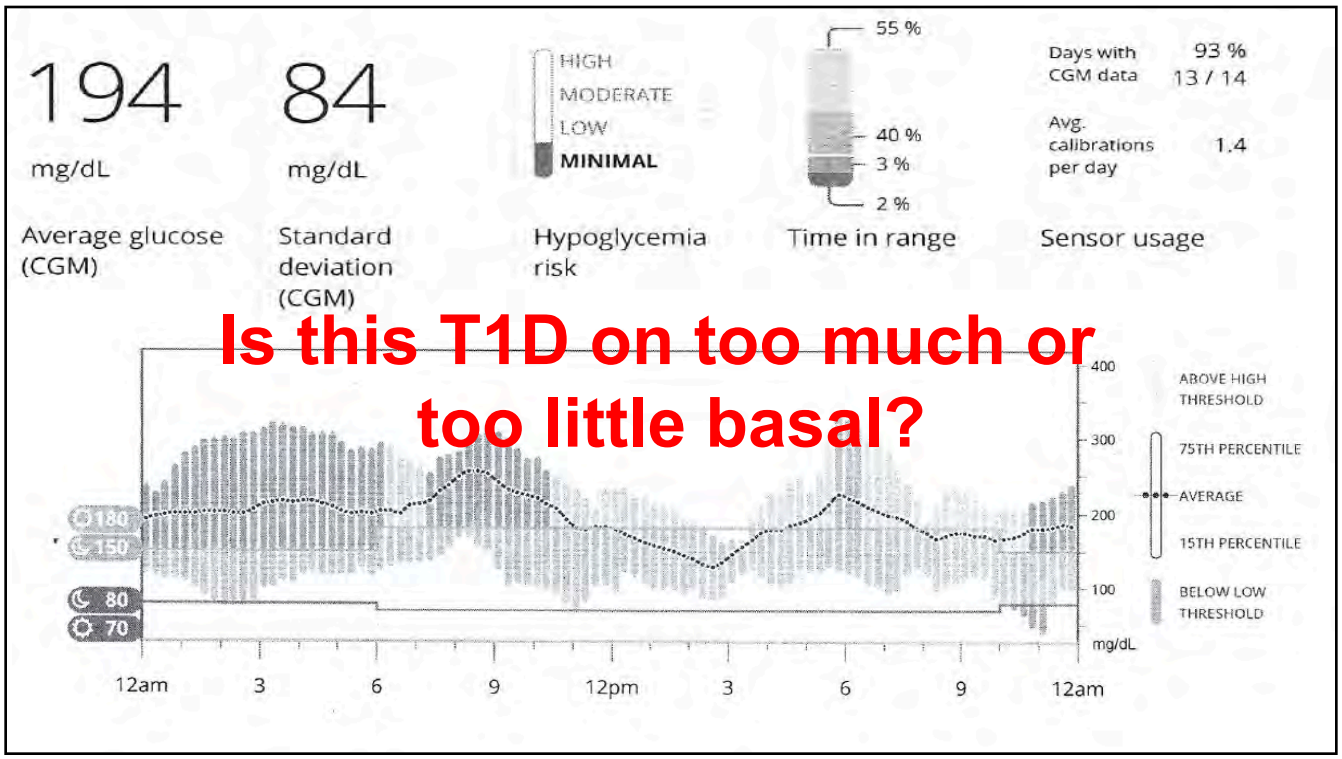
ENDOCRINE SOCIETY

How Do you Know if the Basal Does is "Right"?

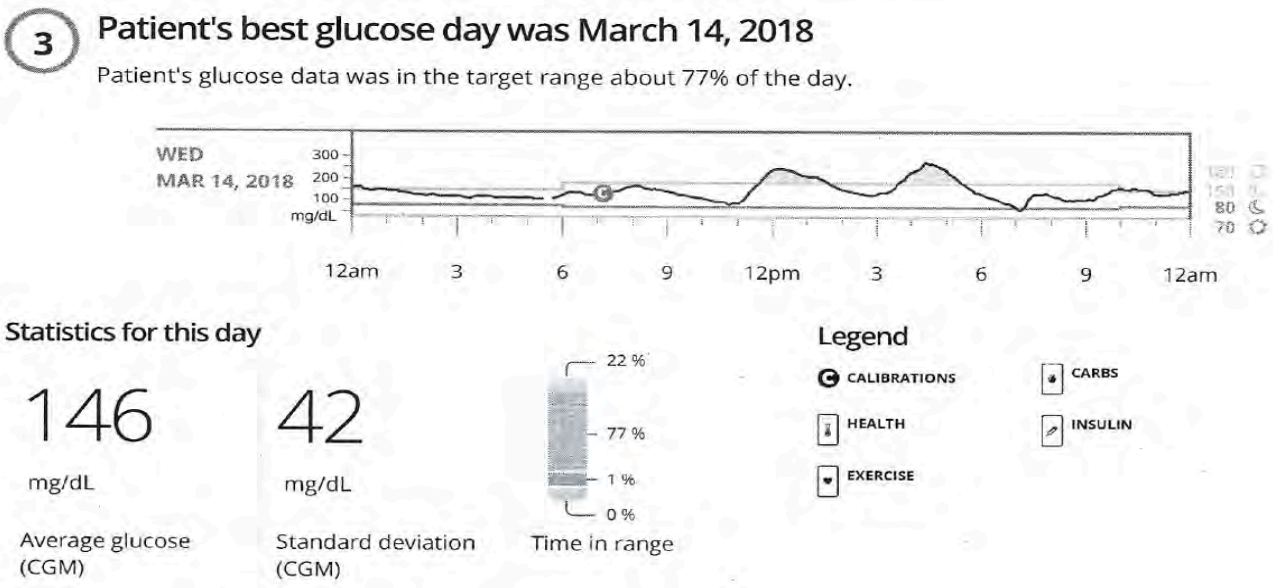
- Check blood sugar when there is no insulin boluses in the system and no carbohydrates from last meal (e.g. 2-4 AM) and compare to morning blood sugar
- Be on the lookout for variable bedtimes
- If ≥30mg/dL rise in glucose raise basal insulin dose
- If ≥30mg/dL fall in glucose decrease basal insulin dose

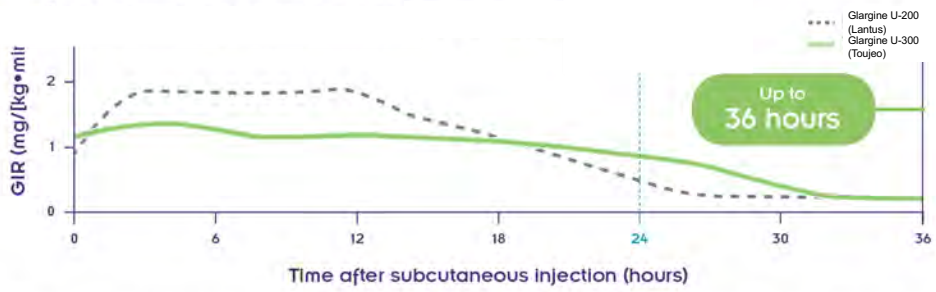
ENDOCRINE SOCIETY

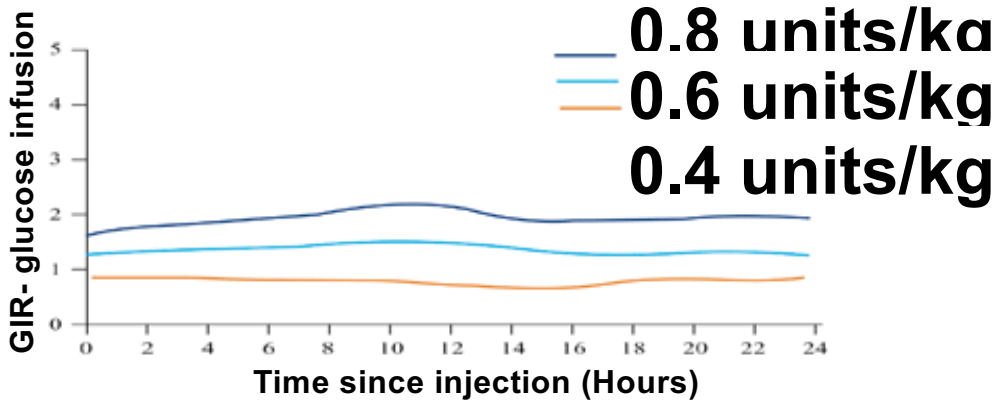
Physiologic Basal



Same Patient Fasting From 9pm Until 7am





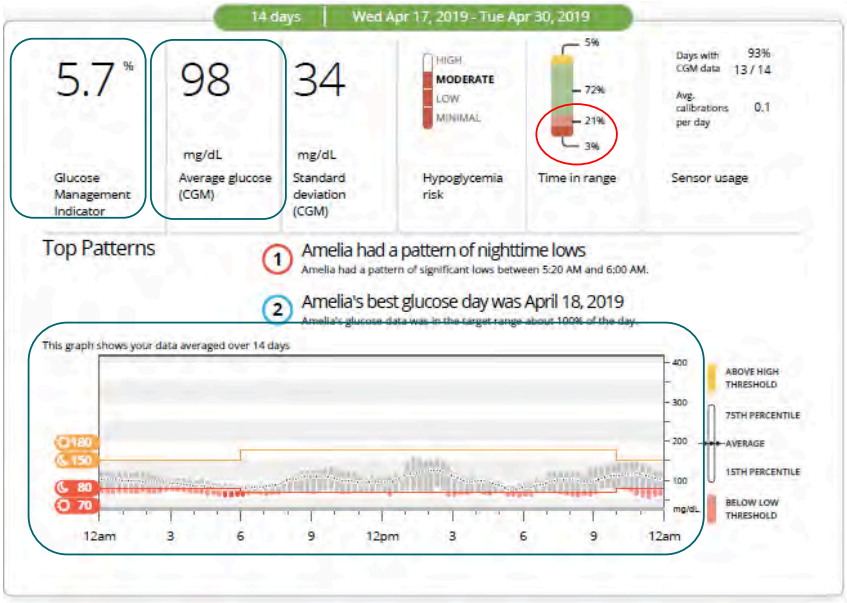


Case 1 Learning Points

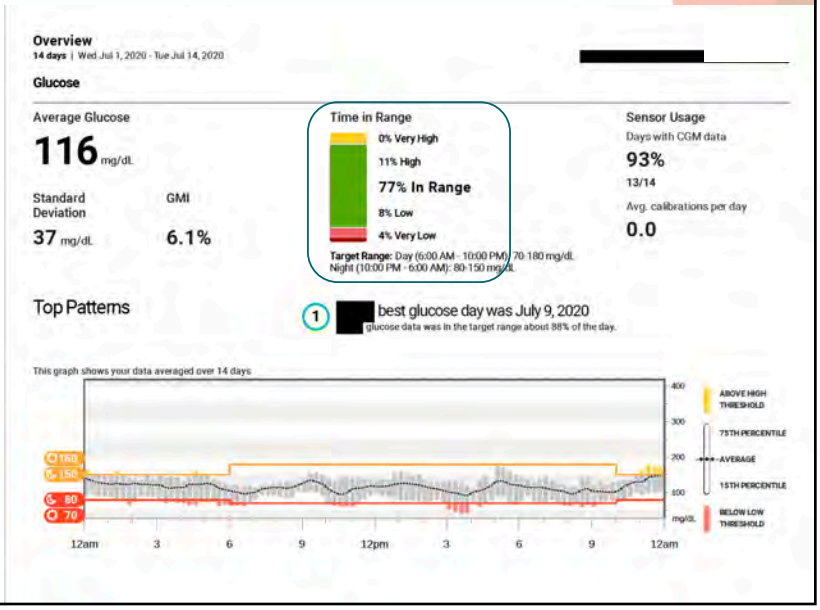
- Type 1 diabetes does not require a midnight snack
- Nighttime highs SHOULD NOT reflex to increasing basal dose
- To determine if the issue is basal or bolus related, do “basal testing” as discussed
- Often, nighttime highs need to be addressed with more insulin before bed rather than changes to basal
- Newer basal insulins (Glargine U-300, Degludec U-00/U-200) are more consistent, have more flexible dosing, and less hypoglycemia

