Lecture 1: 9:15 – 10:15 a.m. PST

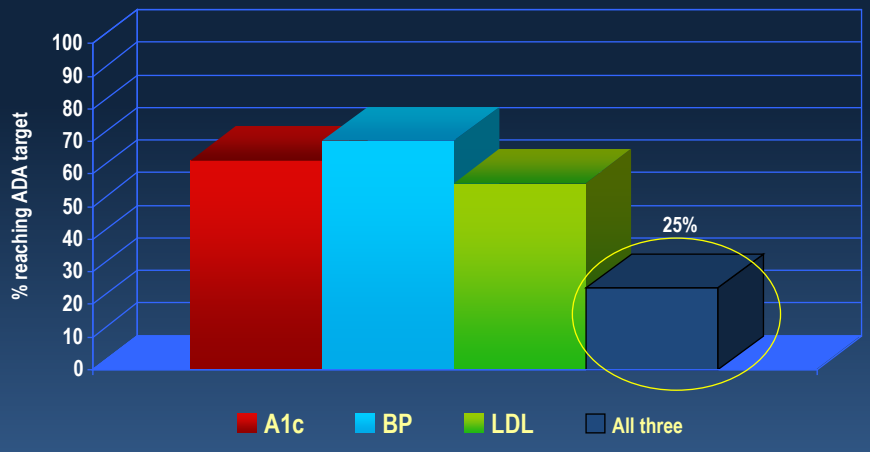
William Polonsky, PhD, CDCES, Presents:

Understanding the emotional and behavioral issues that affect adherence and glycemic control in people living with diabetes

The Behavioral Side of Diabetes:
Top Tricks of the Trade

William H. Polonsky, PhD, CDE
whp@behavioraldiabetes.org

Percentage of Patients Achieving ADA Treatment Targets



Kazemian et al, 2019

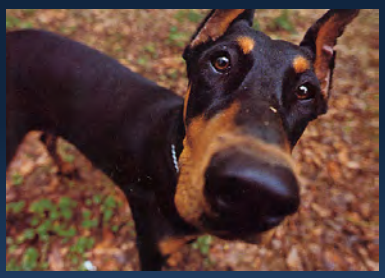
Why Such Poor Cardiometabolic Outcomes?

- Macroeconomic factors (e.g., poverty)
- Limitations of currently available tools
- HCP behavior (e.g., clinical inertia)
- Patient behavior (e.g., self-management)

So What To Do?

Patients who:

- Seem unmotivated
- Frequently miss appointments
- Don't follow recommendations
- Are disengaged during visits
- Don't seem to care
- Miss their medications
- Doubt what you say, but believe what they read on the Internet or hear from friends.



Motivation in Diabetes

- No one is unmotivated to live a long and healthy life
- The real problem: Obstacles to self-care outweigh possible benefits

Real Life with Diabetes

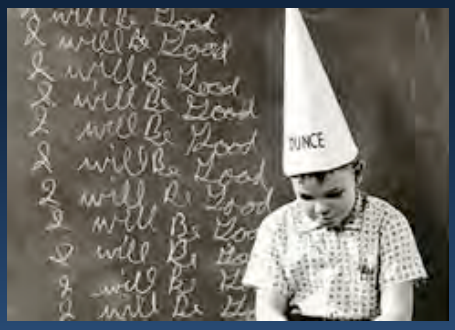
Living with diabetes can be tough

- It is a time-consuming and challenging job
- No one volunteered
- No pay
- No vacations
- Do it forever

Real Life with Diabetes

Living with diabetes can be tough

- It is a time-consuming and challenging job
- No one volunteered
- No pay
- No vacations
- Do it forever
- Can be very discouraging



Seven Activation Strategies

1. Make it real
2. Make it hopeful
3. Make it implementable
4. Make it stick
5. Make it collaborative
6. Make it less isolating
7. Make progress visible

1. Make it Real

Back on Track Feedback			**Name: *Molly B.***	
Tests	Your Targets	Last Results	**FID #:**	
	Your score should be		***SAFE**: At or better than goal*	***NOT SAFE**: Not yet at goal*
A1C	7.0% or less	*8.7%*		x
Blood Pressure	130/80	*125/75*	*x*	
LDL	100 or less	*116*		*x*

1. Make it Real

There is a fire burning; you are in an unsafe place with your diabetes.

Damage is happening now, and it is urgent that we take action.

The good news is that by taking action now, we can help you to reach a safer place with diabetes before more serious damage is done.

Personalized A1C Feedback

Reference	Type	Number of subjects	A1C Difference
Chapin et al, 2003	Chart in medical record, conversation presumed	127 T2D adults	0.7%*
Levetan et al, 2002	Laminated poster, then call from educator	150 T1D/ T2D adults	0.5%*
O'Connor et al, 2009	Periodic brochures, no discussion	3703 T1D/T2D adults	0.0%
Sherifali et al, 2011	Periodic brochures, no discussion	465 T2D adults	0.1%

Most Recent Study Conclusions

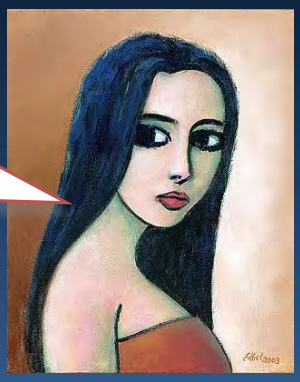
- "Still, this type of communication intervention may be more potent if linked with provider and/or case manager support to identify existing barriers to management or paired with personalized action planning and goal setting.

Gopalan et al, 2020

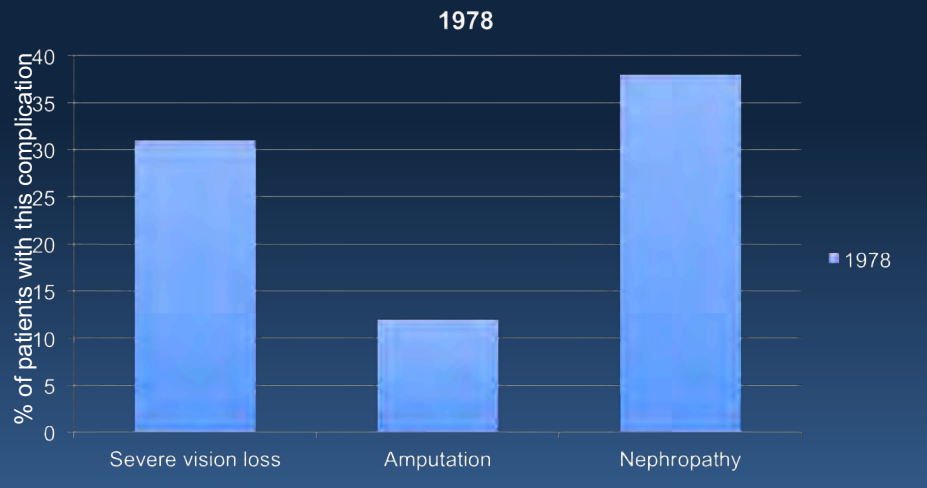
2. Make it Hopeful

- If you don't think it is possible to live a long, healthy life with diabetes, why bother trying?

"My mom ended up on dialysis; that was awful. I'm pretty sure this will also happen to me; I doubt I can do anything about it. It is going to happen. I just hope I die before that."

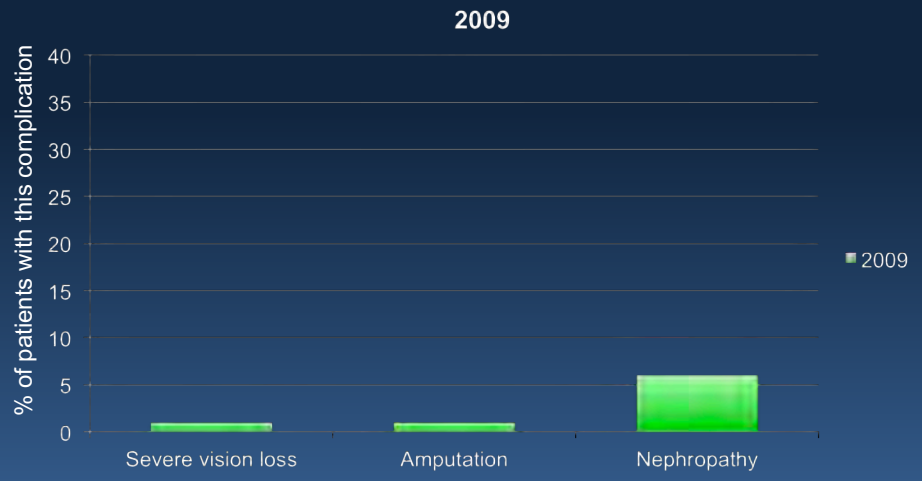


T1D Complications After 30+ Years



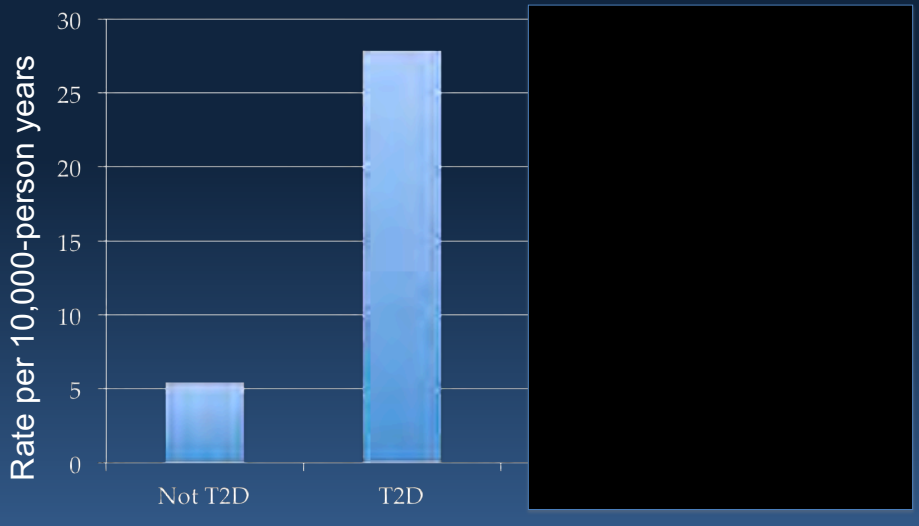
Deckert et al, 1978

T1D Complications After 30+ Years



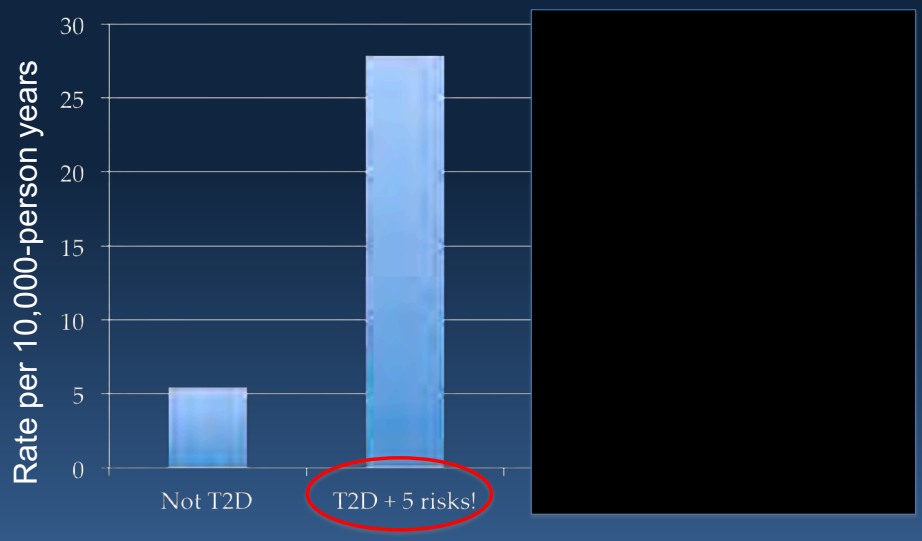
DCCT/EDIC Research Group, 2009

Heart Attacks in Type 2 Diabetes



Rawshani et al, 2018

Heart Attacks in Type 2 Diabetes



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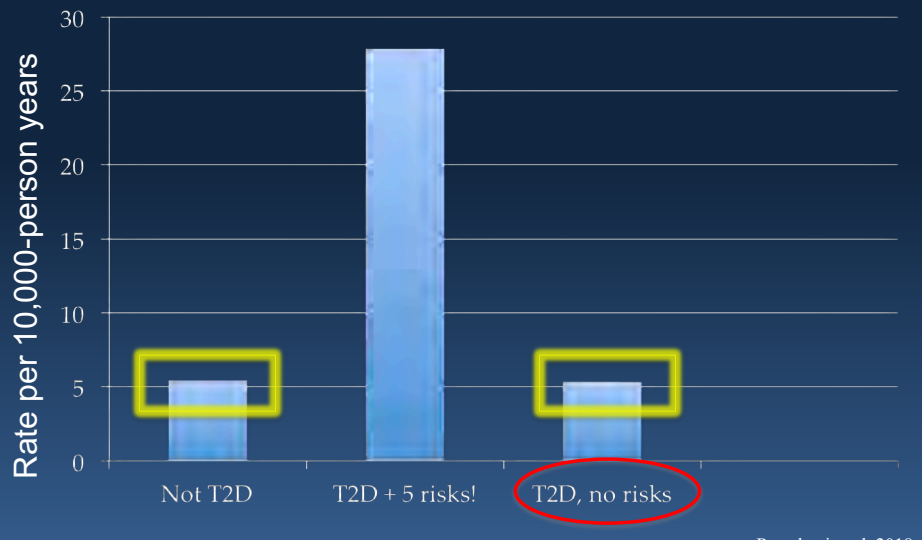
Heart Attacks in Type 2 Diabetes



Rawshani et al, 2018

2. Make it Hopeful (Fact Check)

This doesn't mean: good care will **guarantee** that you will not develop complications

This does mean: with good care, **odds are good** you can live a long, healthy life with diabetes

Effective HCP Behavioral Strategies

Table 2. Behavior Change Strategies Reported by Top- and Bottom-Performing Clinicians

Strategy	Clinicians Reporting Strategy, No.	
	Top-Performing Clinicians (n = 10)	Bottom-Performing Clinicians (n = 10)
Used mainly by top-performing group		
Emphasizing patient ownership	8	3
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Identifying small steps	10	3
Scheduling frequent follow-up visits	7	3
Showing caring	5	1
Used by both groups		
Reliance on team supports	10	7
Used mainly by bottom-performing group		
Describing consequences of bad health behaviors	2	8

Greene et al, 2016

3. Make it Implementable

- 50% of patients leave HCP visit without understanding the advice given

Marvel et al, 1999; Center for Studying Health System Change, Physician Survey. http://CTSonline.s-3.com/psurvey.asp

3. Make it Implementable

- Behaviors, not outcomes
- Concrete and doable
- One step at a time
- *"We've agreed that going for a brisk walk each day is your first step. What exactly does this mean you'll be doing tomorrow?"*

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Greene et al, 2016

4. Make it Stick

- Teach back, or "closing the loop"

  "Just to make sure we're on the same page, can you tell me what's that one major change you're aiming to do over the next few months?"