Case 2: Amelia

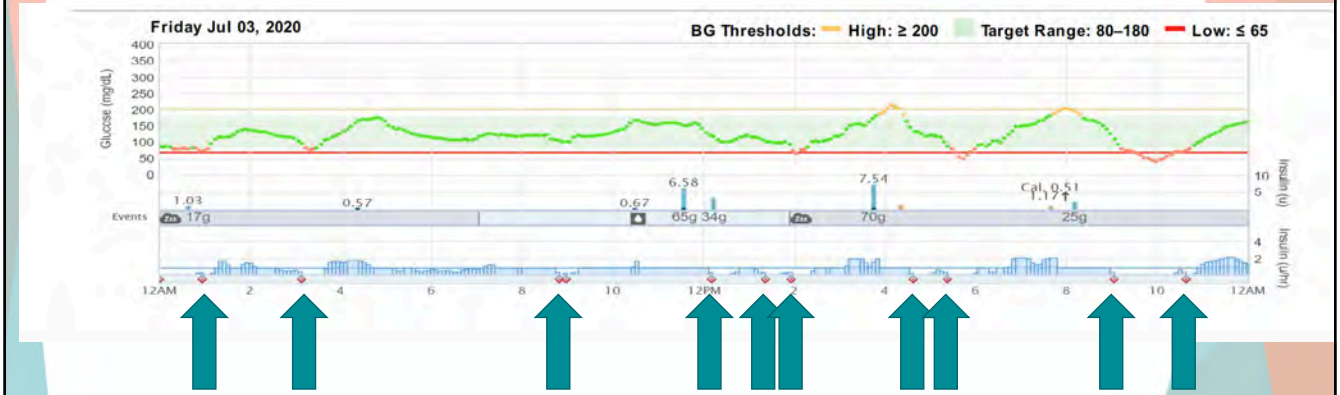
- Amelia is a 57 yo female with Type 1 diabetes since age 2
- Was told she needed tight glucose control to avoid complications
- Has since had a fear of HyPERglycemia and prefers to “Ride low”
- Currently on insulin pump with CGM



- Switched to Tandem CIQ
- Episodes of hypoglycemia markedly reduced…



Suspensions to Reduce Hypoglycemia



New Formulations of Glucagon

Nasal Glucagon

Pre-Filled Syringe

Auto-injector Pen

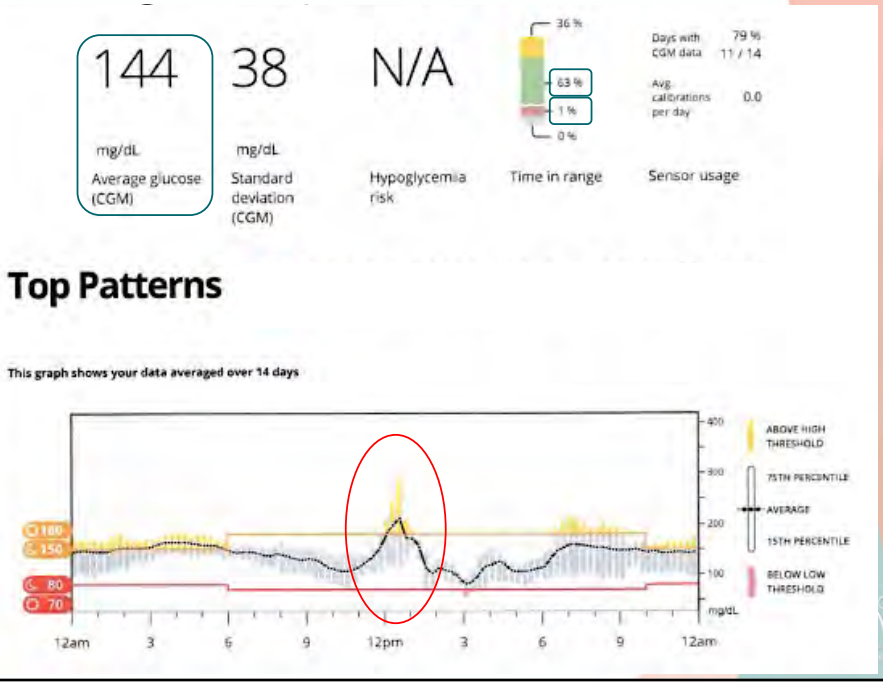
Case 2 Learning Points

- A “good” A1c doesn’t mean good control
- When you see a low A1c, look immediately at percent hypos
- Make sure these patients are on a CGM with alarms turned ON!
- Hybrid closed loop systems can help reduce hypoglycemia
- ALL type 1 patients MUST have glucagon available with loved ones trained on how to use

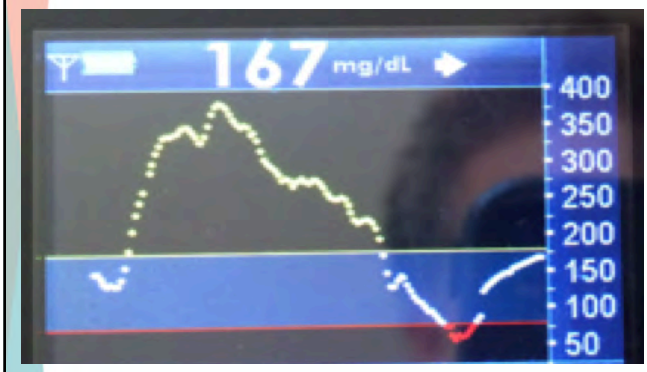
Case 3: Brian

Quick Interpretation

- Overall glucose just slightly below goal
- Low variability
- Hypos NOT a problem
- Spike after lunch

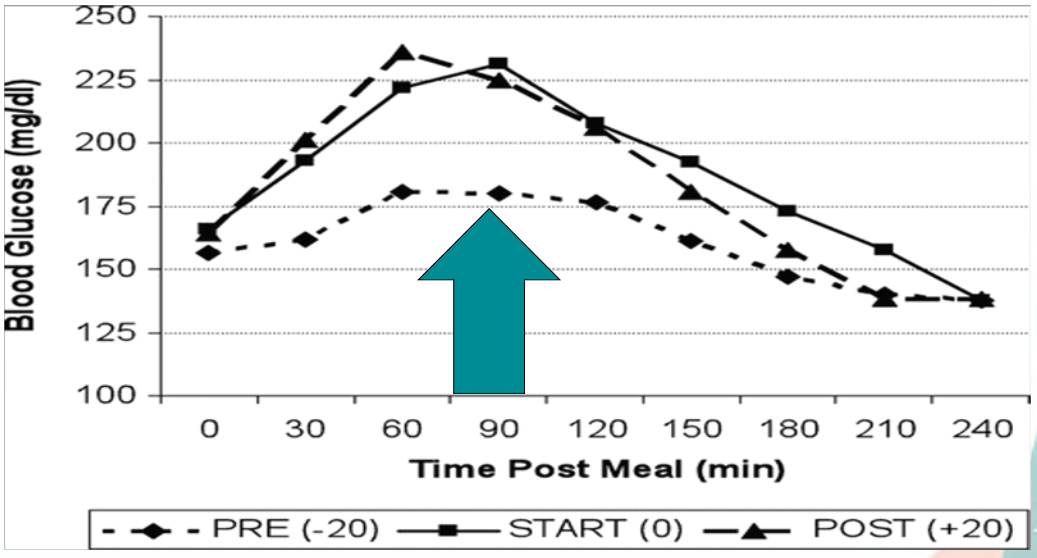


Shark Attack



- Lows after eating are VERY common
- Can result in a "rage bolus"
- Results in lows after and getting on the rollercoaster

Postprandial Glucose bolus at -20/0/+20 mins

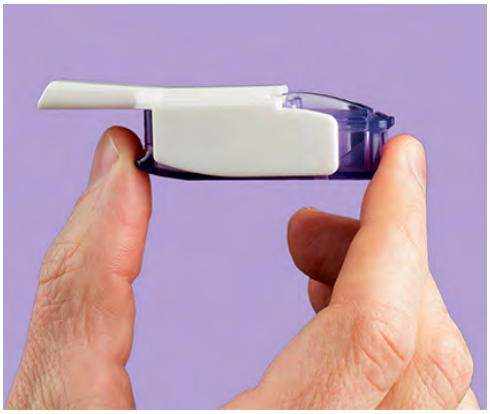


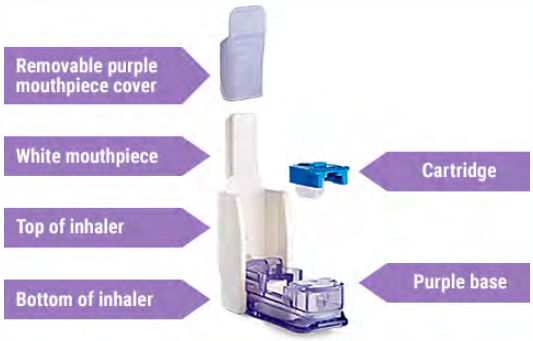
Cobry et al, Diab Tech Therap 2010;12: 173-177

What About the Low Carb Thing?

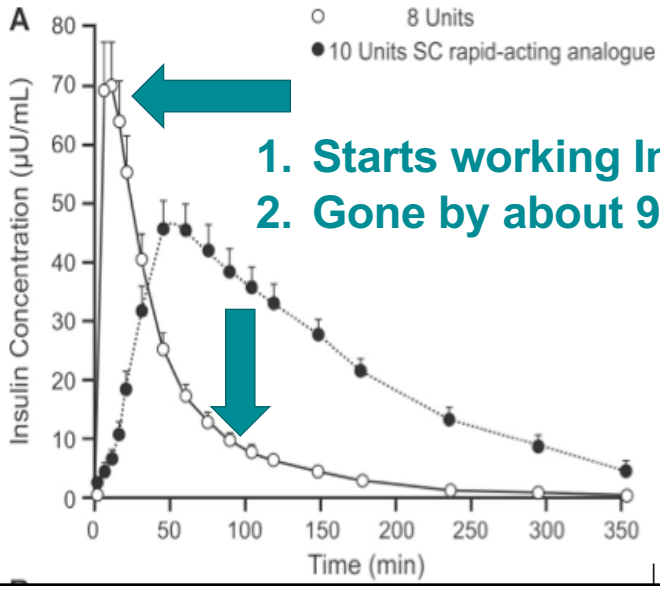
- It works
- Reduces margin of error
- Not easy to adhere to but given "Atkins craze", lots of tips on low carb snacks/meals/etc.
- TRY it for one week to see the effect of carbs on your BG

What is Inhaled Insulin?





Why is it Cool?



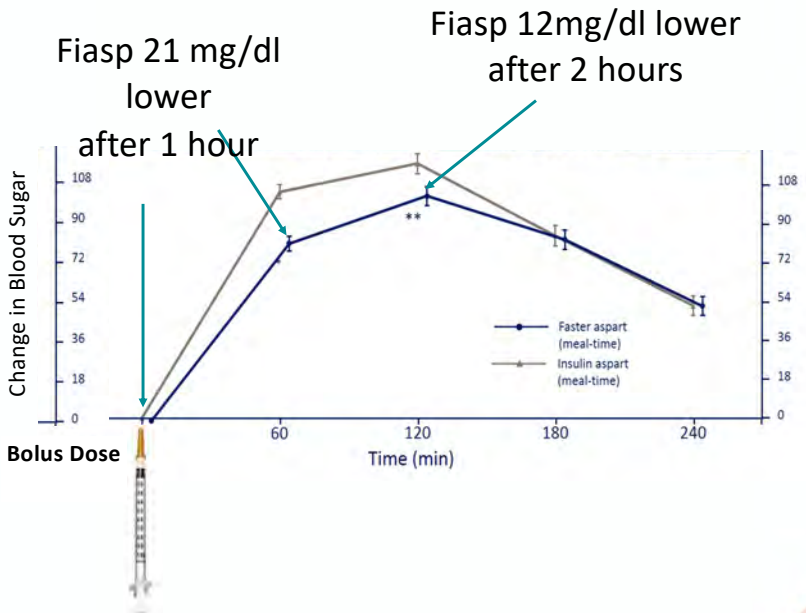
1. Starts working Immediately
2. Gone by about 90 minutes