Association of Patient-Provider Teach-Back Communication with Diabetic Outcomes: A Cohort Study

Young-Rock Hong, PhD, MPH, Jinhai Huo, PhD, MD, MSPH, Ara Jo, PhD, MS, Michelle Cardel, PhD, MS, RD, and Arch G. Mainous III, PhD

Hong et al, 2020

4. Make it Stick

- N = 2901, median age 60, median duration 7 yrs.
- Consistent teach-back experience, 25%
- One year follow-up, retrospective

Table 2. Associations between Teach-Back Experience and Patient Health Outcomes

	Teach-Back			Teach-Back versus Non-Teach-Back			
	Yes	No					
	%, (95% CI)	%, (95% CI)	P-Value	Crude Odds Ratio (OR)	P-Value	Adjusted OR*	P-Value
Complication							
Any	14.0 (10.9 to 17.1)	17.7 (15.8 to 19.7)	.042	0.74 (0.56-0.99)	.045	0.70 (0.52-0.96)	.026
CVD†	6.7 (4.5 to 8.9)	8.3 (6.7 to 9.8)	.281	0.77 (0.50-1.19)	.232	0.71 (0.45-1.11)	.133
Kidney problem	3.1 (1.4-4.7)	4.9 (3.9-5.9)	.052	0.63 (0.36-1.10)	.102	0.62 (0.33-1.14)	.123
Eye problem	5.5 (3.6 to 7.5)	7.1 (5.6 to 8.7)	.200	0.77 (0.50-1.19)	.242	0.76 (00.49-1.18)	.217
Hospitalization							
All cause	5.4 (3.6 to 7.2)	7.8 (6.4 to 9.3)	.051	0.73 (0.49-1.10)	.133	0.72 (0.47-1.09)	.123
DM specific	2.0 (1.1 to 2.8)	2.9 (1.8-4.0)	.085	0.59 (0.30-1.17)	.131	0.58 (0.29-1.14)	.112
Complication related	2.4 (1.2 to 3.7)	4.6 (3.5-5.7)	.011	0.53 (0.30-0.94)	.031	0.51 (0.29-0.88)	.015

Hong et al, 2020

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5. Make it Collaborative

"What's your opinion of these medication changes that I've suggested?"

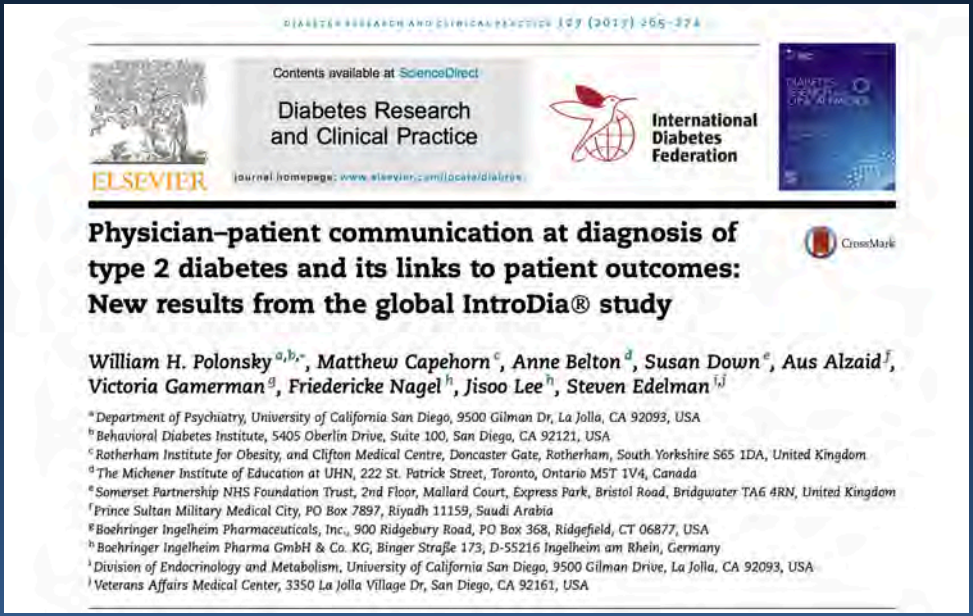
I want you to call me within the week and let me know how this is working out."

"Let's think together to make a plan that seems reasonable for you."

If you can't afford this, we need to brainstorm together about what to do."

5. Make it Collaborative

- Do your patients believe:
  - that you are on their side?
  - that you are making the effort to appreciate their perspective?



Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Physician–patient communication at diagnosis of type 2 diabetes and its links to patient outcomes: New results from the global IntroDia® study

William H. Polonsky [a,b,*], Matthew Capehorn [c], Anne Belton [d], Susan Down [e], Aus Alzaid [f], Victoria Gamerman [g], Friedericke Nagel [h], Jisoo Lee [h], Steven Edelman [i,j]

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[c] Rotherham Institute for Obesity, and Clifton Medical Centre, Doncaster Gate, Rotherham, South Yorkshire S65 1DA, United Kingdom
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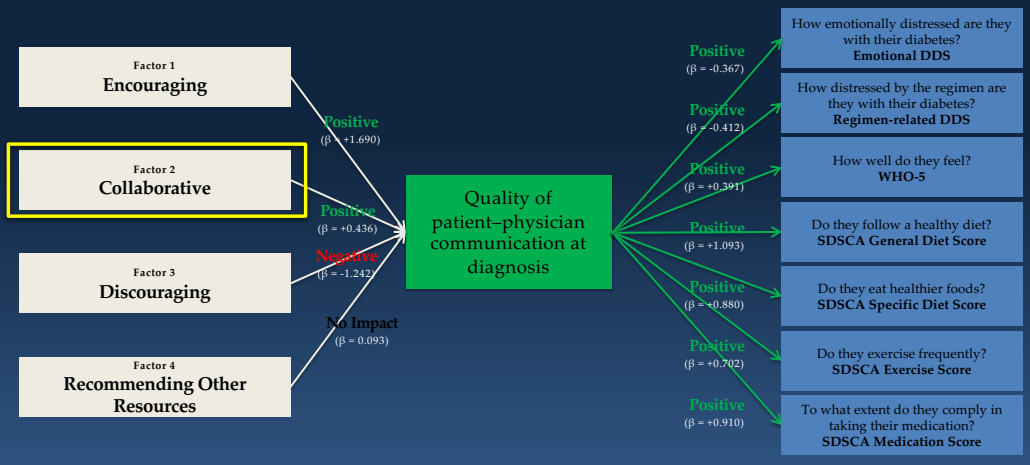
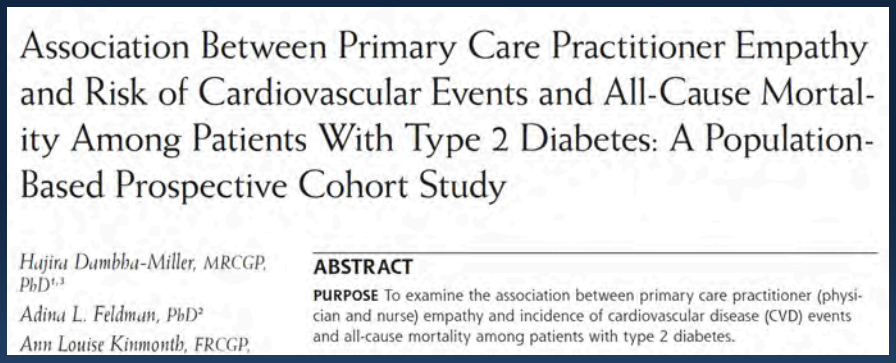
[e] Somerset Partnership NHS Foundation Trust, 2nd Floor, Mallard Court, Express Park, Bristol Road, Bridgwater TA6 4RN, United Kingdom
[f] Prince Sultan Military Medical City, PO Box 7897, Riyadh 11159, Saudi Arabia
[g] Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877, USA
[h] Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Straße 173, D-55216 Ingelheim am Rhein, Germany
[i] Division of Endocrinology and Metabolism, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA
[j] Veterans Affairs Medical Center, 3350 La Jolla Village Dr, San Diego, CA 92161, USA

Conversation Elements



Polonsky et al, 2017



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

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 Collaboration and Outcomes

- 10-year follow up of 628 peoples 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

Effective HCP Behavioral Strategies

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Greene et al, 2016

6. Make it Less Isolating

- Not uncommonly, T2Ds and T2Ds often feel *abandoned* with their diabetes
- Individuals do better when there are more frequent points of contact with caring HCPs
- Even the *illusion* of support can be helpful!

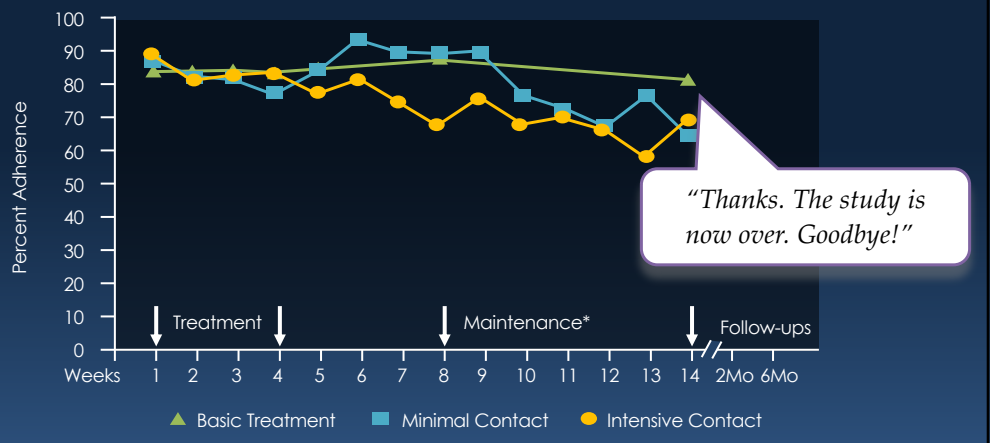
Strom and Egede, 2012

Value of Ongoing "Contact"

- North Dakota State undergraduates who did not floss regularly, n = 45
- **Goal:** Encourage at least once daily flossing
  - Outcome: Three different interventions, all were shown to be highly effective over 4 weeks
  - Then, a minimal contact follow-up period for 10 weeks: what happened to flossing rates?

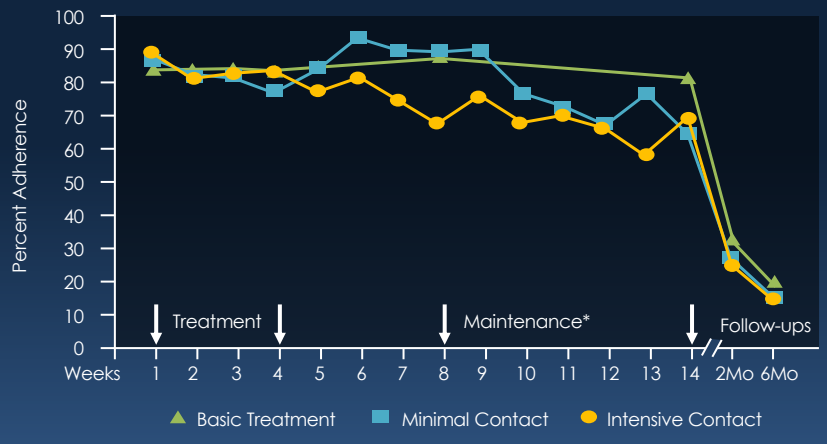
McCaul et al, 1992

The Flossing Intervention



*p = 0.26 at the end of maintenance phase.
McCaul *et al, Health Psychol.* 1992;11:101-10

The Flossing Intervention



*p = 0.26 at the end of maintenance phase.
McCaul *et al, Health Psychol.* 1992;11:101-10.

Value of Ongoing "Contact"

Lessons Learned:

- When subjects believed they were being followed, elevated flossing rates continued.
- When subjects were informed the researchers no longer cared, flossing all but stopped.

McCaul et al, 1992

6. Make it Less Isolating

- Ongoing contact with your patients:
  - ➢ Schedule more frequent visits

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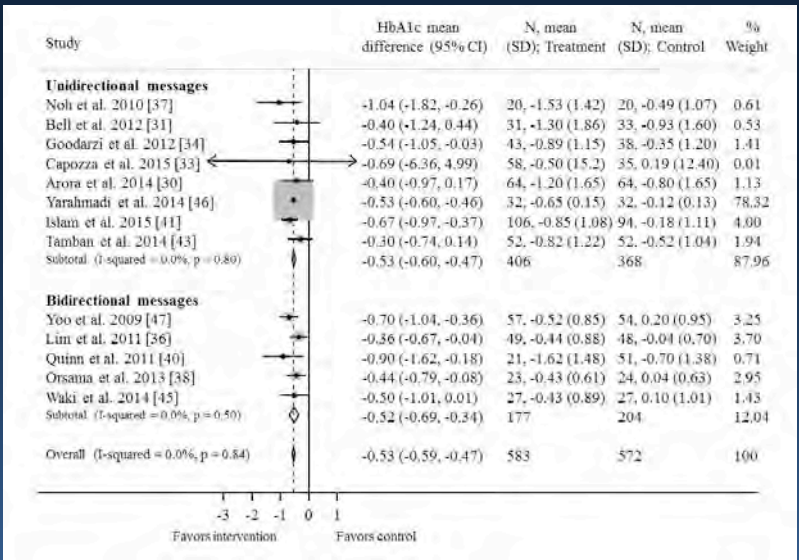
Greene et al, 2016

6. Make it Less Isolating

- Ongoing contact with your patients:
  - Schedule more frequent visits
  - Regular text messaging

Arambepola et al, 2016

Text Messaging and T2D



Arambepola et al, 2016

6. Make it Less Isolating

- Ongoing contact with your patients:
  - Schedule more frequent visits
  - Regular text messaging
- Encourage participation in support group programs (real or virtual), online forums, etc.

7. Make Progress Visible

- Provide regular graphical feedback to highlight positive benefits of treatment efforts
- But why is this necessary?
- "When the individual does not believe that a specific treatment action is accomplishing anything, when no tangible positive outcome is apparent, he/she is likely to lose interest in continuing to perform the action."

Polonsky and Skinner, 2010

Perceived Treatment Inefficacy

Lack of tangible benefits contributes to discouragement and poor adherence

Polonsky, 2015; Polonsky and Skinner, 2010

Paired Testing: Sam's Story

- Age 42, married, school teacher
- T2D 6 yrs, BMI 33, last A1C 7.9%
- Steady weight gain since dx
- Used to be very active, but quit sports 5 years due to injury
- No longer checks BGs due to "consistently high readings"
- Takes glargine, 80 units QD
- Was encouraged to begin walking, but refuses ("won't help").

Sam's Exercise Experiment

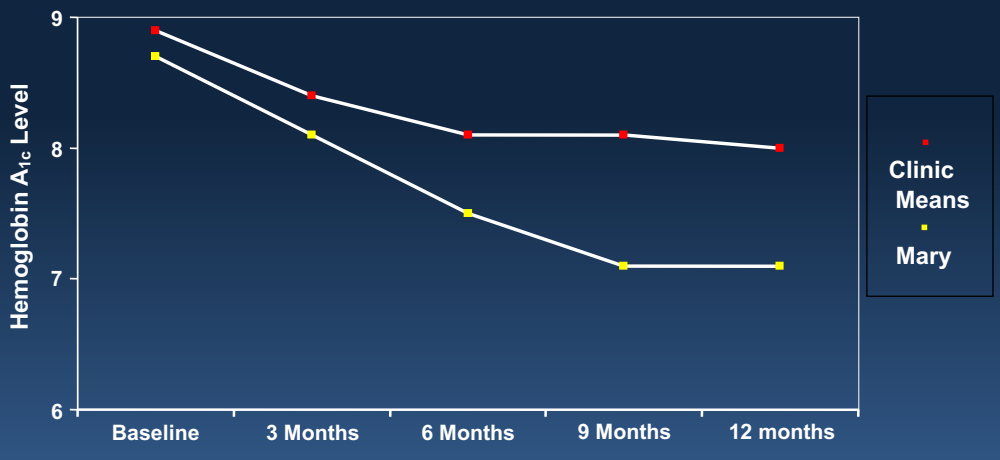
Daily walk (45 minutes)

7 consecutive days: Measure BG right before and after walk

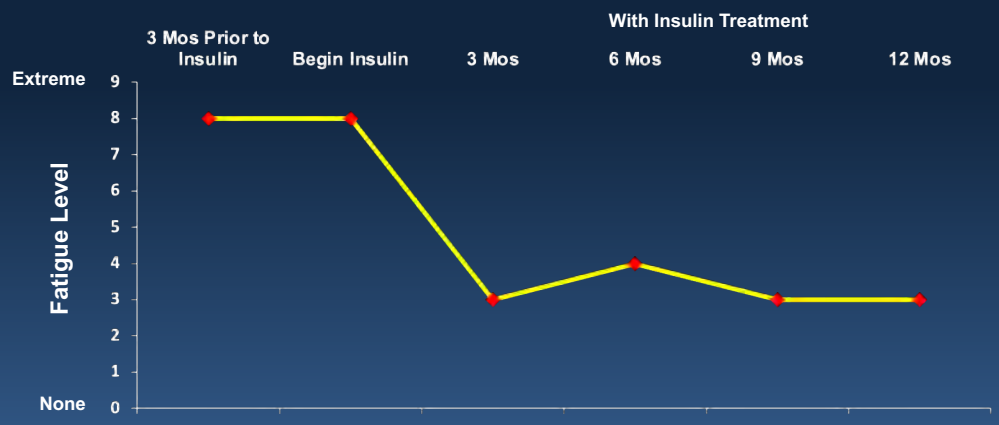
Day	Pre-Exercise	Post-Exercise	BG Change
1	129 mg/dL	101 mg/dL	-28 mg/dL
2	194 mg/dL	153 mg/dL	-41 mg/dL
3	157 mg/dL	94 mg/dL	-63 mg/dL
4	141 mg/dL	108 mg/dL	-33 mg/dL
5	152 mg/dL	127 mg/dL	-25 mg/dL
6	130 mg/dL	98 mg/dL	-32 mg/dL
7	124 mg/dL	102 mg/dL	-22 mg/dL

Average BG change: -35 mg/dL

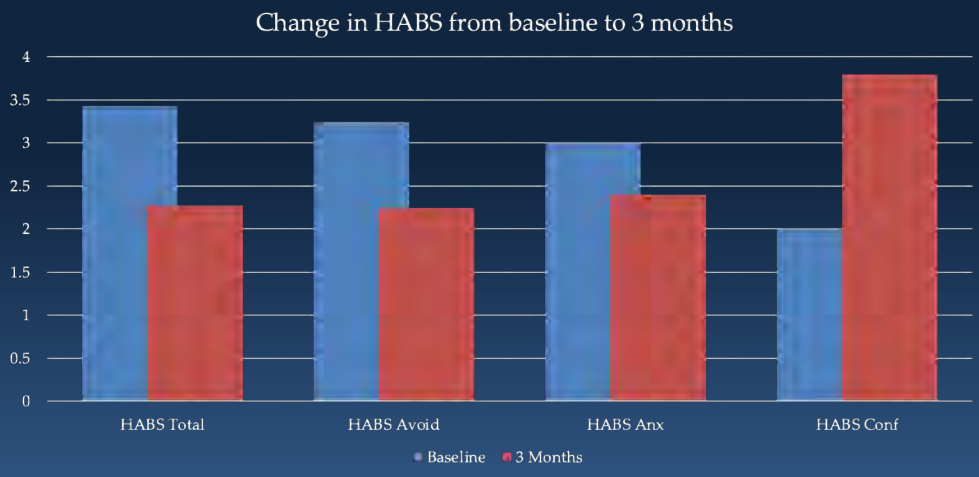
Mary: After 12 Months of Effort



Insulin Use and Your Fatigue



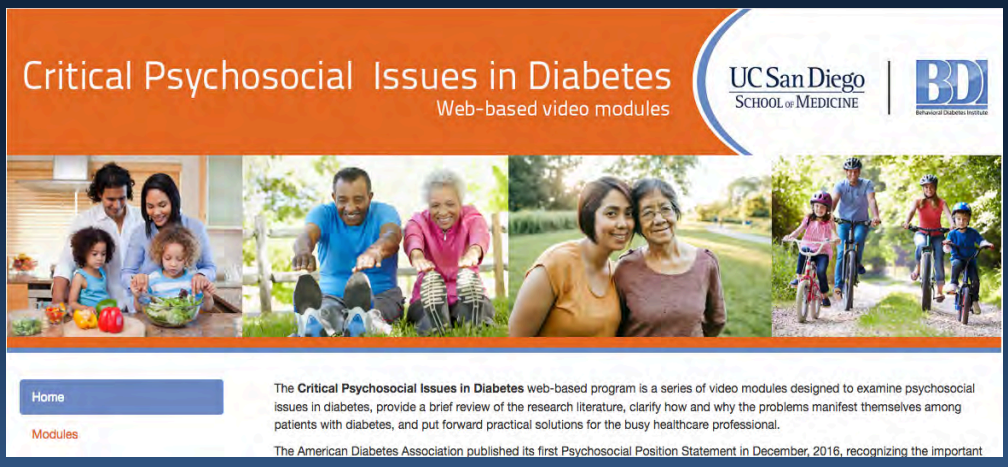
Addressing Hypoglycemic Fear



In Summary

1. Make it real
2. Make it hopeful
3. Make it implementable
4. Make it stick
5. Make it collaborative
6. Make it less isolating
7. Make progress visible

Thanks for Listening!



www.behavioraldiabetes.org

Lecture 2: 10:15 – 11:30 a.m. PST

Jeremy H. Pettus, MD, Presents:

A Focus on Time in Range, Unmet Needs & Modern Management of Type 1 Diabetes: Continuous glucose monitors, insulin pumps, hybrid closed loop systems, adjunctive therapies and techniques to improve time in range

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

Jeremy H. Pettus, MD
Associate Clinical Professor of Medicine
Division of Endocrinology, Diabetes and Metabolism
University of California San Diego School of Medicine

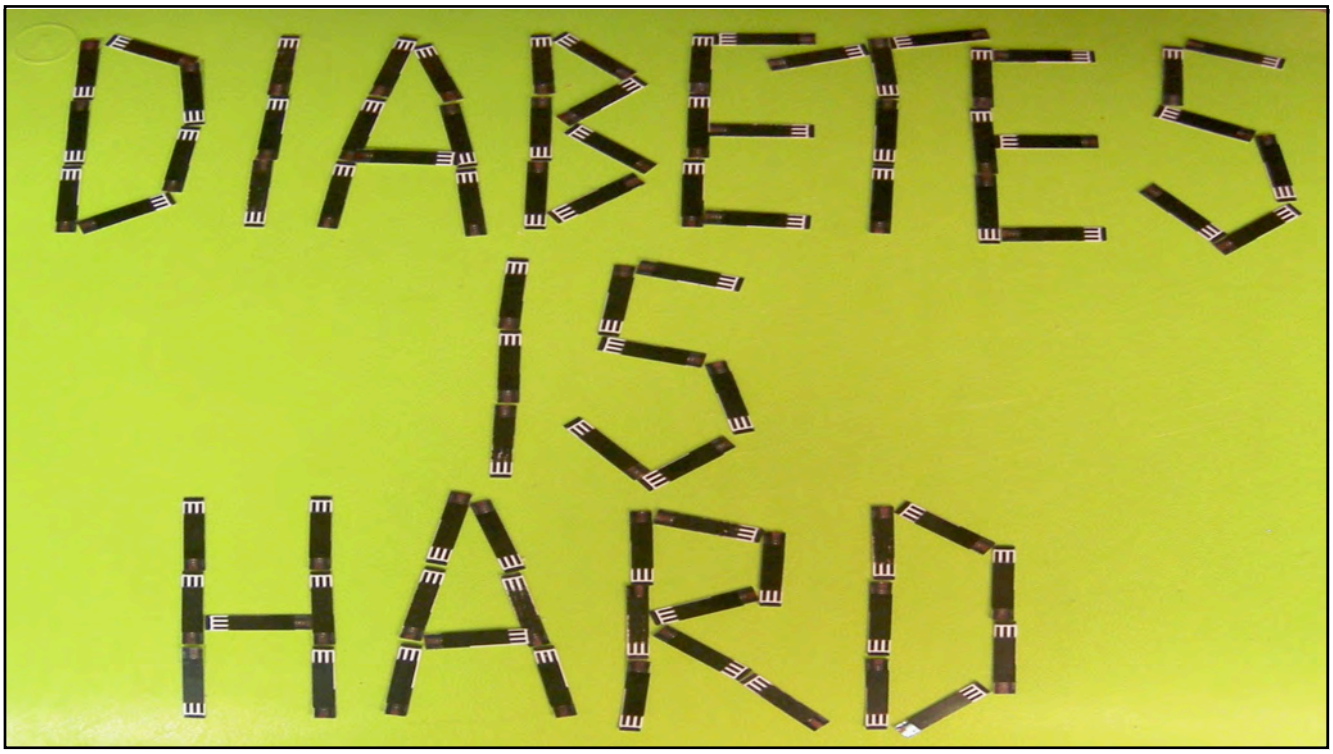
WWW.TCOYD.ORG
Taking Control Of Your Diabetes, 501(c)3 is a not-for-profit educational organization.

1

To Be Discussed…

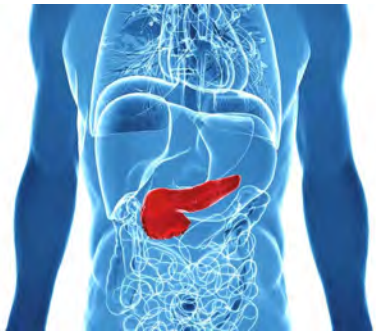
- Incidence and pathophysiology
- Demographics of T1D in the U.S.
- A1c and time in range (TIR)
- Overview of pumps and CGM devices
- Interpreting CGM downloads in ~ 30 secs.
- Identifying and addressing common problems
- New insulin and glucagon formulations
- Advances in hybrid and closed AP

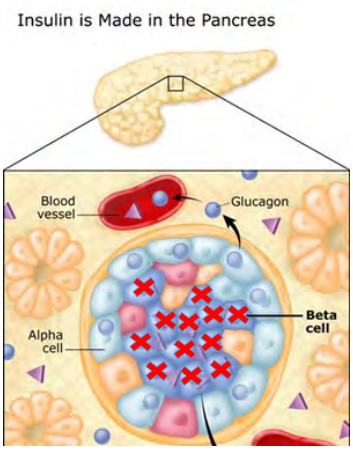
2



3

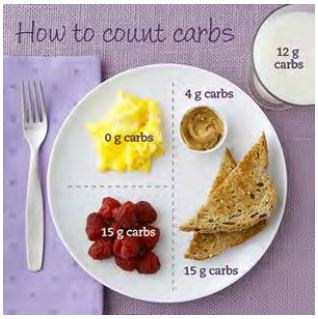
What is Type 1 Diabetes?