New, ”Faster Acting” Insulins

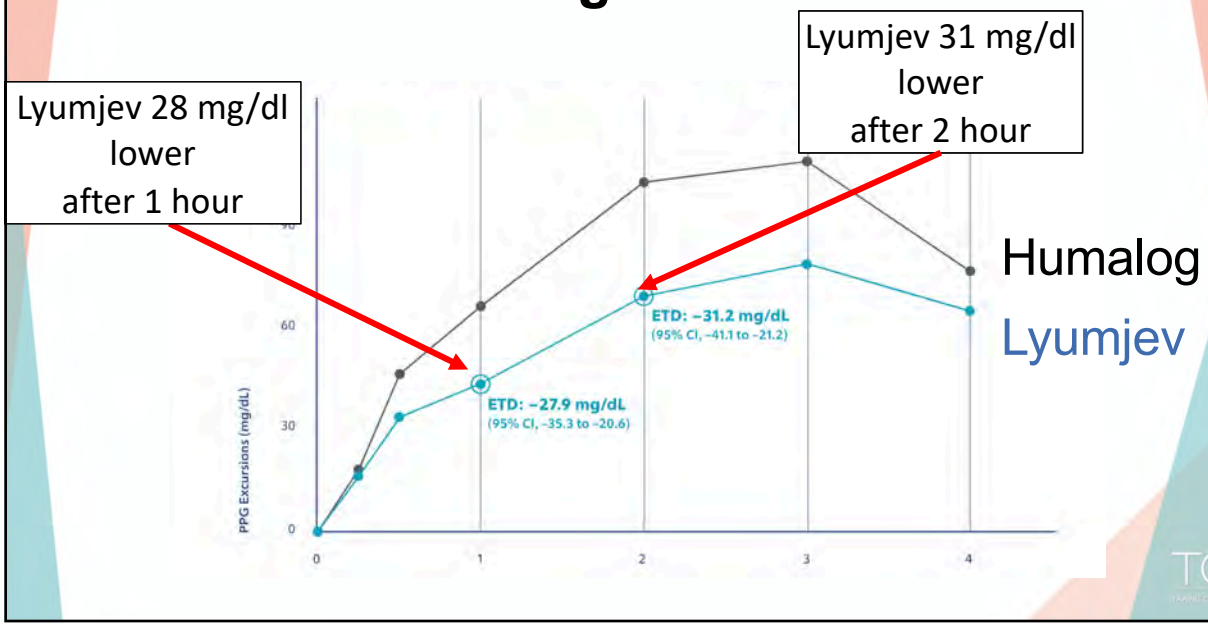
Insulin Aspart (Fiasp)

Insulin Lispro-aabc (Lyumjev)

Insulin Aspart (Fiasp) has Lower Blood Sugars After a Meal Compared to Insulin Aspart (Novolog)



Insulin-Lispro-aabc (Lyumjev) also has lower blood sugars after a meal



Case 3 Learning Points

- Bolus 15-30 minutes BEFORE you eat
- Break up meal into two parts
- Try low carb
- Try inhaled insulin or newer, rapid-acting insulins

To Be Discussed…

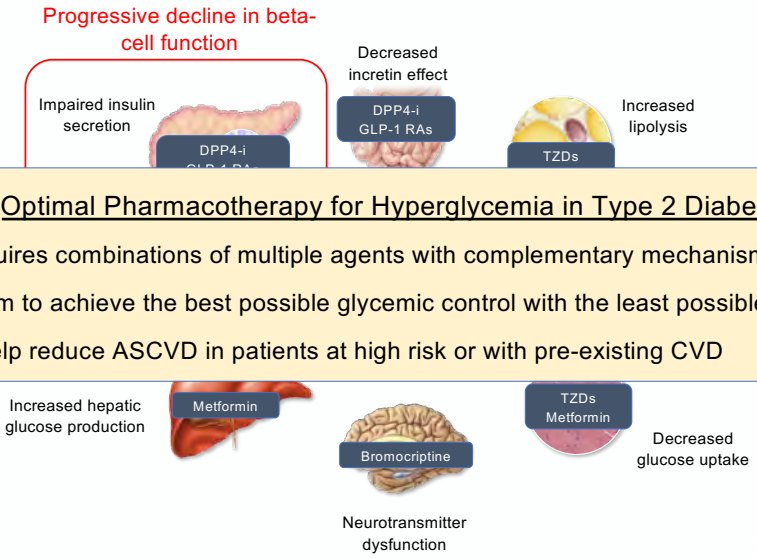
- Incidence and pathophysiology
- Demographics of T1D in the U.S.
- A1c and time in range (TIR)
- Overview of pumps and CGM devices
- Interpreting CGM downloads in ~ 30 secs.
- Identifying and addressing common problems
- New insulin and glucagon formulations
- Advances in hybrid and closed AP

Lecture 3: 11:00 – 12:30 p.m. CDT

Ian Blumer, MD, FRCPC, Presents:

Effective Use of Oral Medications for Type 2 Diabetes:
Lowering Cardiovascular Risk While Improving Glycemic Control

Treatment Should be Individualized and Defects Addressed by Agents with Complementary MOAs

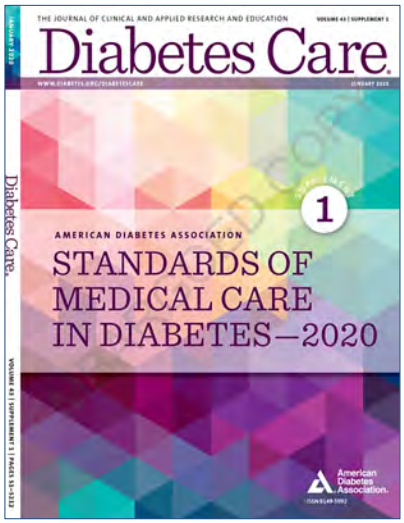


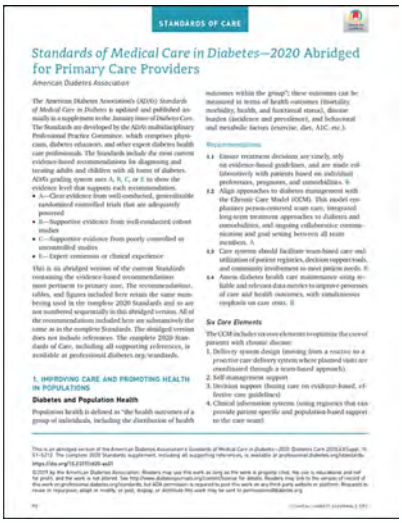
Optimal Pharmacotherapy for Hyperglycemia in Type 2 Diabetes:

- Often requires combinations of multiple agents with complementary mechanisms of action
- Should aim to achieve the best possible glycemic control with the least possible side effects
- Should help reduce ASCVD in patients at high risk or with pre-existing CVD

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

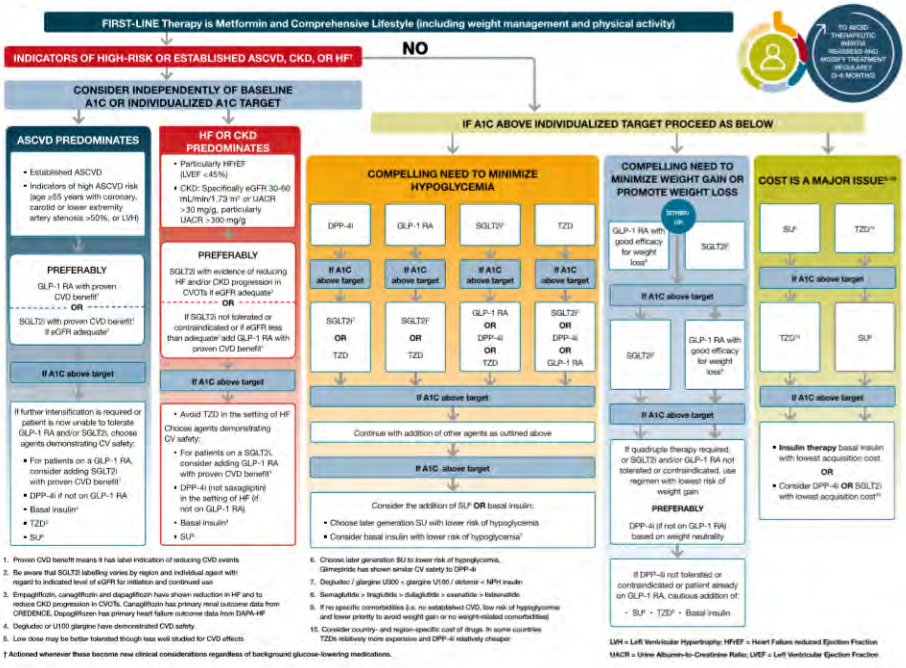
American Diabetes Association Standards of Medical Care in Diabetes - 2020





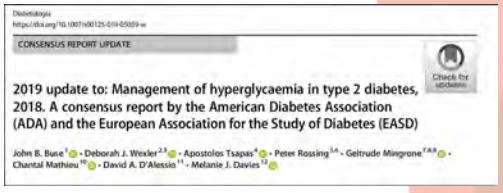
American Diabetes Association. Standards of Medical Care in Diabetes - 2020. *Diabetes Care* 2020;43(Suppl. 1)
Standards of Medical Care in Diabetes – 2020 Abridged for Primary Care Providers. *Clinical Diabetes* 2020;38(1)

Glucose-lowering medication in T2D: Overall Approach



Diabetes Care Volume 43, Supplement 1, January 2020, S98-S110

Key Updates to the 2018 ADA/EASD Consensus Recommendations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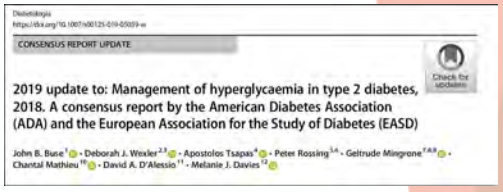
General Recommendations

- In appropriate, high-risk individuals with T2D, decision to treat with GLP-1 RA or SGLT-2 inhibitor to reduce MACE, hHF, CV death or CKD progression should be considered independently of baseline A1c or A1c target
- Providers should engage in shared decision making around initial combination therapy in new onset cases of T2D

GLP-1 RA Inhibitor Recommendations

- For patients with T2D and established ASCVD, where MACE is the gravest threat, the level of evidence for MACE benefit is greatest for GLP-1 RAs
- To reduce risk of MACE, GLP-1 RA can also be considered in patients with T2D without established CVD with indicators of high risk (>55 y/o with coronary, carotid, or LE artery sclerosis >50%, LVH, eGFR <60 ml/min/1.73, or albuminuria

Key Updates to the 2018 ADA/EASD Consensus Recommendations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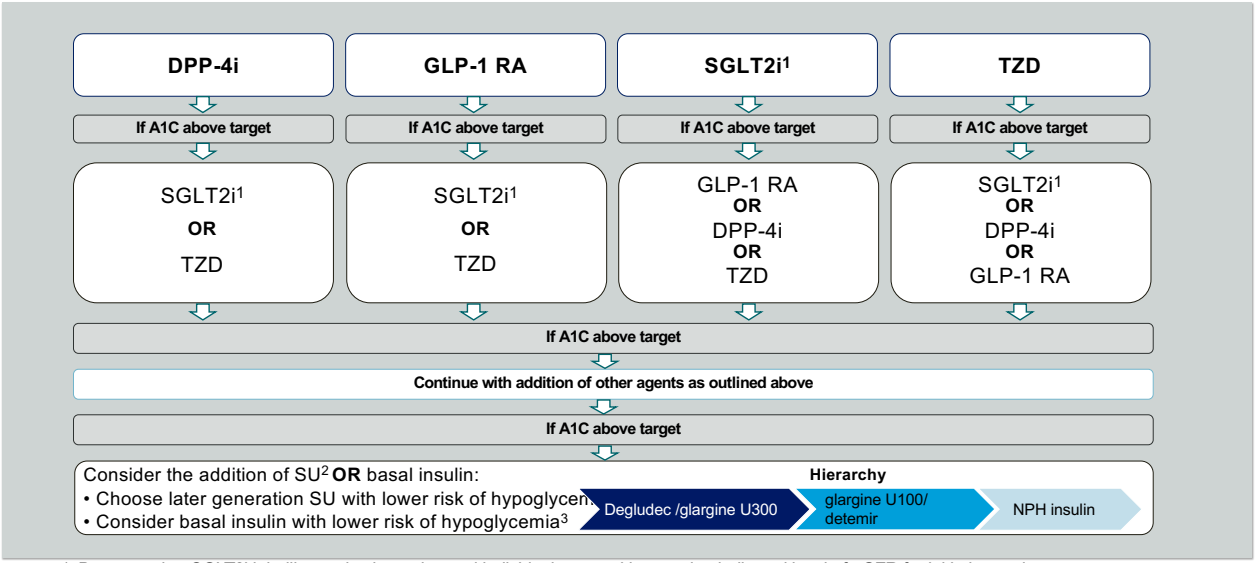
SGLT-2 Inhibitor Recommendations