Natural Progression is typically years

4



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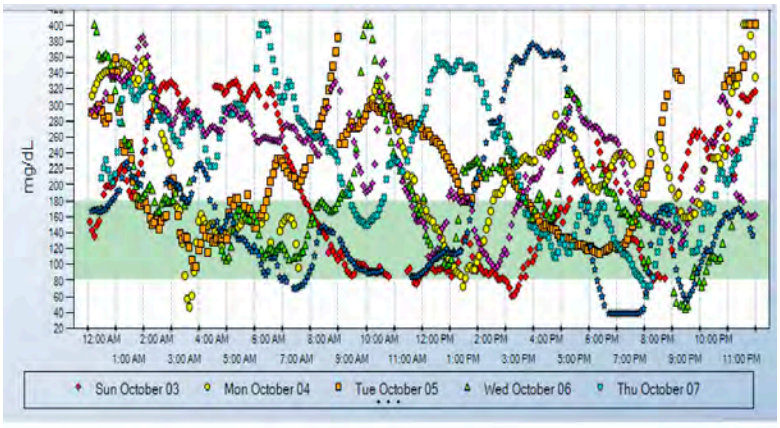
What Type 1 Diabetes Look Like



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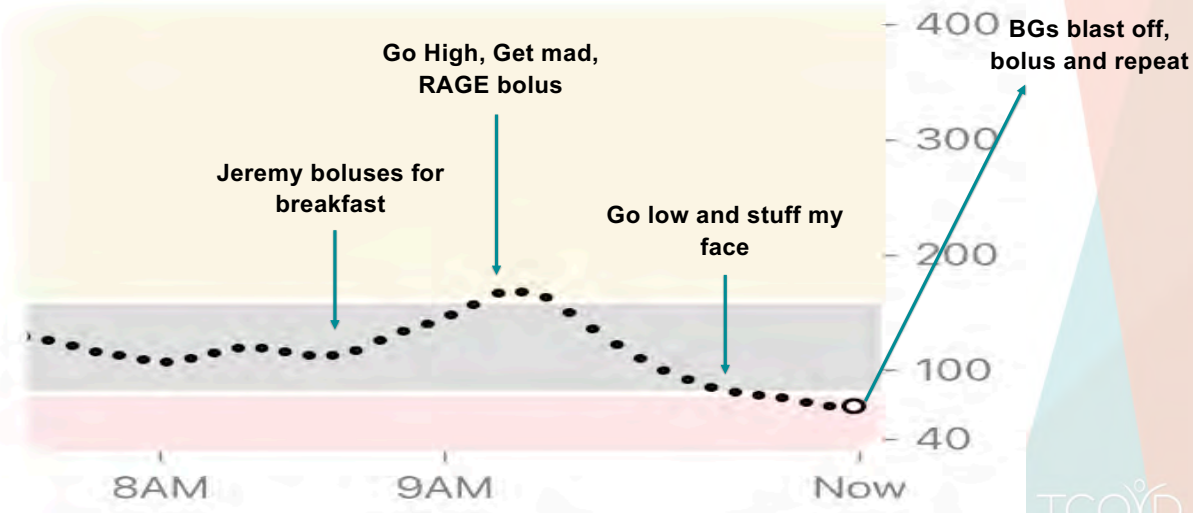
What this Looks Like in Real Time



CGM download Jeremy Pettus, Personal Dexcom archives 2020

Rollercoaster video short clip?

- Erik will send and I will embed it here

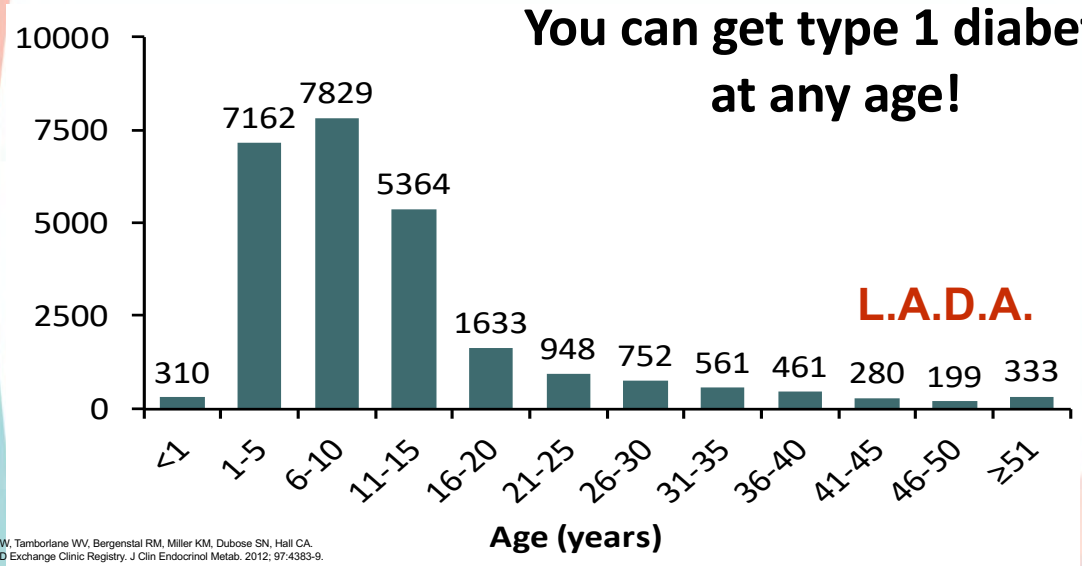
Prevalence of T1D Is Increasing!

- 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

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.

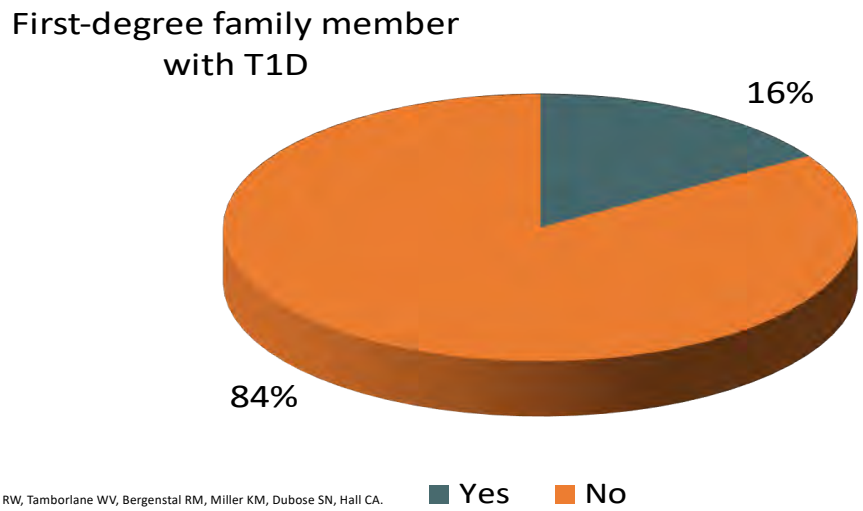
11

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.

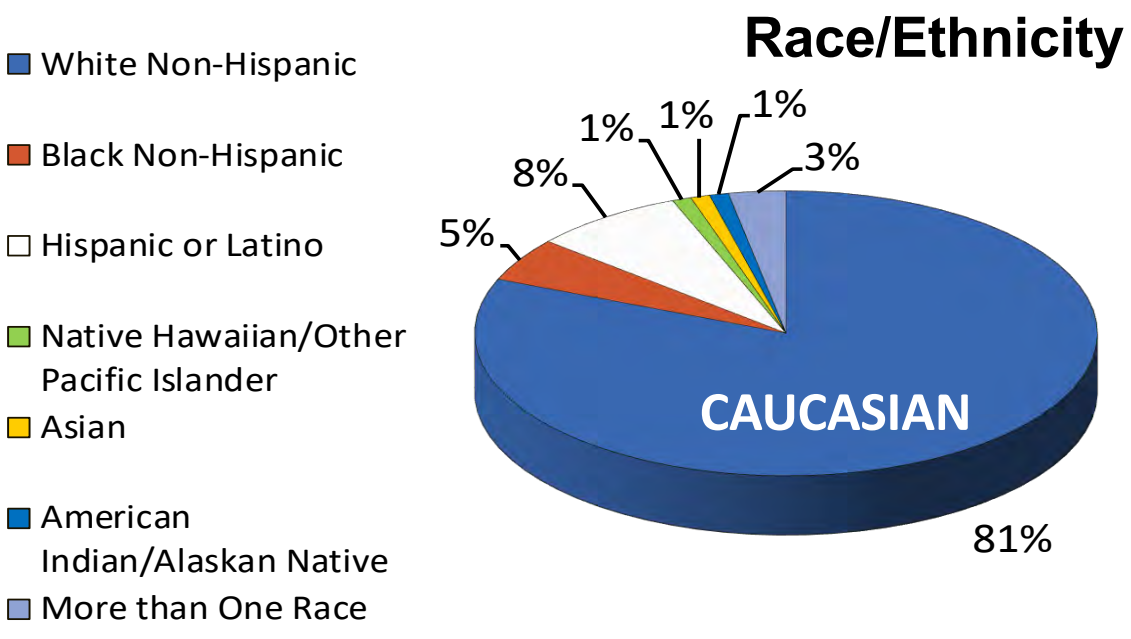
Risk of Developing Type 1 vs Type 2

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.

14

Race/Ethnicity



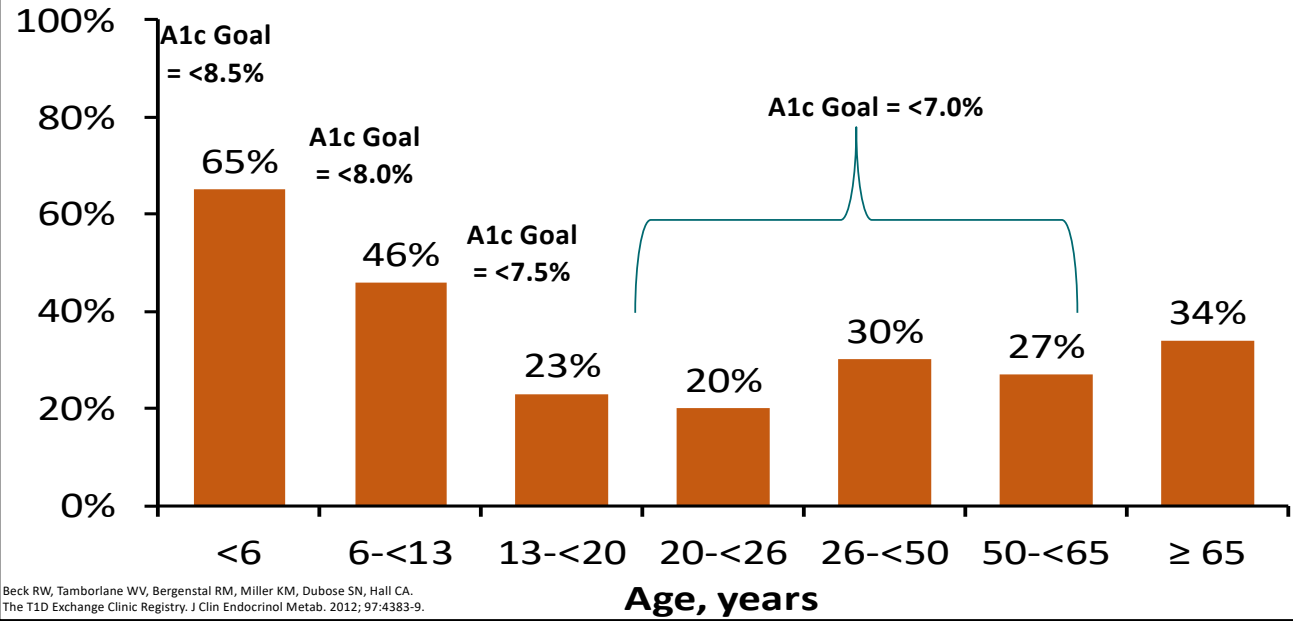
Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

15

How Are Type 1s in The Country Doing?

16

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



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

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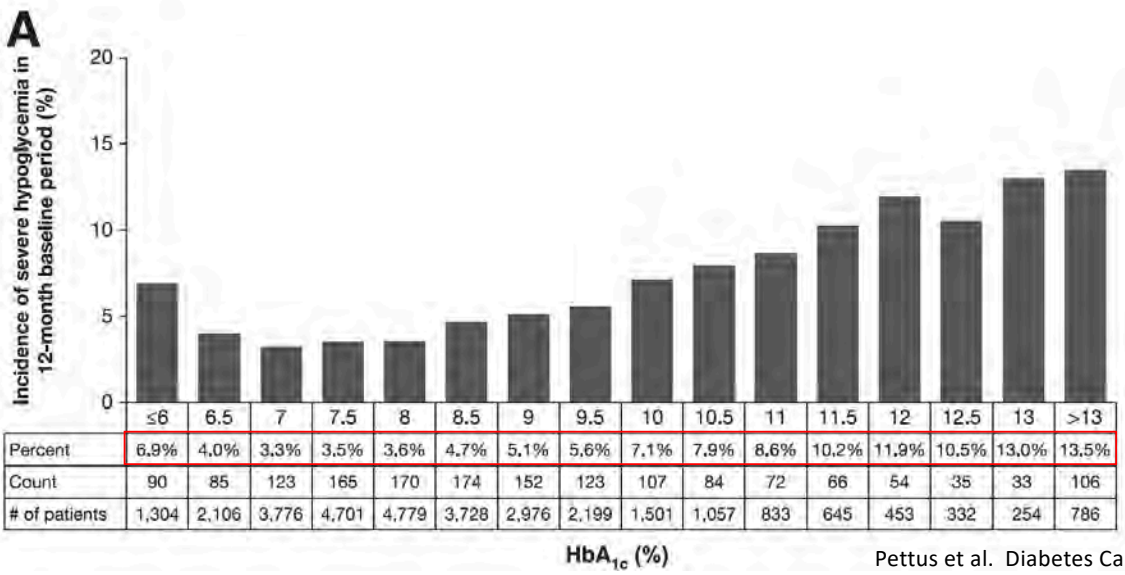
Hypoglycemia requiring ER or Hospitalization



	≤6	6.5	7	7.5	8	8.5	9	9.5	10	10.5	11	11.5	12	12.5	13	>13
Percent	6.9%	4.0%	3.3%	3.5%	3.6%	4.7%	5.1%	5.6%	7.1%	7.9%	8.6%	10.2%	11.9%	10.5%	13.0%	13.5%
Count	90	85	123	165	170	174	152	123	107	84	72	66	54	35	33	106
# of patients	1,304	2,106	3,776	4,701	4,779	3,728	2,976	2,199	1,501	1,057	833	645	453	332	254	786