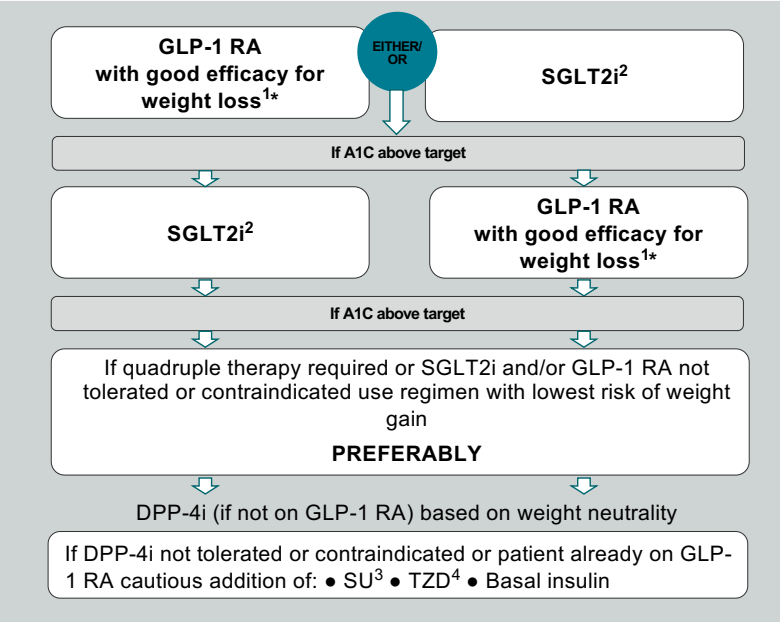
- For patients with or without established ASCVD, but with HFrEF (EF <45%) or CKD (eGFR 30 to 60 ml/min/1.73 m2 or UACR >30mg/g, particularly UACR >300mg/g), the level of evidence for benefit is greatest for SGLT2 inhibitors
- SGLT2 inh. are recommended in patients with T2D and HF, particularly those with HFrEF, to reduce hHF, MACE and CV death
- SGLT2 inh. are recommended to prevent the progression of CKD, hHF, MACE and CV death in patients with T2D and CKD
- Patients with foot ulcers or at risk of amputations should only be treated with SGLT2 inh. after careful shared decision making around risks and benefits with comprehensive education on foot care and amputation prevention

Compelling Need to Minimize Hypoglycemia



1. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Choose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i
3. Degludec / glargine U300 < glargine U100 / detemir > NPH insulin

Compelling Need to Minimize Weight Gain or Promote Weight Loss

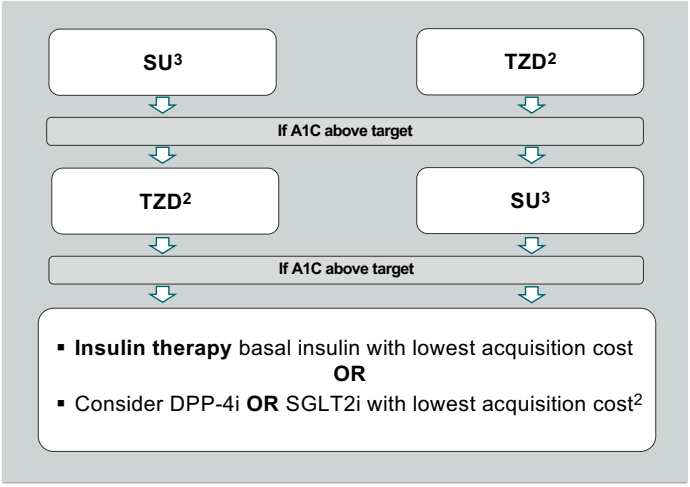


[1]Hierarchy

Semaglutide > Liraglutide > Dulaglutide > Exenatide > Lixisenatide

2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Chose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i
4. Low dose may be better tolerated though less well studied for CVD effects

Second-Line Therapy for T2D if Cost if a Major Issue



1. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
2. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper
3. Chose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i

Case 1: 32-year-old male with T2D for two years

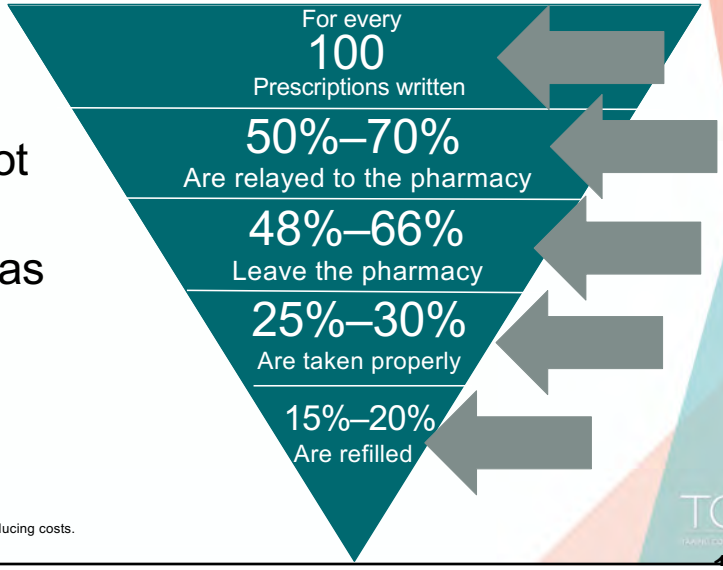
- Medical history: central obesity, dyslipidemia, HTN, and CAD s/p MI
- Family Hx: Strongly positive for T2D, obesity, and CAD
- Notes: Very few home glucose monitoring results
  - Diabetes meds: metformin, SFU, DPP-4 inh., SGLT-2 inh., and basal insulin
  - Current A1c: 11.4% (10.6% one year ago, 10.1% two years ago)
  - Creatinine: 1.4 mg/dL, eGFR 65, mL/min/1/73 m^2

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

A	He needs prandial insulin
B	He needs a GLP-1RA
C	Poor adherence with his medication
D	His diabetes regimen is too complicated

"Poor Adherence" with Type 2 Medications in the Real World

Prescriptions are not always filled, taken properly, or refilled as directed



National Association of Chain Drug Stores. Pharmacies: improving health, reducing costs. PrinciplesOfHealthcare.pdf. Accessed September 28, 2017.

Nine FDA-Approved Classes of Oral Meds for T2D

- 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)
- NEW ORAL GLP-1 Receptor Agonist (oral semaglutide)
- Bile acid sequestrant (colesevelam)*
- Dopamine receptor agonists (bromocriptine mesylate)*
- 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
- Always address the modifiable risk factors (hypertension, dyslidemia, smoking)
- Spending time with the patient and his/her support person(s) in meaningful shared decision-making addressing their health care priorities and 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) https://www.youtube.com/watch?v=x24AbWnjVa8

Case 2: 69-year-old centrally obese female with T2D for nine years

- Medical history: Obesity (BMI 34 kg/m^2), dyslipidemia, OSA, breast cancer s/p lumpectomy and hormonal therapy remission
- Family Hx: Both parents had type 2 diabetes
- Notes:
  - eGFR 75 mL/min/m^2, UACR normal (<30mg/g creatinine)
  - A1C 8.5%
  - Diabetes therapy is metformin and a SFU
  - LDL 121 mg/dL, triglycerides 266 mg/dL, HDL 39 mg/dL

What class of agent would you add to this patient's current regimen of metformin and a SFU

A	Thiazolidinedione (pioglitazone)
B	DPP-4 inhibitor (sita-, lina-, saxa- and 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)

Update on Metformin, SFUs, and TZDs (all generic)

Metformin

- eGFR <60 to ≥45 OK to use full dose/monitor kidneys
- eGFR <45 to ≥30 OK to use 50% maximum dose/monitor renal function every 3-6 months (PI says yearly)
- Check B-12 levels

SFU

- High secondary failure rate; however, when you stop them, the patient's A1c typically goes up
- Increase risk of hypoglycemia (elderly, CKD, CAD), weight gain

TZD (pioglitazone)

- Effective in prediabetes, best used early in the natural history (balance with potential side effects)
- Be cautious in combo with insulin (fluid retention)
- Contraindicated in the setting of heart failure
- Weight gain
- Fracture risk is increased
- Risk of bladder cancer questionable, and the risk is low (~1/5000 in the general population)

Case 3: 56-year-old AA female diagnosed with type 2 diabetes at age 46

- PMH: HTN, dyslipidemia, obesity and NAFLD (non alcoholic fatty liver disease)
- A1C 9.2% on maximum doses of metformin and SFU
- Occasional mild hypoglycemia
- No home glucose monitoring data
- eGFR 50 mL/min/m^2, BMI 51 kg/m^2
- BP normally above 140/90 mmHg; on no HTN meds

What therapeutic intervention would you change/initiate if you were evaluating this patient, once you have confirmed she is adherent with her medications?

A	Add pioglitazone
B	Add a DPP-4 inh.
C	Add a SGLT-2 inh.
D	Add a GLP-1 RA
E	Combination of a DPP-4 inh & SGLT-2 inh.

High CV Risk or Established ASCVD, CKD, and/or HF

Consider independently of baseline A1C of individualized A1C target

ASCVD PREDOMINATES

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

PREFERABLY
GLP-1 RA with proven CV benefit[1]
OR
SGLT2i with proven CVD benefit if eGFR adequate

If A1C above target

If further intensification is required or patients is no unable to tolerate GLP-1 RA and /or SGLT2i, choose agents demonstrating CV safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1]
- DPP4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/2.73 m2 or UACR >30mg/g, particularly UACR >300 mg/g

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i is not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1RA with proven CVD benefit

If A1C above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety

- For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
- DPP4i (not saxagliptin) in the setting of HP (if not not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

Case 3 Continued: Treatment History

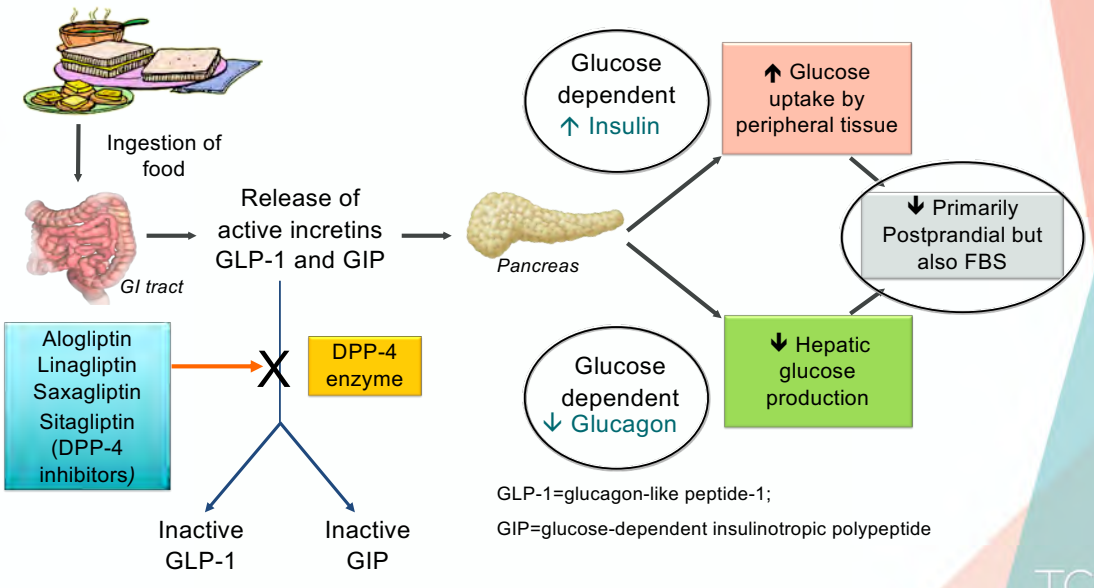
- A DPP-4/SGLT2 inhibitor combination pill was added to her regimen (once a day and one co-pay)
- Follow up was arranged for one month instead of the usual 3 to 4 months to confirm adherence and engage patient
- She did well with a 10-pound weight loss and no hypoglycemia after the SFU dose was cut in half
- The A1C fell from 9.5% to 7.4%
- SBP decreased from 150 to 141 mmHg
- After 6 months she was started an ARB and a statin to get her BP below 140/90 mmHg and her LDL <100 mg/dl

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 •Warnings and precautions: pancreatitis, heart failure, acute renal failure, angioedema, Stevens-Johnson, severe arthralgia, bullous pemphigoid
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 empa-; new metformin XR, saxa-, dapa- tablet approved)

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

Mechanism of Action: DPP-4 Inhibitors



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: DPP-4 Inhibitors

	Generic Name	Trade Name
DPP-4 Inh.	Alogliptin	Nesina
	Linagliptin	Tradjenta
	Saxagliptin	Onglyza
	Sitagliptin	Januvia

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/metformin ER	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 daily
Alogliptin/metformin	Kazano	12.5/500, 12.5 mg/1000	Twice with meals
Ertugliflozin/sitagliptin	Steglujan	5/100, 15, 100	Once daily
Saxagliptin/dapagliflozin/ metformin XR	Qternmet XR	2.5/2.5/1000, 2.5/5/1000, 5/5/1000, 5/10/1000	Once daily

Newest triple combination: Empagliflozin/linagliptin/metformin (Trijardy XR)

Case 4: 70-year-old obese female with T2D for 25 years

- A1C 8.4% on maximum doses of metformin, a SFU, and a DPP-4 inh.
- Medical Hx: HTN, arthritis, recent admission for CHF
- Family Hx: Type 2 diabetes and obesity (both parents)
- Notes:
  - Fearful of injections and gaining weight BMI 31 kg/m^2
  - HTN, osteoporosis, and CKD 3A (eGFR 58 mL/min/m^2)
  - Home glucose monitoring shows FBS (147-219 mg/dL) with a few post dinner values (188 to 275 mg/dL)

How would you treat this patient to lower her A1c?

A	Add a TZD
B	Add a SGLT-2 inh. (cana-, dapa-, empa-, ertugliflozin)
C	Try to convince her to add a GLP-1 RA (exena-, liraglu-, dulaglu-, semaglutide
D	Try to convince her to add a basal insulin at bedtime

Case 4 Continued

- Low dose SGLT-2i was added to her regimen and then titrated to the maximum dose after one month
- A1C dropped to 7.3% (baseline 8.4%) and she lost 15 lbs
- She experienced a yeast infection which was easily treated with oral fluconazole and she did not want to stop the SGLT2i
- LDL-C increased from 100 to 108 mg/dL (8% rise), HDL-C increased 10%, and her TGs decreased by 25%

SGLT-2 Inhibitors

Mechanism of Action	Reduce 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), risk of amputation (discussed later), bone fractures, Fournier's Gangrene, acute kidney injury, UTI
Clinical Pearls	•Cana now approved for renal protection and can be used with a eGFR down to 30 •Empa- Dapa-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 miconazole)

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: SGLT-2 Inhibitors

	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 >45 mL/min)/with CKD can use to a eGFR of 30ml/min
- Increase to 300 mg daily if tolerating 100 mg daily and eGFR > 60 mL/min

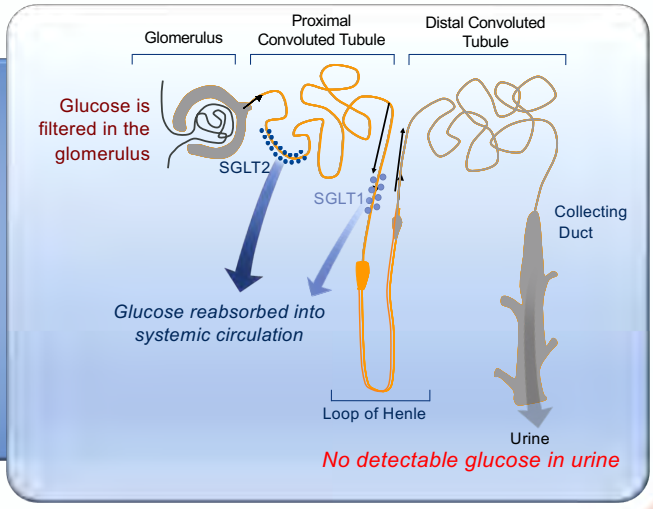
Dapagliflozin:
- Starting dose: 5mg daily in morning with or without food (eGFR for both doses > 60 mL/min)
- Increase to 10 mg daily if tolerating and need additional glycemic control

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

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

Renal Handling of Glucose in a Non-Diabetic Patient

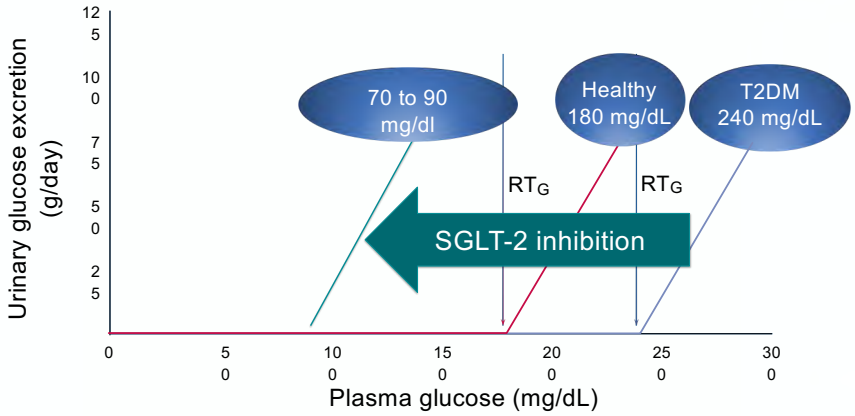
- 180 g/day/1.73 m^2 is filtered glucose load[1]
- SGLT-2 transports 90% of filtered glucose out of the tubular lumen[1-4]



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.

Renal Glucose Reabsorption in Normal, T2D, and with SGLT-2 Inhbition



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 <u>ALL SGLT-2 inhibitors was updated to include new Warnings and Precautions for ketoacidosis, urosepsis and pyelonephritis</u>
December 14, 2015

1. Extremely low incidence, mostly type 1's and type 2's receiving insulin
2. Complex mechanism related to paradoxical increase in glucagon promoting ketosis in the setting of glycosuria so extreme hyperglycemia is limited
3. Be especially cautious in women with a history of UTIs, pyelonephritis and/or genital mycotic infections
4. August 2018: New warning for extremely rare but serious infection called Fournier's gangrene

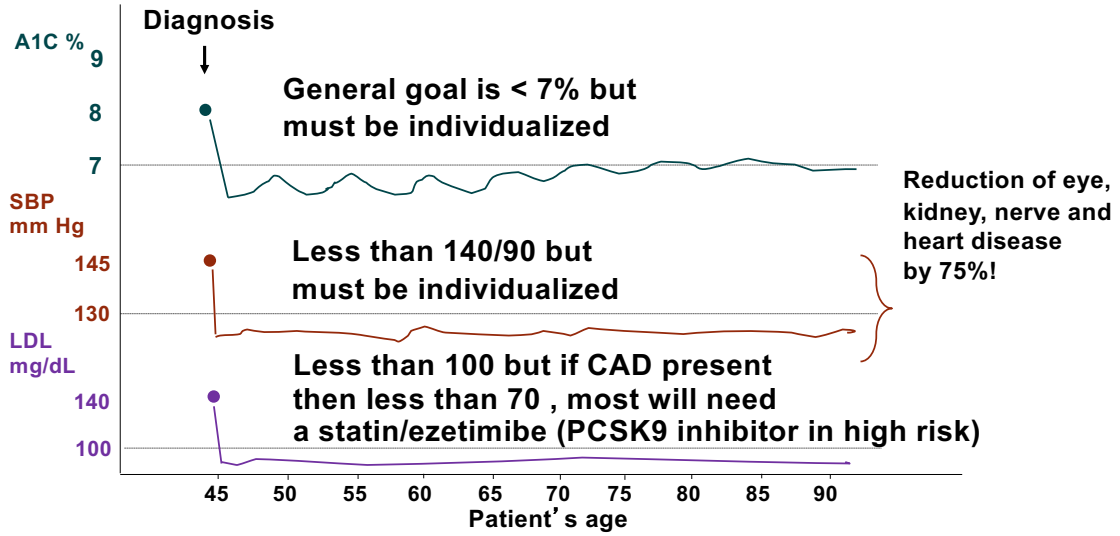
Brooks M. SGLT2 Inh Diabetes Drugs May Cause Ketoacidosis: FDA. Retrieved from http://www.medscape.com/viewarticle/844754
Erondu N, et al. Diabetes Care September 2015 38:1680-1686; 2015

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	Heart disease or stroke
D	Complications from obesity
E	Peripheral arterial disease

Primary Objectives of Effective Management:

Important Basics…The 'ABCs"



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

Blood Pressure Management

Individualize BP Goals:

<140/90 mmHg (10-yr CV risk <15%)

<130/80 mmHg (10-yr CV risk >15%)

Dyslipidemia Management

Individualize lipid Goals:

LDL< 100mg/dl in all PWD

LDL<70 mg/dl if ASCVD present

Triglycerides less than 200mg/dl

HDL as high as you can get it!

Diabetes Care Volume 43, Supplement 1, January 2020, S111-S134

Table 10.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

PCSK9 inhibitors (evolocumab and alirocumab) if LDL not at goal on maximally tolerated statin/ezetimide

Just approved in 2020 bempedoic acid (Nexletol), first in class LDL medication

*Once-daily dosing. XL, extended release.

Diabetes Care Volume 43, Supplement 1, January 2020, S111-S134

Management Of Hypertriglyceridemia

1. Elevated triglycerides combined with low HDL levels are part of the insulin resistant state and metabolic syndrome.
2. Diet, exercise and improved glycemic control will improve but not typically normalize elevated TG levels in type 2 DM.
3. The goal is to get the TGs to below 200mg/dl, which in term will elevate the HDL levels
4. Fibric acid derivatives such as fenofibrate are commonly used to treat high TGs.
5. Icosapent ethyl is an omega-3 fatty acid that has the formal indication from the FDA to reduce heart attacks and strokes in patient who have or are at risk for ASCVD.

N Engl J Med 2019; 380:11-22 reduce it trial

Non-Insulin CVOTs in T2D: DPP-4 Inhibitors

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo ✓	placebo ✓	placebo ✓	sulfonylurea ✓	placebo ✓
N	16,500 NEUTRAL	5,4[illegible] NEUTRAL	14,00[illegible] NEUTRAL	6,0[illegible] NEUTRAL	8,3 NEUTRAL
Results	[illegible]013	2013	J[illegible]e 2015	2017	2017

Non-Insulin CVOTs in T2D: SGLT-2 Inhibitors (Primarily driven by a reduction in heart failure)

Study	EMPA-REG	CANVAS	DECLARE	VERTIS CV
SGLT-2-i	empagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
N				3900
Results	Sept 2015	2017	2018	Late2020

POSITIVE POSITIVE POSITIVE

Non-Insulin CVOTs in T2D: GLP-1 RA (Primarily driven by a reduction in death due to cardiovascular disease)

Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	HARMONY	REWIND	PIONEER 6
GLP1-RA	Lira-glutide	Lixi-senatide	Sema-glutide	Exe-natide LR	Albi-glutide	Dula-glutide	Oral semaglutide
Comparator	placebo	placebo	placebo	placebo	placebo	placebo	placebo *
N							
Results	2016	2015	2016	2018	2019	2019	2019

POSITIVE NEUTRAL POSITIVE NEUTRAL POSITIVE POSITIVE* POSITIVE*

*CV death less with oral sema; no difference in non-fatal MI or non-fatal stroke. Median time in study: 15.9 months NEJM 2019;381:841-851.

Adapted from a slide courtesy of Silvio Inzucchi MD, Yale University

Diabetes Medications FDA Approved for CV Risk Reduction

Empagliflozin (based on EMPA-REG data)
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease

Liraglutide (based on LEADER data)
- to reduce the risk of major adverse cardiovascular (CV) events (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established CV

Canagliflozin (based on CANVAS program data)
- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease

Semaglutide (based on SUSTAIN 6)
- the indication of reducing the risk of major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal heart attack, or non-fatal stroke in adults with type 2 diabetes and established cardiovascular disease (CVD).

Dulaglutide (based on REWIND data)
- for the reduction of major adverse cardiovascular events (MACE) in adults with type 2 diabetes who have established cardiovascular (CV) disease or multiple cardiovascular risk factors.