Pettus et al. Diabetes Care 2019

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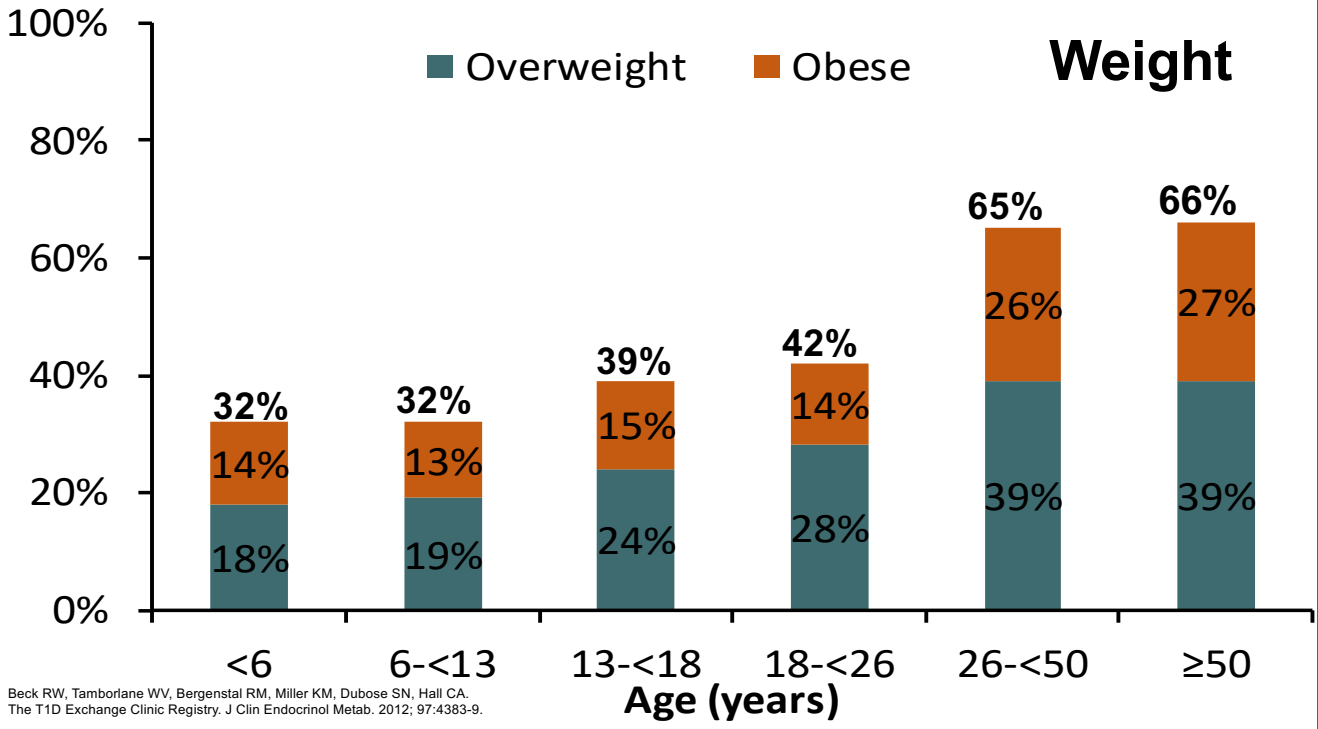

Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

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What New Stuff Do We Have to Help?

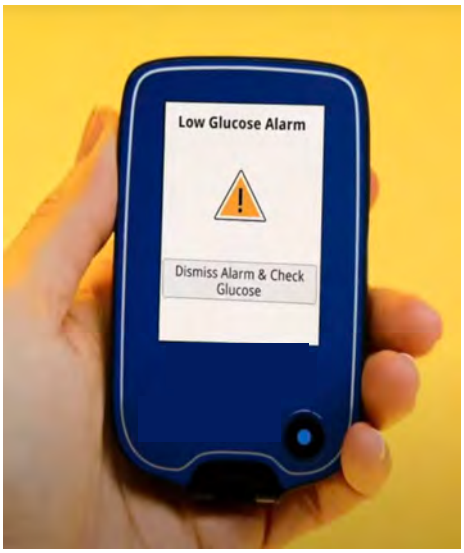
1. CGM
2. Technology/ Artificial Pancreas
3. New Insulins (injected and Inhaled)
4. New glucagon formulations

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

22



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IMPLANTABLE CGM

Sensor

Sensor lasts up to 90 days

Smart Transmitter

Removable and rechargeable

On-body vibe alerts

Mobile App

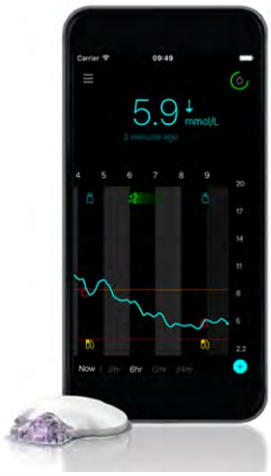
No extra device to carry

iOS and Android platform

Alarm settings & reports

Implantable CGM

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

CGM Benefits

- Better glucose Control
- Less Hypoglycemia
- More Time in Range
- Better Quality of Life

28

Who is CGM primarily for?

- When we asked 222 successful CGM uses with TYPE 1 Diabetes what the MOST useful feature of CGM was, they said:

Pettus J et al. Endocrine Practice 2015

29

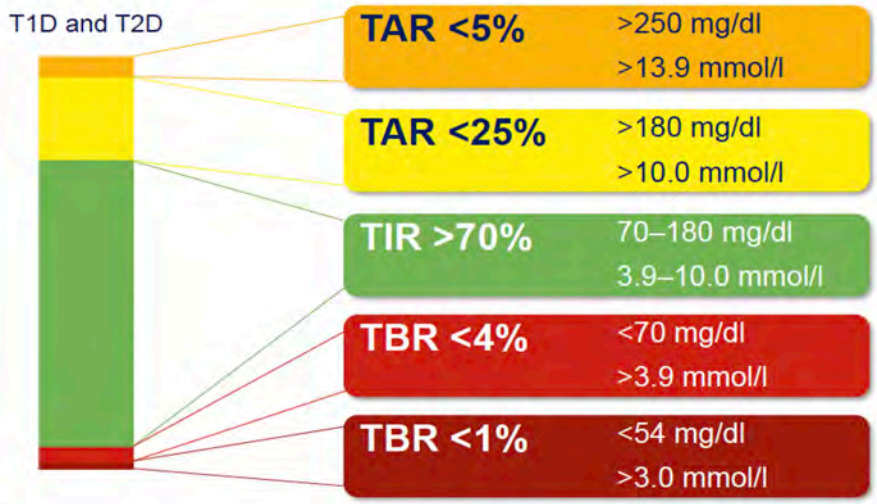
CGM is for the PATIENT PRIMARILY and the provider Secondarily

Famous quote from Steve Edelman 2014

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

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

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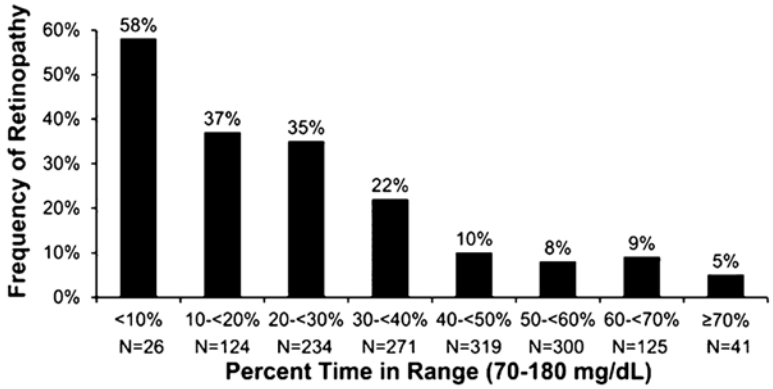
Improved TIR is Associated with Lower Microvascular Disease

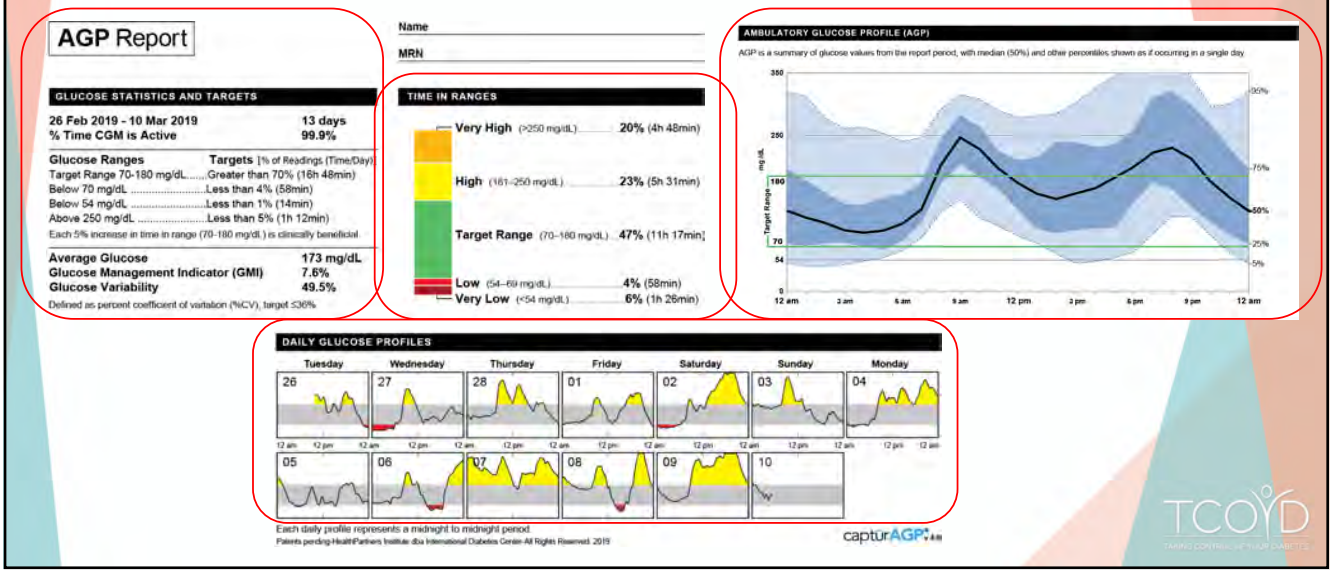
- Beck 2019 – Looked back at DCCT data for mean TIR of 7-point profiles (n=1440, 32,528 fingerstick glucose)



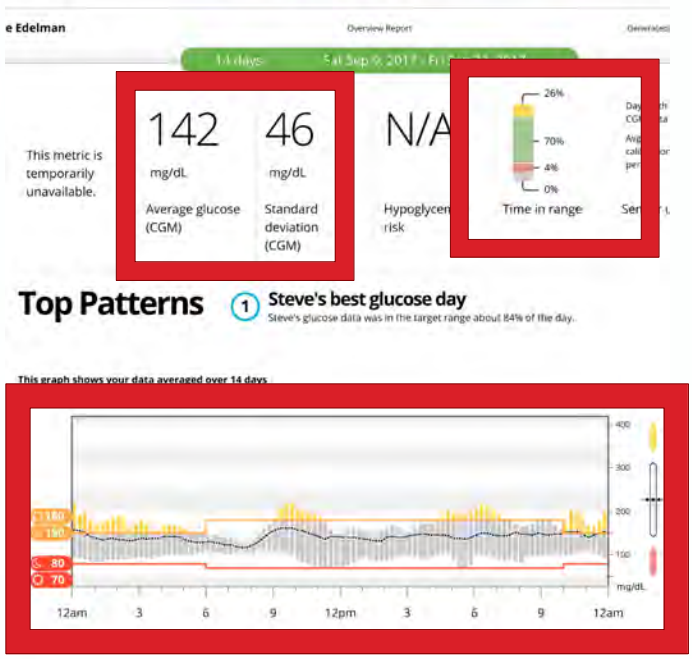
DCCT = Diabetes Control and Complications Trial

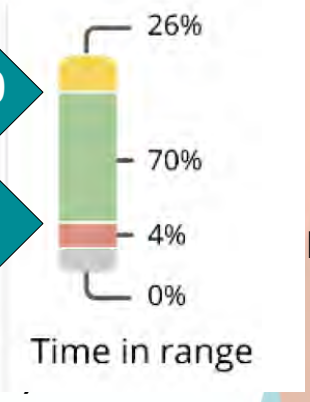
33

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



EXAMPLE REPORT





- **TI**
- **Getti**
- **Mea**
- **Sta** **D)**
- **Time**
  - **Time >180 mg/dl**
  - **Time <70 mg/dl**
- **24-hour multiday profile**

Available CGM + Pump Systems

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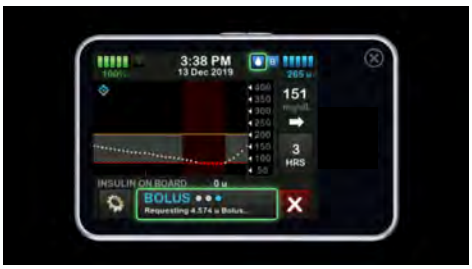
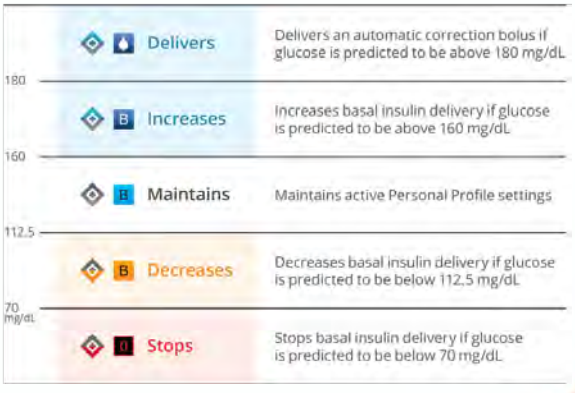
How Does The Hybrid Closed System Keep You In Range?