Not All CVOTs are Created Equal

- Differences in study design: powered for safety or superiority
- Patient characteristics: age, weight, co-morbid complications, presence of CVD and risk factors
- Comparators may be different
- Weight gain and hypoglycemia differences
- Regional differences
- Outcomes differ: overall mortality, non-fatal and fatal MI, stroke, etc.
- Study conduct and adherence may effect results

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

Diabetes Medications FDA Approved for Renal Disease

- Canagliflozin (CREDENCE study)
  - Reduce the risk of end-stage kidney disease, doubling of the serum creatinine, cardiovascular death and hospitalization for CHF in patients with type 2 diabetes with nephropathy (eGRF between 30 and 90 ml/min) and albuminuria > 300mg
- EMPA-KIDNEY: On-going

Jardine MF et al. Am J Nephrol. 2017;46(6):462-472; Perkovic V et al. N Engl J Med. 2019;380(24):2295-2306; Neal B et al. N Engl J Med. 2017;377(7):644-657; Zinman B et al. N Engl J Med. 2015;373(22):2117-2128

Key Principles of Management of T2D

- Glycemic targets and glucose-lowering therapies should be individualized
- Diet, exercise, and diabetes self-management education and support are the foundations of therapy
- Unless contraindicated, metformin is the preferred first line drug
- After metformin, the first consideration is whether the patient has established ASCVD or CKD. If not, then whether hypoglycemia, weight or financial status are dominant issues. Shared decision making is KEY!

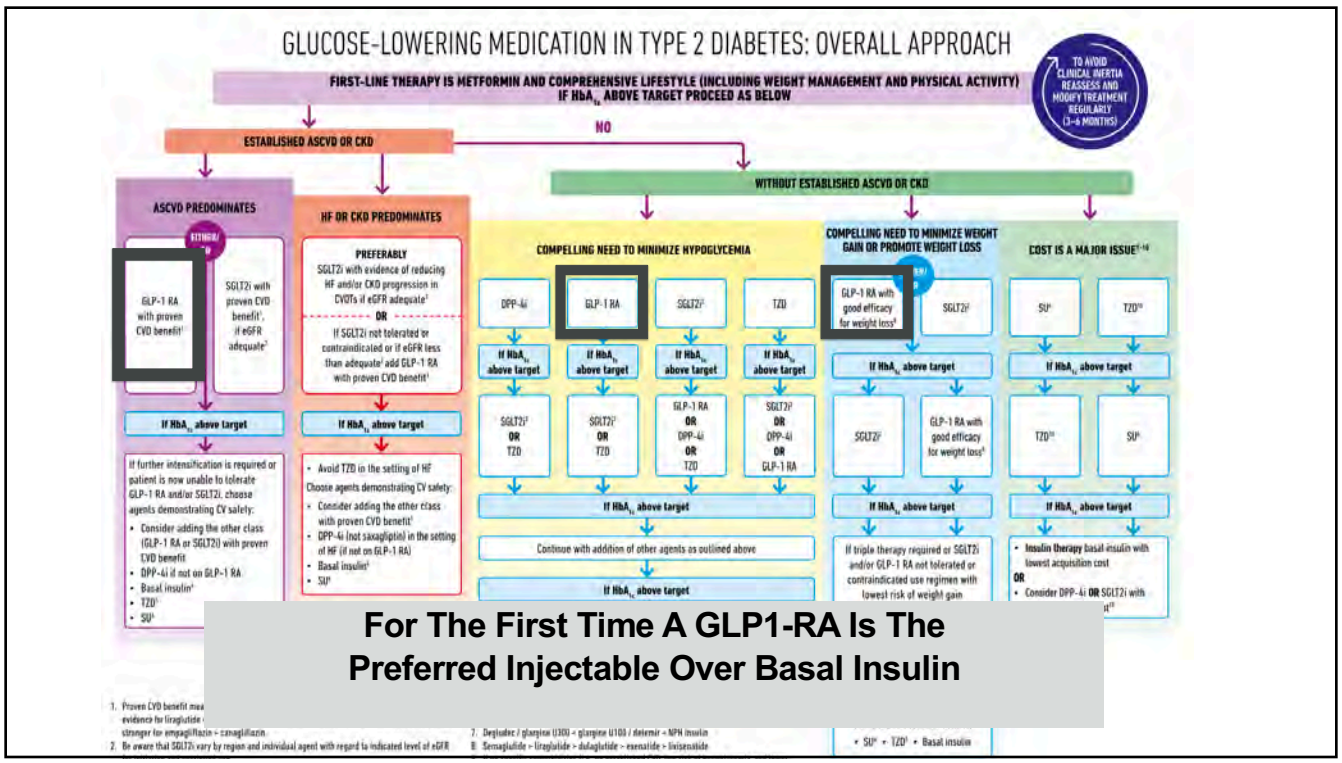
Key Principles of Management of T2D

- GLP-1 RA are the preferred first injectable therapy over basal insulin except patients with very poor glycemia control
- Many patients over time will require insulin therapy alone or in combination with other agents to maintain glycemic control
- Vascular disease is the most common cause of death and prevention strategies need to be emphasized (A1c, aspirin, blood pressure, cholesterol, smoking cessation, and diabetes drugs that reduce ASCVD/heart failure)

Lecture 4: 1:00 – 2:15 p.m. CDT

Steven V. Edelman, MD, Presents:

Practical Application of Injectable Agents and Their Cardiovascular Effects: Individualized Treatment Strategies



Case 1: 54 year old male with type 2 diabetes for 10 years

- History of dyslipidemia, hypertension, NAFLD
- Strong family history of type 2 diabetes
- Currently on metformin, SFU and a DPP4 inhibitor
- Recent myocardial infarction s/p 4 cardiac stent insertions
- A1c 9.3%
- Creatinine 1.3 eGFR 70
- HGM data: ranges from 82 to 379 mg/dl
- Bedtime average 210 mg/dl SD 76mg/dl
- Morning average 221 mg/dl

Which of the following would you recommend for this patient?

A	Initiate basal insulin
B	Initiate a GLP-1 Receptor Agonist (RA)
C	Initiate premixed insulin (70/30) BID
D	Initiate a fixed combination of a basal insulin and a GLP-1RA

High CV risk or established ASCVD, CKD and/or HF

Consider independently of baseline A1C of individualized A1C target

ASCVD PREDOMINATES	HF OR CKD PREDOMINATES
• Established ASCVD • Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)	• Particularly HFrEF (LVEF <45%) • CKD: Specifically eGFR 30-60 mL/min/2.73 m2 or UACR >30mg/g, particularly UACR >300 mg/g
PREFERABLY GLP-1 RA with proven CV benefit[1] **OR** SGLT2i with proven CVD benefit if eGFR adequate	**PREFERABLY** SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3] **OR** If SGLT2i is not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1RA with proven CVD benefit
If A1C above target	**If A1C above target**
If further intensification is required or patients is no unable to tolerate GLP-1 RA and /or SGLT2i, choose agents demonstrating CV safety: • For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1] • DPP4i if not on GLP-1 RA • Basal insulin[4] • TZD[5] • SU[6]	• Avoid TZD in the setting of HF Choose agents demonstrating CV safety • For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1] • DPP4i (not saxagliptin) in the setting of HP (if not not on GLP-1 RA) • Basal insulin[4] • SU[6]

1. Proven CVD benefit means it has label indication of reducing CVD events 2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use 3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary HF outcome data from DAPA-HF 4. Degludec and U100 glargine have demonstrated CVD safety 5. Low dose may be better tolerated though less well studied for CVD effects 6. Chose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i.

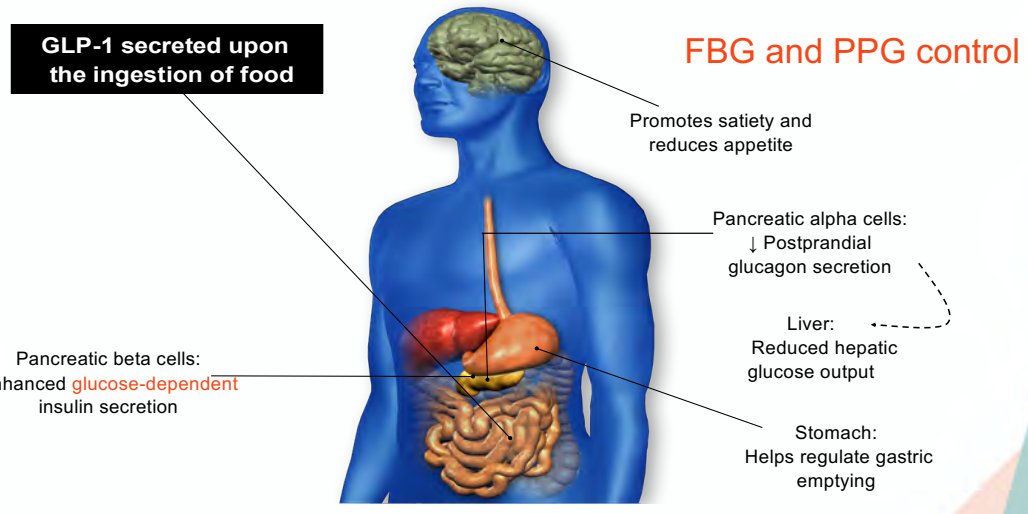
Basal Insulin vs GLP-1 RA

(an incretin hormone)

Insulin: Injected once or twice a day	GLP-1 RA: Injectable once or twice a day, injectable once weekly, or oral once daily
Need to titrate dose to achieve the desired FBS	Titrate to the highest acceptable dose to avoid nausea
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.

GLP-1 Effects: Glucoregulatory Role of Incretins



Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520.; Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422.; Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553.; Adapted from Drucker DJ. *Diabetes*. 1998;47:159-169.

GLP-1 Receptor Agonists

Mechanism of Action	• Mimic the effects of human GLP-1
Benefits	• Significant A1c reductions (1.0 to 3.0% depending on baseline) • Shorter acting GLP-1 RAs have greater effects on PPG • Weight loss • No hypoglycemia • Once daily, twice 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 • Several with positive CVOT results

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: 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
	Oral Semaglutide	**Rybelsus**
	Once daily	

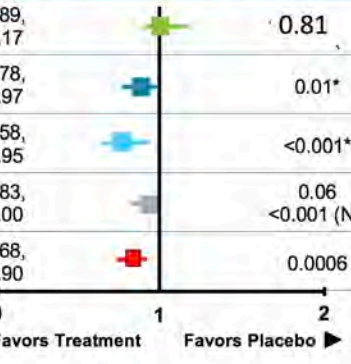
Generic and Trade Names: GLP-1 RAs, Continued

	Generic Name	Trade Name
Basal Insulin/GLP-1 Receptor Agonist Fixed Combination	Glargine/lixisenatide once daily Degludec/liraglutide once-daily	Soliqua Xultophy

Summary of Completed GLP-1 receptor agonists Cardiovascular Outcome Trials (CVOTs)

MACE Outcomes

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	P-Value (superiority)
ELIXA (lixisenatide vs PBO)	406/3034 (13.4%)	399/3034 (13.2%)	1.02	0.89, 1.17	0.81
LEADER (liraglutide vs PBO)	609/4668 (13%)	694/4672 (14.9%)	0.87	0.78, 0.97	0.01*
SUSTAIN-6* (semaglutide vs PBO)	108/1648 (6.6%)	146/1649 (8.9%)	0.74	0.58, 0.95	<0.001*
EXSCEL (exenatide vs PBO)	839/7356 (11.4%)	905/7396 (12.2%)	0.91	0.83, 1.00	0.06 <0.001 (NI)
Harmony Outcomes (albiglutide vs PBO)	338/4731 (7.1%)	428/4732 (9.1%)	0.78	0.68, 0.90	0.0006



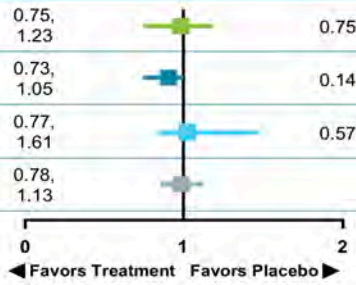
*Superiority testing not a prespecified analysis

1. Pfeffer MA, et al. N Engl J Med. 2015;373(23):2247-57. 2. Bentley-Lewis R, et al. Am Heart J. 2015;169(5):631-638.e7. 3. Marso SP, et al. Am Heart J. 2013;166(5):823-30.e5. 4. Marso SP, et al. N Engl J Med. 2016;375(4):311-22. 5. Marso SP, et al. N Engl J Med. 2016;375(19):1834-1844. 6. Holman RR, Bethel MA, et al. N Engl J Med. 2017;377(13):1228-1239. 7. Hernandez A, et al. Lancet. (online first October 2, 2018).

CVOTs of GLP-1 RAs
(SGLT2 Inhibitors Indicated for CHF/CKD)

Hospitalization for Heart Failure

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	P-Value
ELIXA (lixisenatide vs PBO)	122/3034 (4.0%)	127/3034 (4.2%)	0.96	0.75, 1.23	0.75
LEADER (liraglutide vs PBO)	218/4668 (4.7%)	248/4672 (5.3%)	0.87	0.73, 1.05	0.14
SUSTAIN-6 (semaglutide vs PBO)	62/1648 (3.6%)	54/1649 (3.3%)	1.11	0.77, 1.61	0.57
EXSCEL (exenatide vs PBO)	219/7356 (3.0%)	231/7396 (3.1%)	0.94	0.78, 1.13	



Harmony Outcomes
(albiglutide vs PBO)
HR 0.85 (0.70, 1.04); p=0.113
Composite of CV death or HHF

1. Pfeffer MA, et al. N Engl J Med. 2015;373(23):2247-57. 2. Bentley-Lewis R, et al. Am Heart J. 2015;169(5):631-638.e7. 3. Marso SP, et al. Am Heart J. 2013;166(5):823-30.e5. 4. Marso SP, et al. N Engl J Med. 2016;375(4):311-22. 5. Marso SP, et al. N Engl J Med. 2016;375(19):1834-1844. 6. Holman RR, Bethel MA, et al. N Engl J Med. 2017;377(13):1228-1239. 7. Hernandez A, et al. Lancet. (online first October 2, 2018).

ITCA 650—Medical Device To Deliver a GLP-1RA (exenatide)

TECHNOLOGY

- Subcutaneous delivery system; short office procedure
- Small micropump

−maintains stability at temps ≈37ºC

−secretes medication 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: 72 year old Caucasian woman with type 2 diabetes for 23 years

- On maximal doses of metformin, SU, and a SGLT-2 inhibitor
- She adamantly does not want to take insulin for fear of weight gain
- PMH: dyslipidemia, hypertension, papillary thyroid cancer and obesity (BMI=31)
- Both parents and two siblings have type 2 diabetes and early CVD
- eGFR 65 ml/min
- Her A1c is 8.8 % (goal for this patient at least less than 8%)
- Average FBS is in the 180s (does not test at other times)

What would you recommend now for this patient?

A	Start a DPP4 inhibitor
B	Try to convince her to start basal insulin and titrate the dose to get her FBS less than 140mg/dl
C	Start a GLP1-RA
D	Initiate a fixed combination of a basal insulin and a GLP-1RA

Case 2 continued

- She agreed to start a once weekly GLP-1RA (exenatide, dulaglutide or semaglutide)
- When 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 (self limited and resolve in a few days to weeks).
- She experienced no nausea or hypoglycemia. Over the next three months she lost 13 pounds and her A1c fell from 8.8% to 7.2%.

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

Before GLP-1*

FBS (mg/dl)	PPG (mg/dl)
Average 188	

After GLP-1*

FBS (mg/dl)	PPG (mg/dl)
Average 139	Average 167

Fixed Combinations Of Basal Insulin and GLP- Receptor Agonist

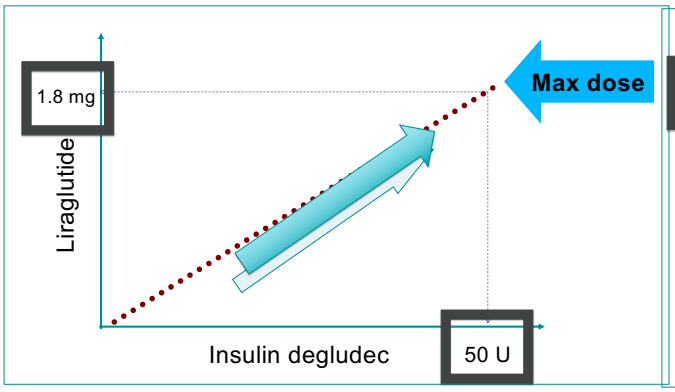
Insulin degludec/liraglutide
Insulin glargine/lixisenatide

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

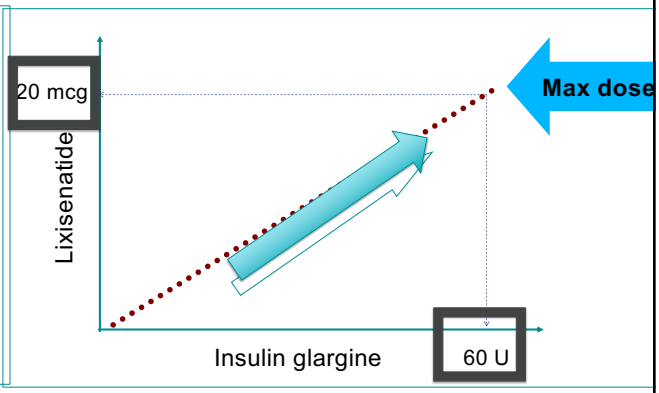
- 1 dose step (unit) has 1 unit insulin glargine and 0.33 mcg lixisenatide (max. dose is 60 insulin glargine/20 mcg lixisenatide)
- Injected once daily within one hour prior to the first meal of the day

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

Fixed-Ratio Combination of Insulin Degludec And Liraglutide And U-100 Glargine and Lixisenatide



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



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

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

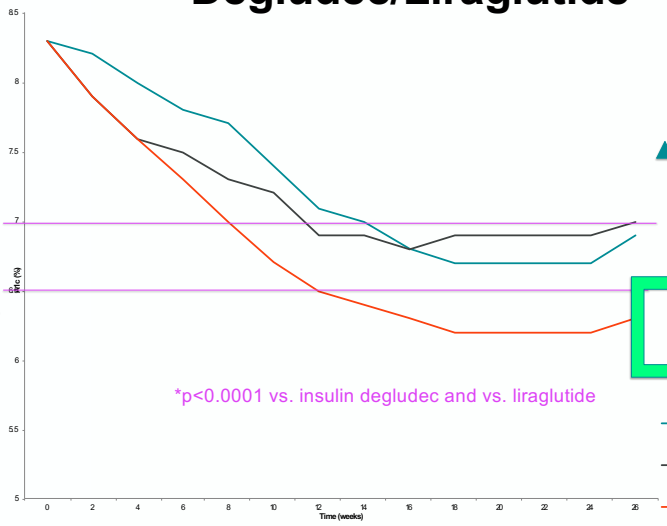
Insulin Degludec/Liraglutide vs. Insulin Glargine/Lixisenatide

Pen dose steps (units): insulin degludec + liraglutide	Pen dose steps (units): insulin glargine + lixisenatide
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

PDR (PI for both) 2017

A1c of 8.3% at baseline drops to 6.4% with Insulin Degludec/Liraglutide

Inclusion Criteria:
- Type 2 diabetes
- Insulin naïve treated with metformin ± pioglitazone
- A1c 7.0 – 10.0%
- BMI ≤ 40 kg/m2
- Age ≥ 18 years



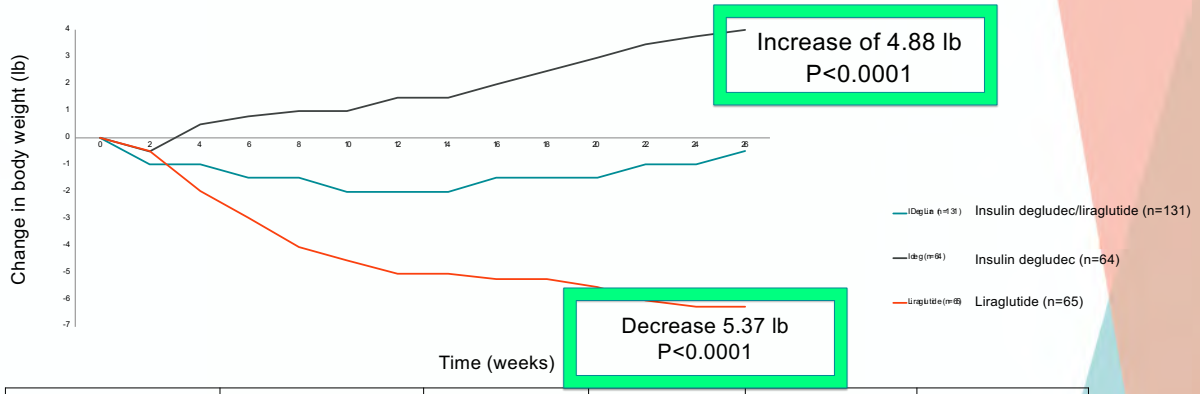
	A1c	EOT
Insulin degludec (n=413)	-1.28%	7.0%
Liraglutide (n=414)	-1.44%	6.9%
Insulin degludec/liraglutide (n=833)	-1.91% *	6.4%

*p<0.0001 vs. insulin degludec and vs. 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

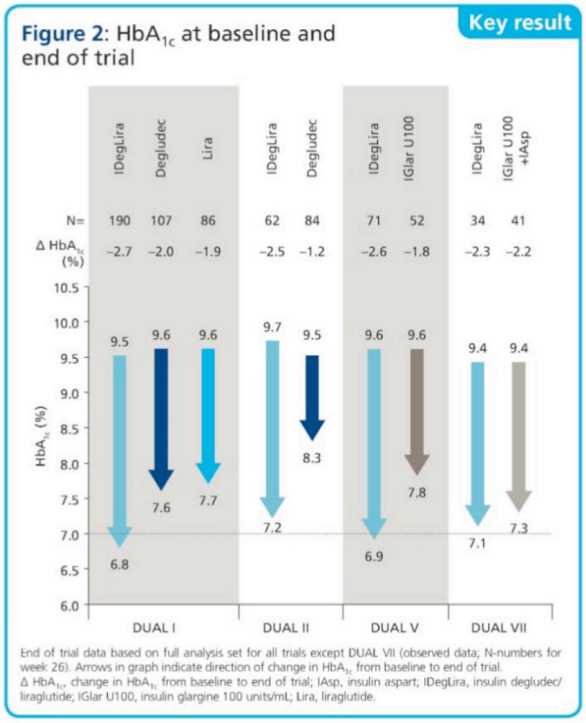


	Insulin degludec/liraglutide Rate (episodes/PYE)	Insulin degludec Rate (episodes/PYE)	Liraglutide Rate (episodes/PYE)	Insulin degludec/liraglutide vs. insulin degludec RR Estimate (95% CI)	Insulin degludec/liraglutide vs. liraglutide RR Estimate (95% CI)
Hypoglycemia	1.80	2.57	0.22	0.68 (0.53; 0.87)*	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

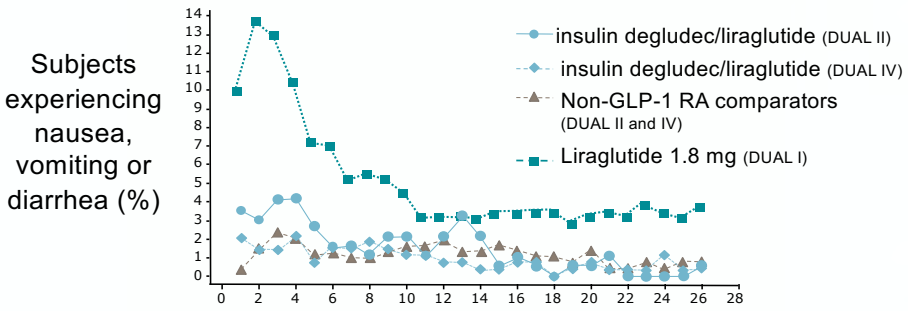
Buse J et al. ADA 2013, 65-OR

Effects of insulin degludec/liraglutide in patients with poorly controlled type 2 diabetes with HbA1c >9%: analyses from the DUAL program



Frias JP et al. Diabetes 2018 Jul; 67(Supplement 1): - . https://doi.org/10.2337/db18-1092-P