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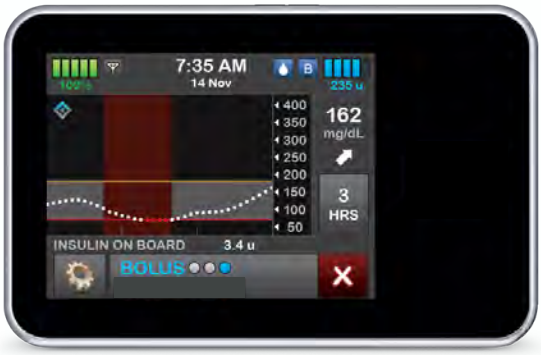
The NEW ENGLAND JOURNAL of MEDICINE

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

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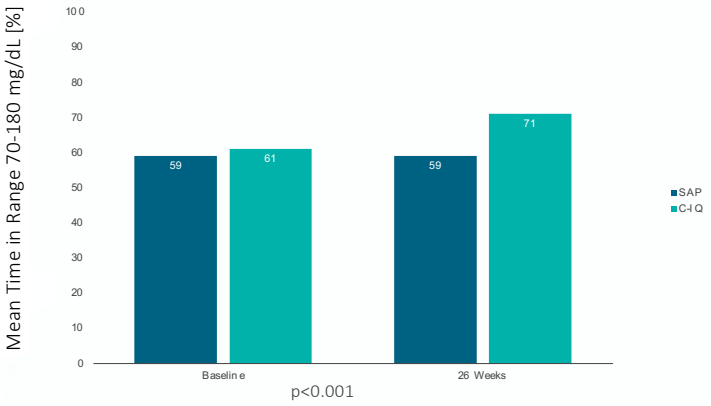
Results

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



2.6 hours

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

*As measured by CGM

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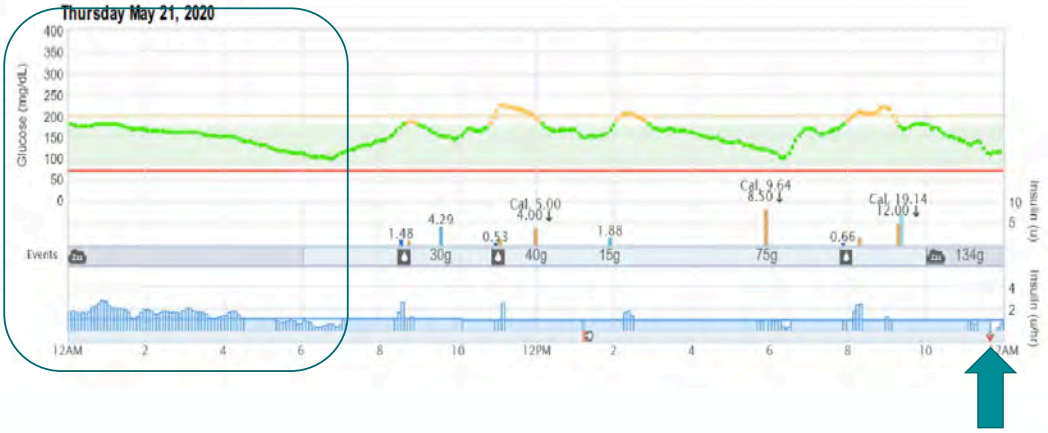
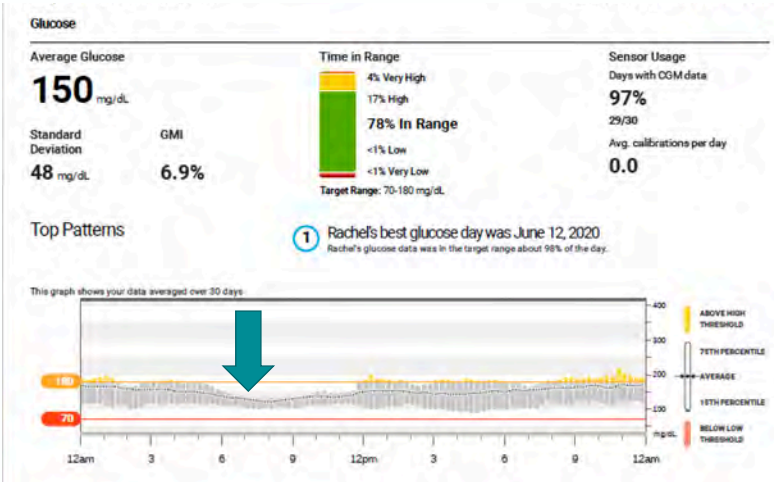
Basal Rate Modulation Overnight to Improve Control…



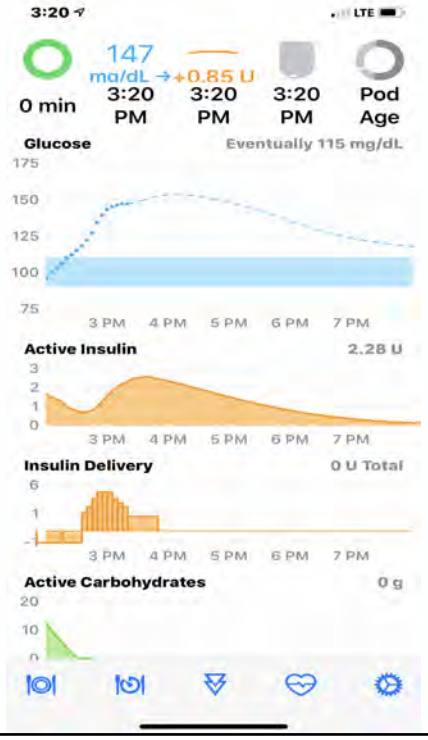
AP Systems Very Effective Overnight



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)

42



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

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Tubeless Insulin Pump

Tubeless pump that
can be used for looping

Tubeless pump that
Has Bluetooth and will be used
In an hybrid closed loop system
(waiting for FDA approval)

Smart Pens: Same Software Programs as Pumps

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

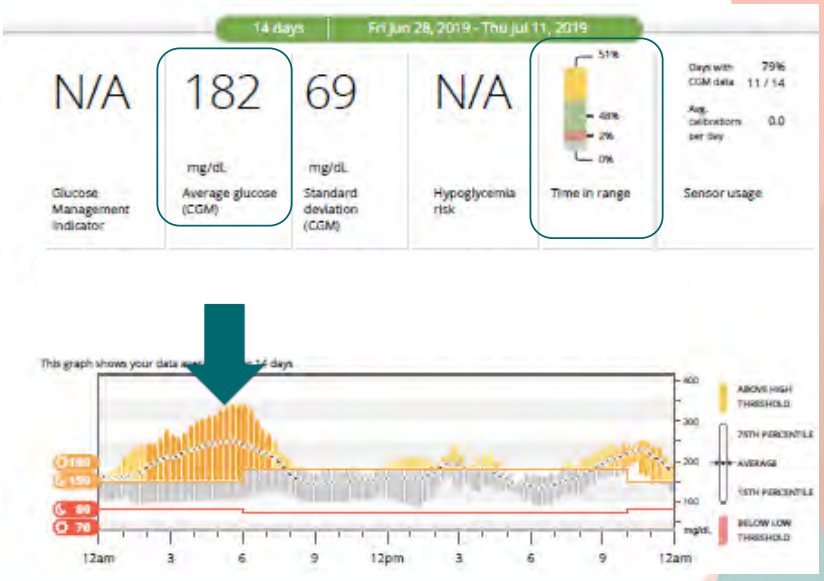
Let's Practice

Example Cases

Case 1: Sam

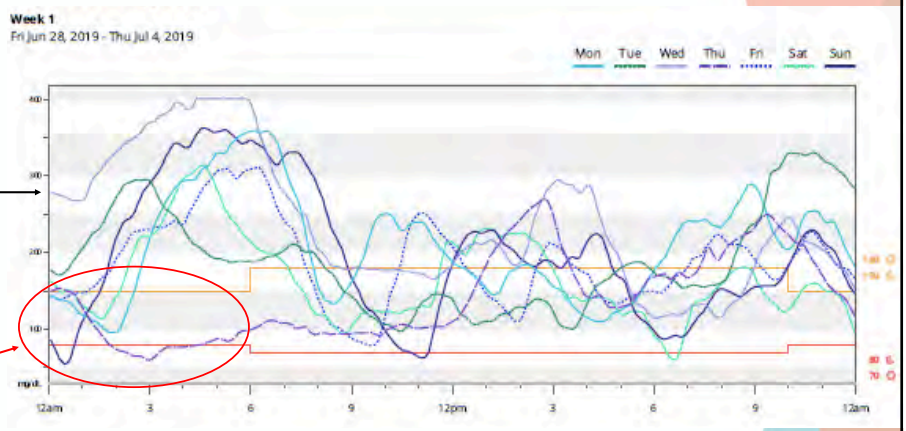
<u>Quick Interpretation</u>

- 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

48

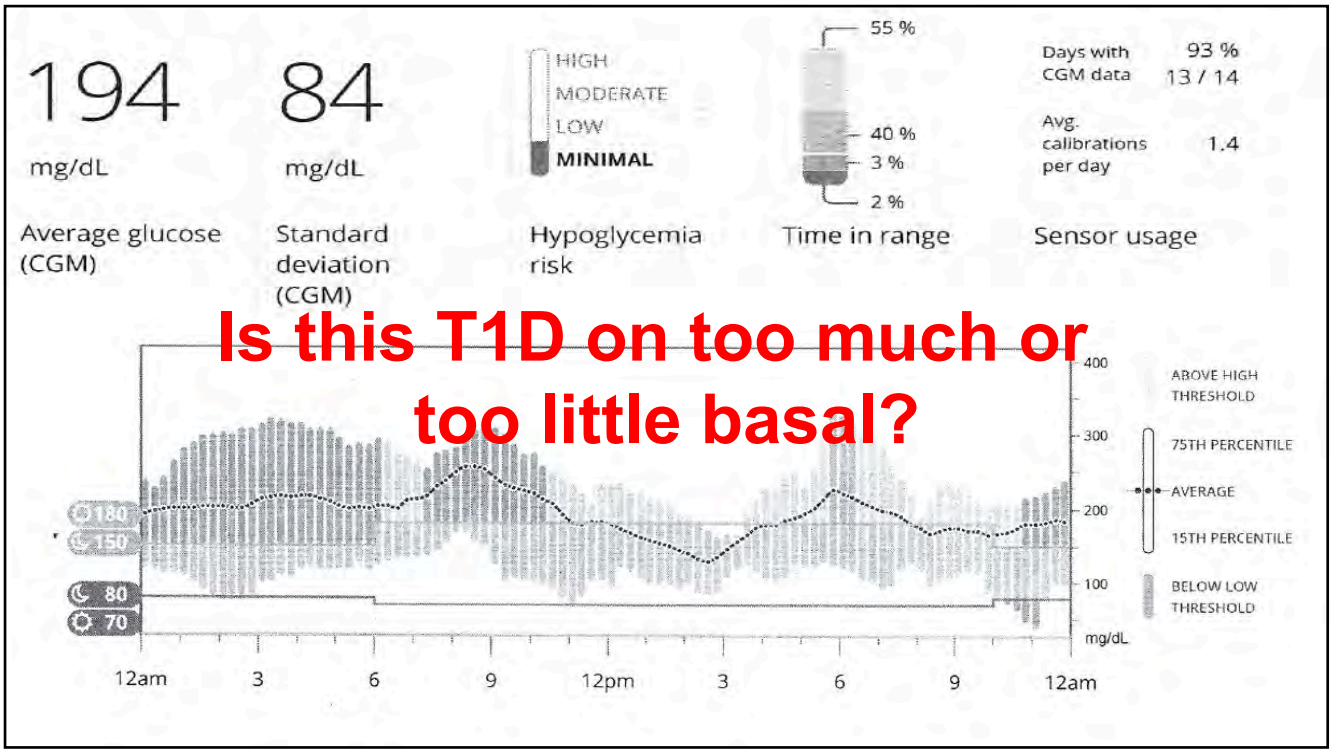
How Do you Know if the Basal Does is "Right"?

- 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

49

Physiologic Basal

50



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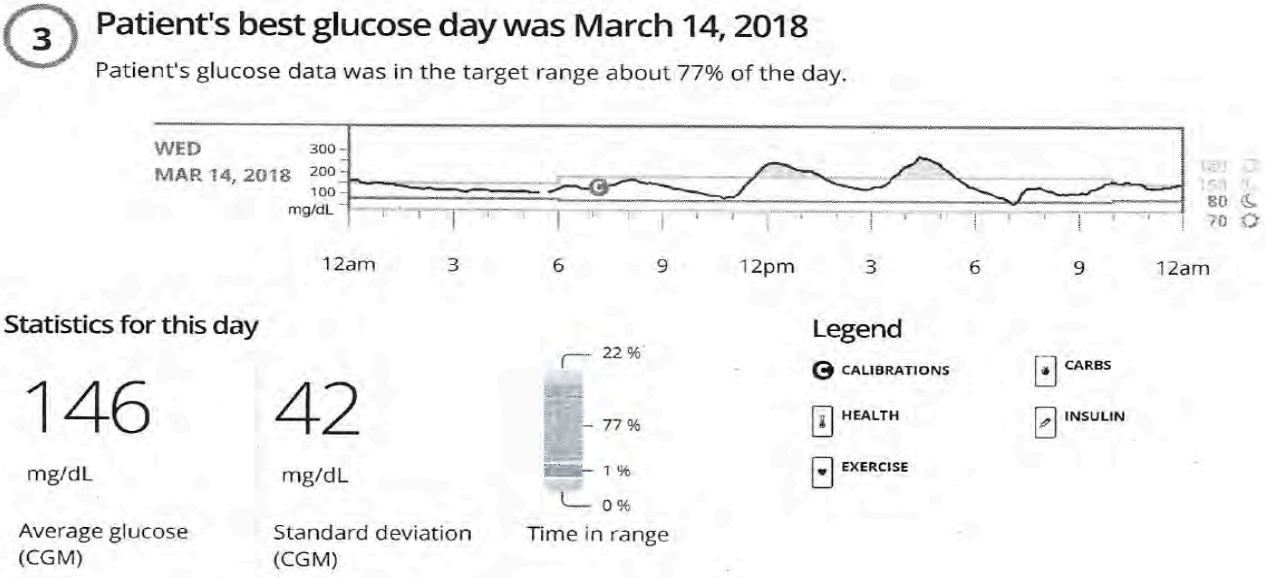
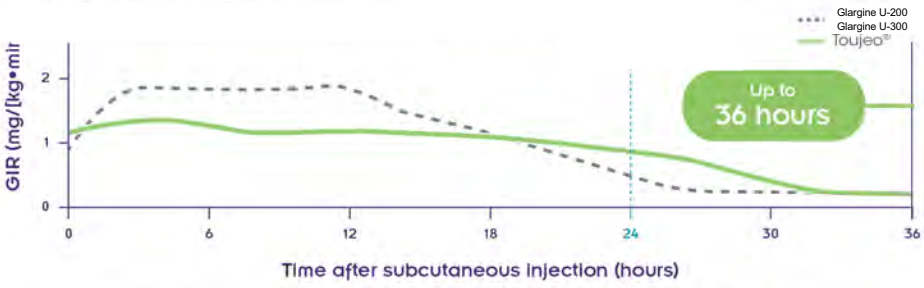
Same Patient Fasting From 9pm Until 7am

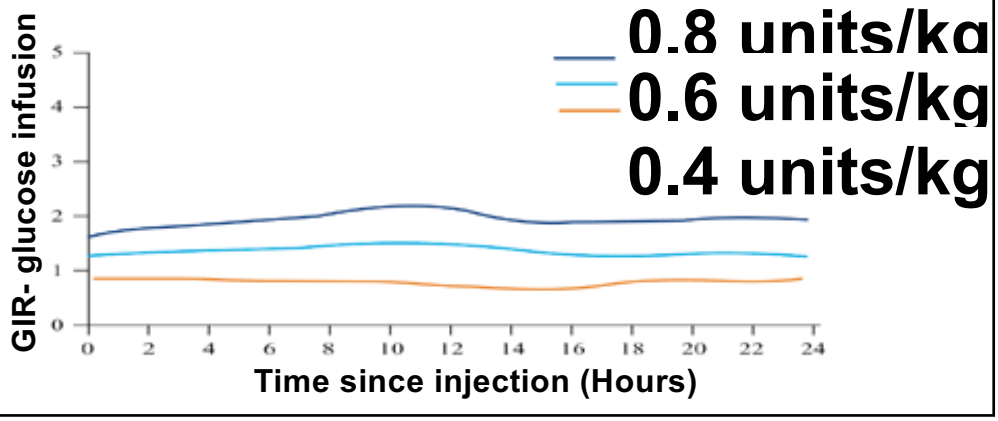


52

Aabc lispro



Faster acting asp.