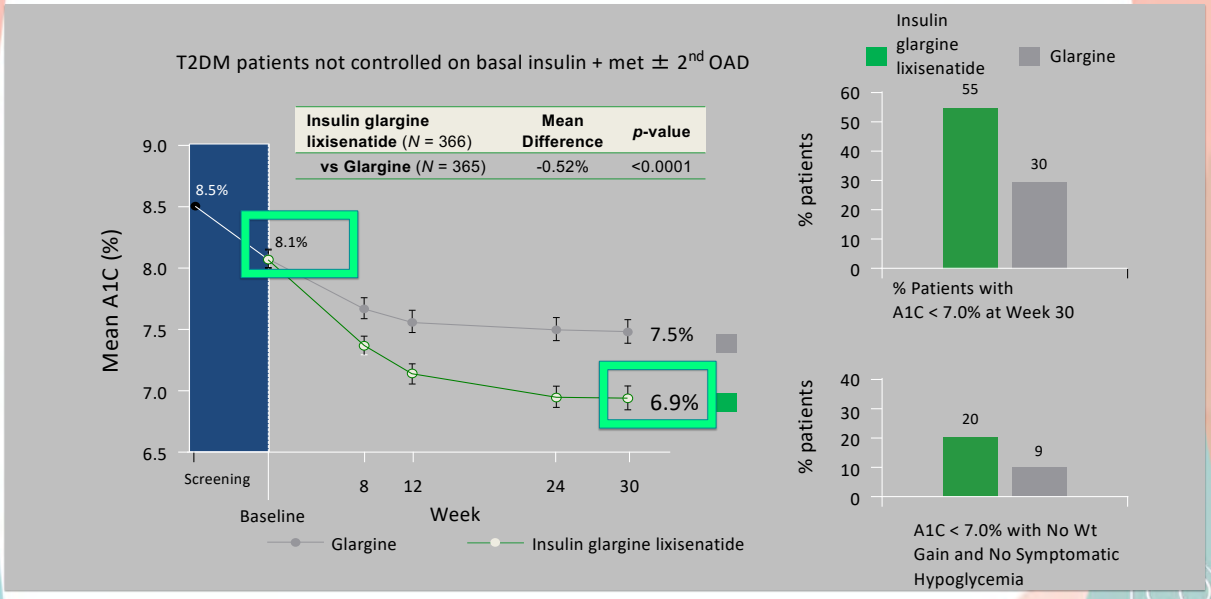
Gastrointestinal Side Effects: Gradual Titration Helps



p=non-significant for odds of experiencing gastrointestinal side effects for subjects on insulin degludec/liraglutide versus non-GLP-1 RA comparator

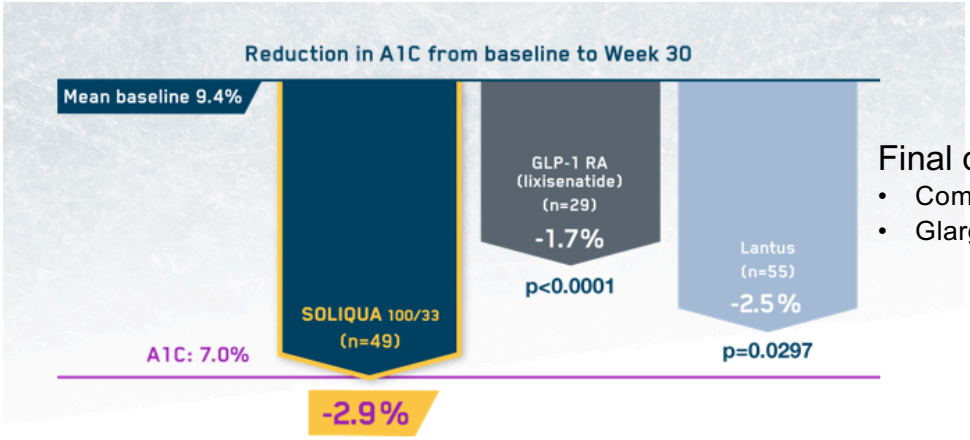
Aroda *et al. Diabetes* 2015;64 (Suppl. 1):A235; abstract 1009-P

Efficacy of Fixed-Ratio insulin glargine lixisenatide in T2DM Patients Not Controlled on Basal Insulin



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

Post Hoc Analysis insulin glargine/lixixenatide In Patients With Very Poor Glycemic Control (A1c >9%). LixiLan O Study



Final doses
- Combination: 45 units
- Glargine only: 44 units

Davis MF, et al. Diab Obes Metab. 2019. https://doi.org/10.1111/dom.13791.

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

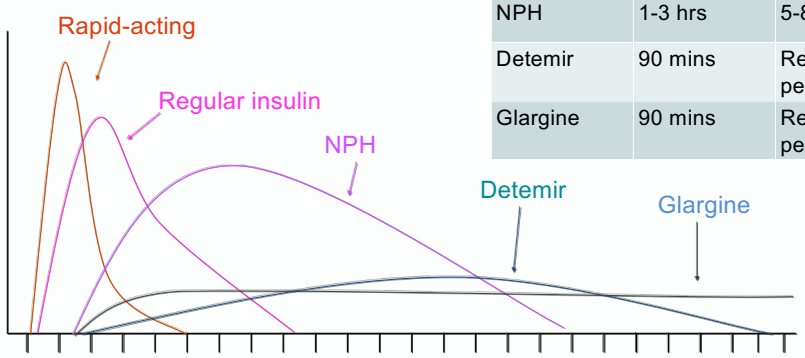
- Combined glycemic effects of GLP-1RA and basal insulin provides greater glycemic efficacy than either of its component parts.
- Dose related adverse effects of each component (nausea and weight gain) are minimized.
- No increased risk of hypoglycemia in the setting of improved glycemic control as compared 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) Follow on biologic lispro inhaled insulin	Humulin R, Novolin R Humulin R U-500 NovoLog Fiasp Apidra Humalog Admelog Afrezza
Basal Insulin	intermediate-acting: NPH long-acting: detemir glargine (U-100) glargine (U-300) degludec (U-100/200) follow-on biologic glargine (U-100)	Humulin N Novolin NPH Levemir Lantus Toujeo Tresiba Basaglar

Time Action Profiles: Traditional Insulins

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



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;28:1107-1112;; Wittlin SD et al. Insulin Therapy. Marcel Dekker, Inc.;2002:73-85.

Benefits Of U-300 Glargine And Degludec In Type 1 and Type 2 Diabetes

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

Riddle MC *et al. Diabetes Care.* 2014;37:2755-2762; Yki-Järvinen H *et al. Diabetes Care.* 2014; Published ahead of print: doi: 10.2337/dc14-0990
Bolli GB *et al.* Poster presented at EASD 2014: P947; Bajaj H. Oral presentation at CDA 2014: #14; Home P *et al.* Abstract presented at EASD 2014: 0148
Bajaj H *et al.* Poster presented at CDA 2014: P112; Matsuhisa M *et al.* Poster presented at EASD2014: P975; Terauchi Y *et al.* Poster presented EASD 2014: P976

Case 3: 66 year old obese female diagnosed with type 2 diabetes 9 years ago

- **Currently on maximum doses of 3 oral agents: metformin 1000 mg BID, SFU and a SGLT2 inhibitor. She was intolerant to GLP-1RAs.**
- **Her PCP started 10 units of insulin 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, eGFR 89, LFTs normal**
- **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	Poor adherence
B	Initial dose was too little
C	Inadequate titration of the glargine U-100
D	Glargine U-100 should have been given at bedtime

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

* Daily titration works well with all old and new basal insulins

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.

Self Titration Clinic Form

Starting/Adjusting Long-Acting Basal Insulin

1. Give Basal insulin once a day at Morning
2. Starting dose: 20 units
3. Every 1 day(s), adjust your dose based on your fasting blood sugar that morning before eating or drinking:
   a. If fasting blood sugar is over 140, then increase your dose by 2
   b. If fasting blood sugar is under 90, then decrease your dose by 2
   c. If fasting blood sugar is between 90 and 140, then keep the same Lantus dose

Important:
The purpose of long active basal is to provide a background amount of insulin throughout the day and at night while you sleep. It is not meant to treat high blood sugars caused by eating food, so you should not change your dose based on blood sugar numbers during the day when you are eating.

Case 4: 55 year old obese Latino male with a 22 year history of type 2 diabetes

- CKD stage 3b (eGFR 37 ml/min)
- History of ASCVD s/p MI and CHF
- HTN, dyslidemia, OSA , NAFLD and h/o pancreatitis
- Currently treated with low dose metformin, SFU, DPP4 inhibitor and canafliflozin (initiated by nephrology)
- A1c 8.9%

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 this patient?

A	Initiate pioglitazone
B	Initiate basal insulin
C	Start a GLP-1 RA and stop his DPP-4 inhibitor
D	Change to a different SGLT-2 Inhibitor

Case 4: 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

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.

Second Pitfall In Initiating/Titrating Basal Insulin

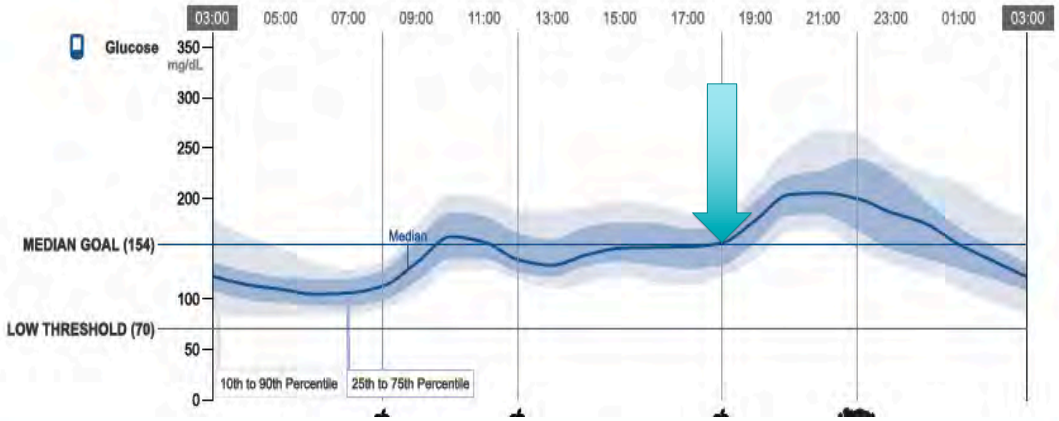
(First one is too slow titration after starting)

Not Paying Attention To
Bedtime Glucose Value So You Avoid Overbasalinization

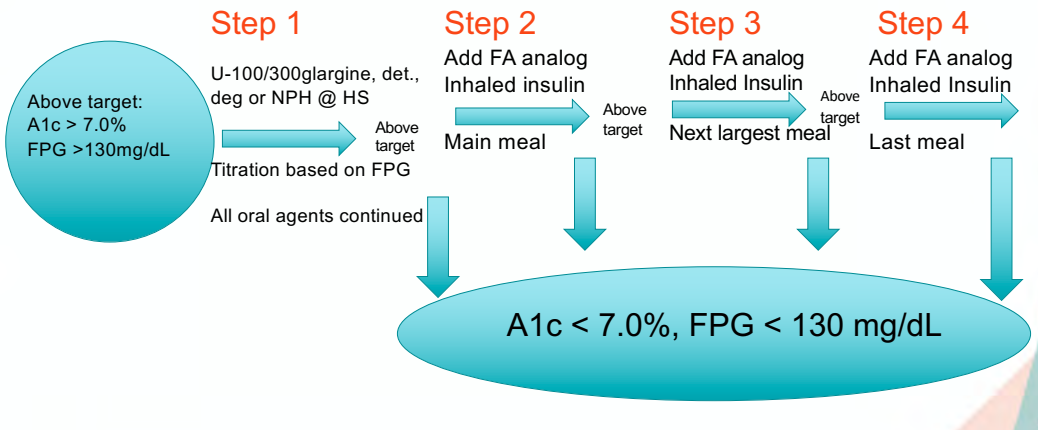
1. Ask the patient to do paired testing (test at bedtime and again the next morning).
2. If the bedtime BG is high, it needs to be addressed by either lifestyle modification including reduced caloric consumption and/or post dinner exercise.
3. Other options include prandial insulin or a GLP-1 RA.

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

68 Year Old Male On Oral Agents and Basal Insulin:
Need For Prandial Insulin Only At Dinner



Transitioning From Basal to Basal/Bolus Insulin Therapy in Type 2 Diabetes Mellitus



Adapted with permission from Karl DM. Curr Diab Rep. 2004;4:352-357.

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 if very poor glycemic control (A1c>9%) or in addition to a GLP-1RA
- Titrating the dose is essential (self titration can work well)
- Use a fast-acting analog as an add on to basal dose when indicated (may only needed to be given with the largest meal)
- Self-monitoring of blood glucose (SMBG) and CGM are important tools 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.

Summary

- GLP-1 RAs represent a tremendous advance in the treatment of type 2 because of significant glucose lowering in addition to weight loss and reducing the risk of hypoglycemia
- Combination therapy (adding basal insulin to daytime OHAs/GLP1-RAs) 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 (pens, patch pumps and inhaled insulin to improve adherence)
- Adherence and persistence needs to be addressed at every visit
- Protection for ASCVD