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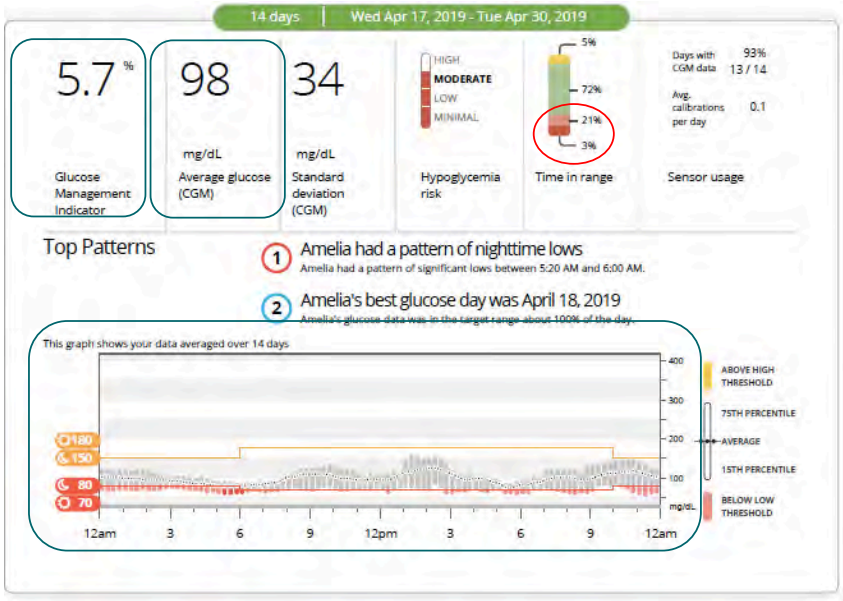
Case 1 Learning Points

- 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 pumps
- Episodes of hypoglycemia markedly reduced…

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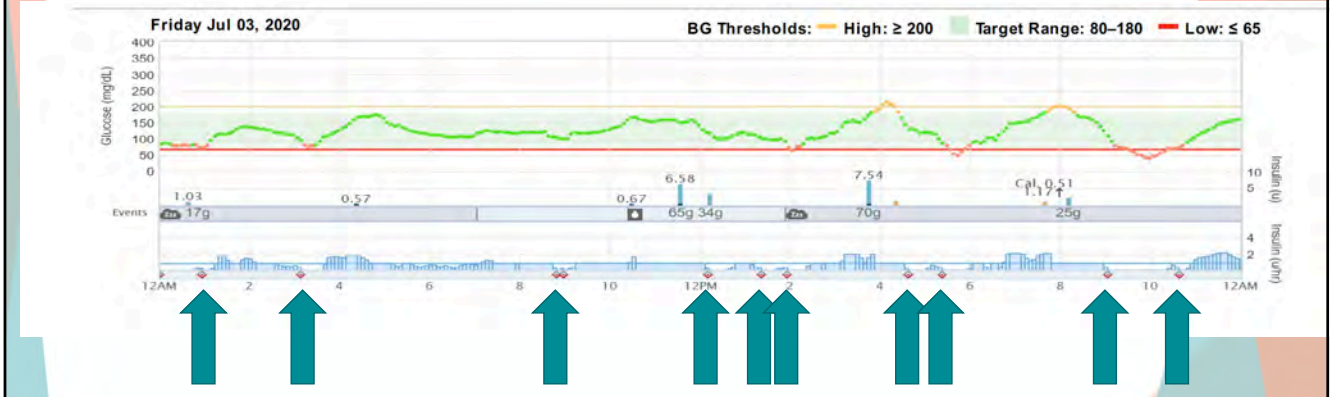
Suspensions to Reduce Hypoglycemia



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New Formulations of Glucagon

Nasal Glucagon

Pre-Filled Syringe

Auto-injector Pen

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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

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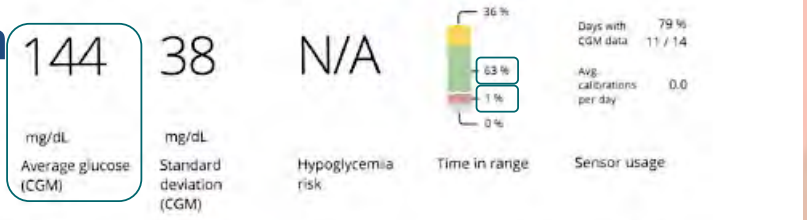
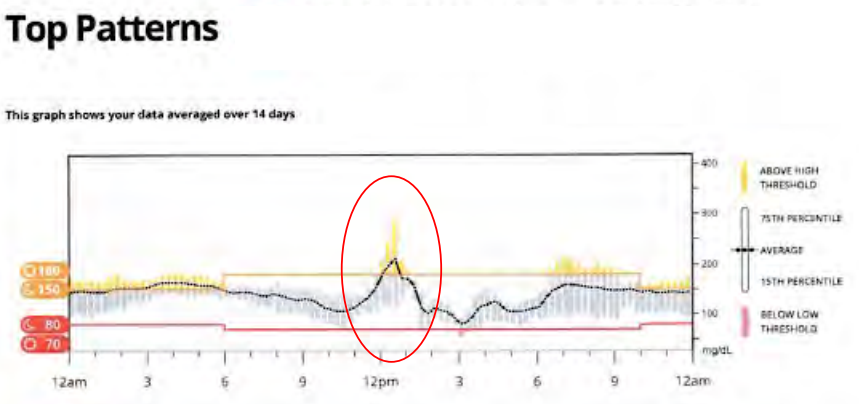
Case 3: Brian



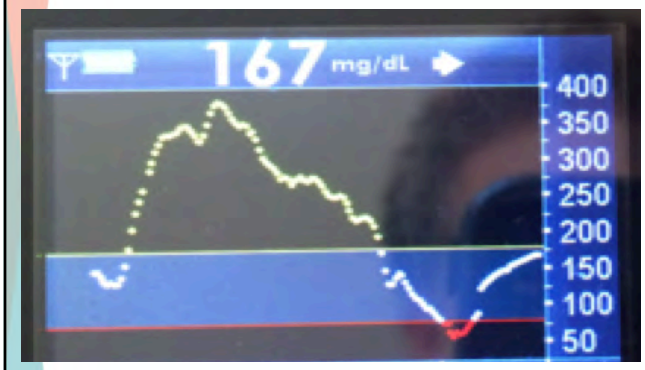
Quick Interpretation

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



60

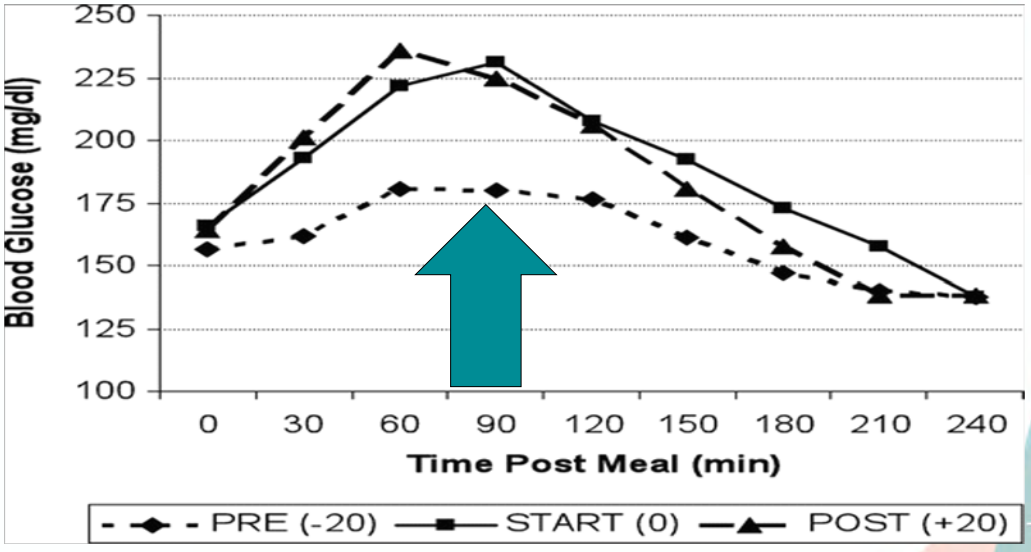
Shark Attack



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

61

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

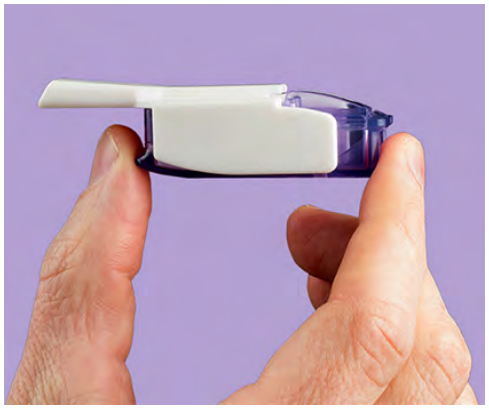


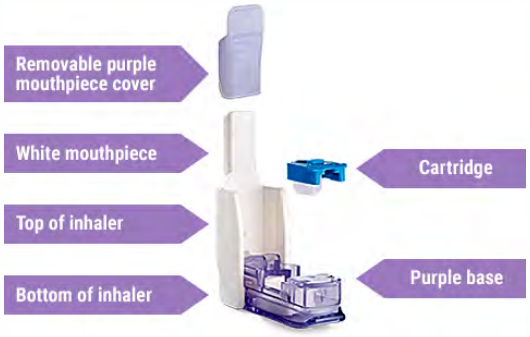
Cobry et al, Diab Tech Therap 2010;12: 173-177

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

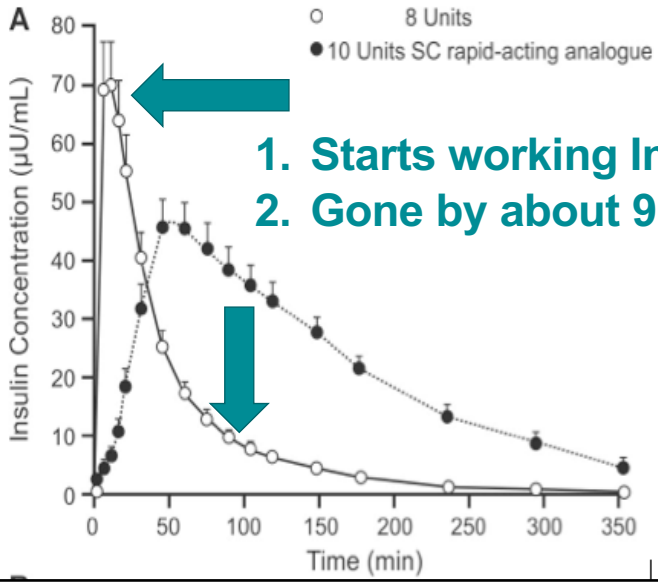
What is Inhaled Insulin?





64

Why is it Cool?



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

65

New, ”Faster Acting” Insulins

Insulin Aspart

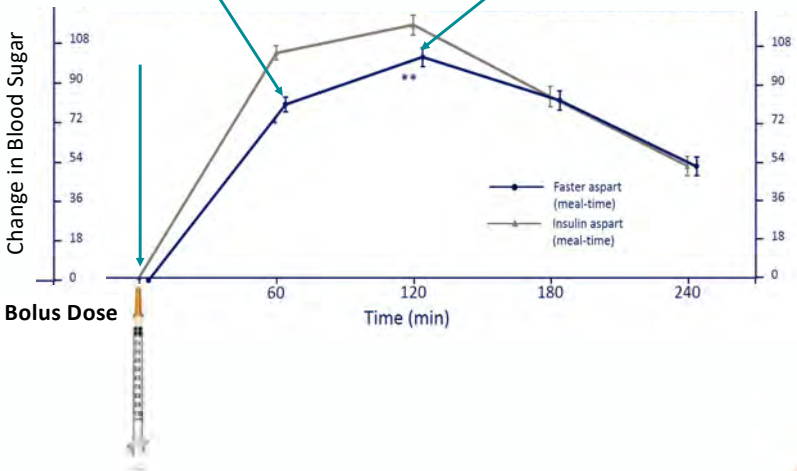
Insulin Lispro-aabc

66

Newer Insulin Aspart has Lower Blood Sugars After a Meal Compared to Insulin Aspart

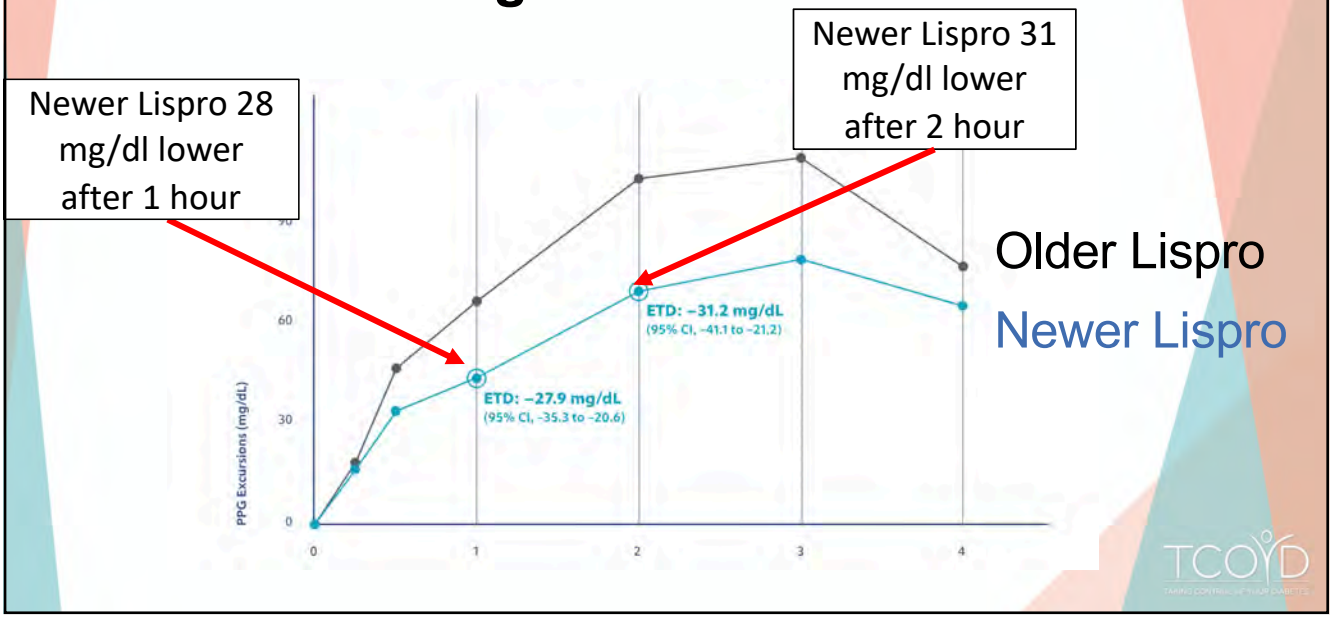
New Insulin Aspart 21 mg/dl lower after 1 hour

New Insulin Aspart 12mg/dl lower after 2 hours



67

New Insulin-Lispro-aabc also has lower blood sugars after a meal



68

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

69

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

70

Thank you!

Jeremy Pettus

WWW.TCOYD.ORG

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71

Lecture 3: 12:00 – 1:30 p.m. PST

Schafer Boeder, MD, Presents:

Lowering Cardiorenal Risk While Improving Glycemic Control with oral agents: Understanding and effective use of the new ADA treatment algorithm

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

Schafer Boeder, MD

Endocrinologist, Assistant Professor of Medicine, UCSD School of Medicine

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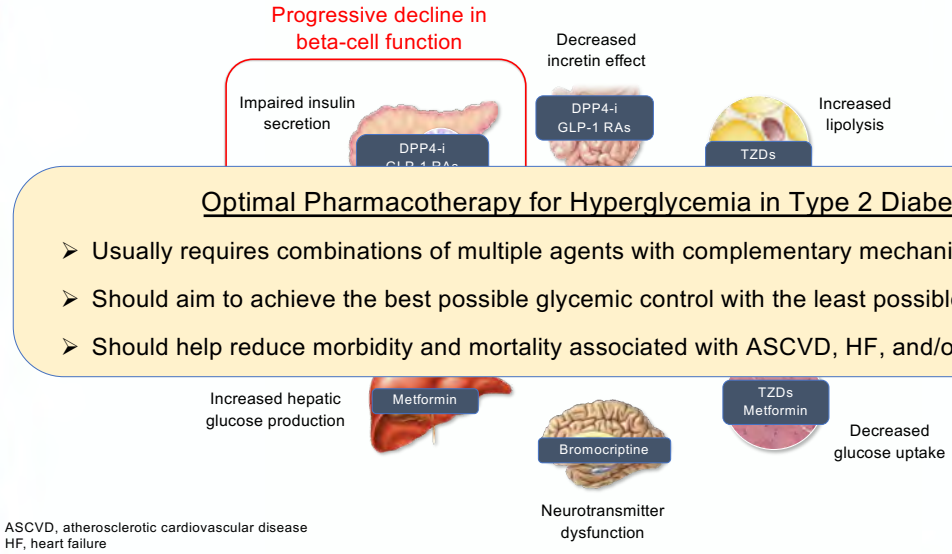
1

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



Optimal Pharmacotherapy for Hyperglycemia in Type 2 Diabetes:

- Usually 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 morbidity and mortality associated with ASCVD, HF, and/or CKD

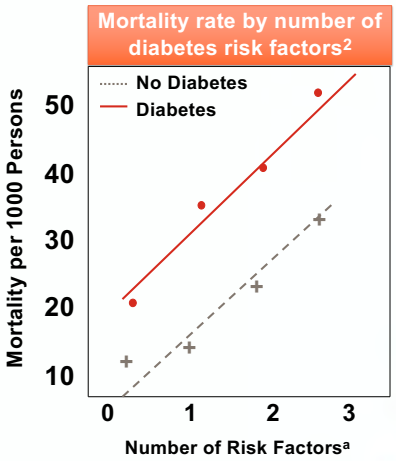
ASCVD, atherosclerotic cardiovascular disease
HF, heart failure
CKD, chronic kidney disease

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

2

Impact of Diabetes on Cardiovascular Mortality

- CV disease is the major cause of morbidity and mortality for individuals with diabetes[1]
- Presence of these risk factors[a] in diabetic patients results in increased incidence of coronary heart disease, CV disease, and mortality in this population[1]
- Life expectancy is reduced by ≥12 years in patients aged 60 years with diabetes and previous CV disease[b,3]
  - Estimated reductions in life expectancy were greater in younger patients

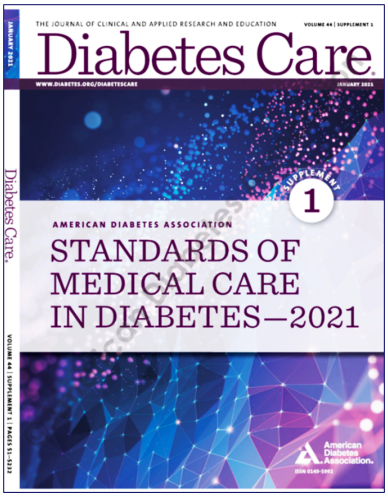


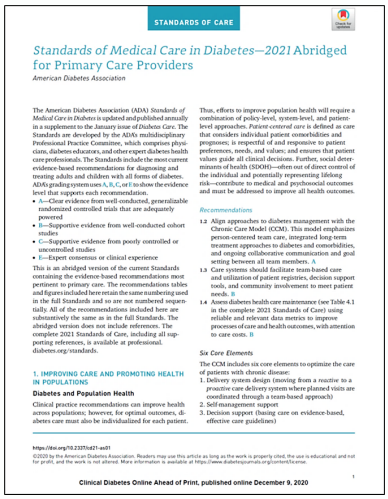
[a]Risk factors analyzed were smoking, dyslipidemia, and hypertension
[b]History of myocardial infarction or stroke

1. American Diabetes Association. *Diabetes Care* 2017;40(Suppl 1):S75-87
2. Data from American Diabetes Association. *Diabetes Care* 1989;12:573-9
3. Emerging Risk Factors Collaboration et al. *JAMA* 2015;314:52-60 (updated 314:1179)

3

American Diabetes Association Standards of Medical Care in Diabetes - 2021




STANDARDS OF CARE

Standards of Medical Care in Diabetes—2021 Abridged for Primary Care Providers

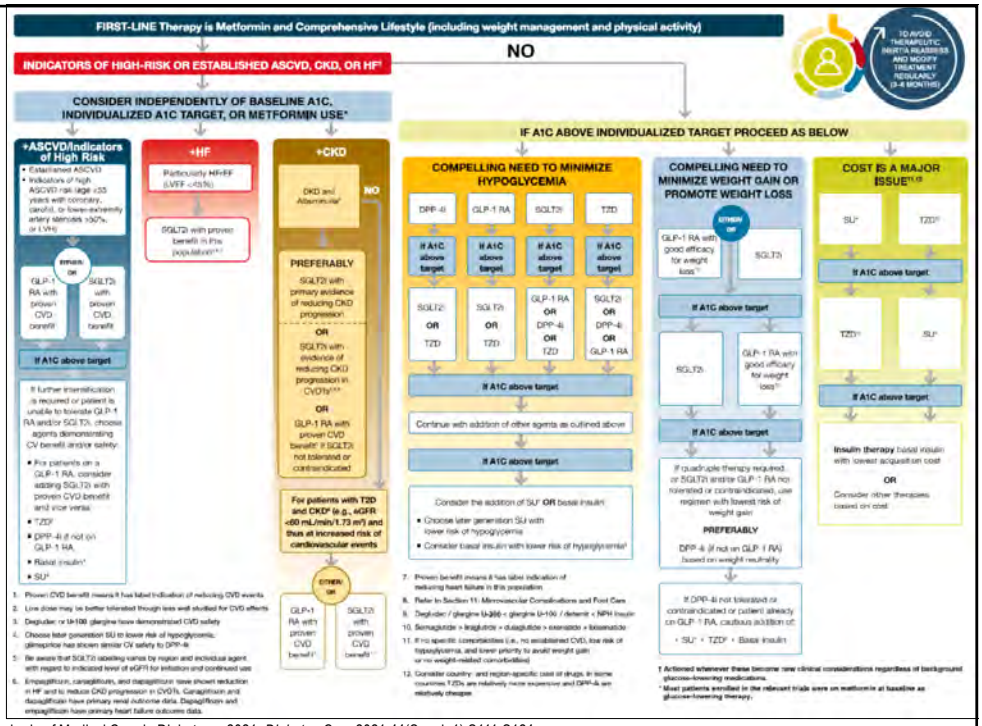
American Diabetes Association

Clinical Diabetes Online Ahead of Print, published online December 9, 2020

American Diabetes Association. Standards of Medical Care in Diabetes - 2021. *Diabetes Care* 2021;44(Suppl. 1):S1-S232
Standards of Medical Care in Diabetes—2021 Abridged for Primary Care Providers. American Diabetes Association. *Clinical Diabetes* 2021;39:14-43.

4

Glucose-lowering Medication in T2D: Overall Approach



Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S111-S124

5

Considerations when deciding upon pharmacotherapy for Type 2 Diabetes

- First-line therapy comprehensive **lifestyle management** and **metformin**
- **QUESTION:** High risk or established **ASCVD, HF or CKD**?
- If **YES**, does ASCVD predominate or does HF or CKD predominate?
- If **NO**, and patient not achieving glycemic targets with metformin alone, consider other factors (need to minimized hypoglycemia, to minimize weight gain or promote weight loss, cost)

Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S111-S124

TCOYD
TAKING CONTROL OF YOUR DIABETES

6

High-risk or established ASCVD, CKD or HF

Consider independently of baseline A1C of individualized A1C target

+ASCVD/Indicators of High Risk

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

Either/Or

GLP-1 RA with proven CV benefit[1]

OR

SGLT2i with proven CVD benefit[1]

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 and vice versa[1]
- TZD[2]
- DPP4i if not on GLP-1 RA
- Basal insulin[3]
- SU[4]

+HF

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]

+CKD

DKD and Albuminuria

NO

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

OR

SGLT2i with evidence of reducing CKD progression in CVOTs

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

For patients with T2D and CKD and thus at increased risk of CV events

Either/Or

GLP-1 RA with proven CV benefit[1]

OR

SGLT2i with proven CVD benefit[1,7]

Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S111-S124

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

Compelling Need to Minimize Hypoglycemia

DPP-4i	GLP-1 RA	SGLT2i[1]	TZD
If A1C above target	If A1C above target	If A1C above target	If A1C above target
SGLT2i[1] **OR** TZD	SGLT2i[1] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[1] **OR** DPP-4i **OR** GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU[2] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[3]

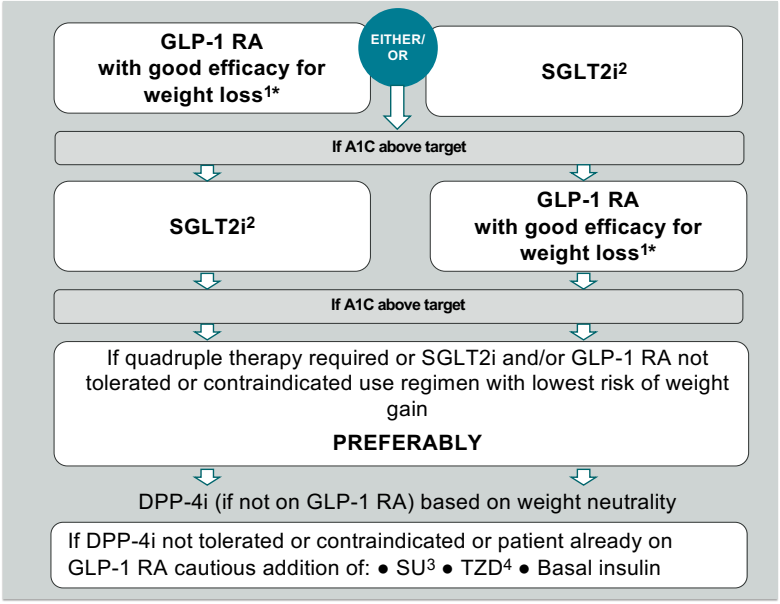
Hierarchy

Degludec/ glargine U300 → glargine U100/ detemir → NPH insulin

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

Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S111-S124

Compelling Need to Minimize Weight Gain or Promote Weight Loss



[1]**Hierarchy (for weight loss effect)**

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

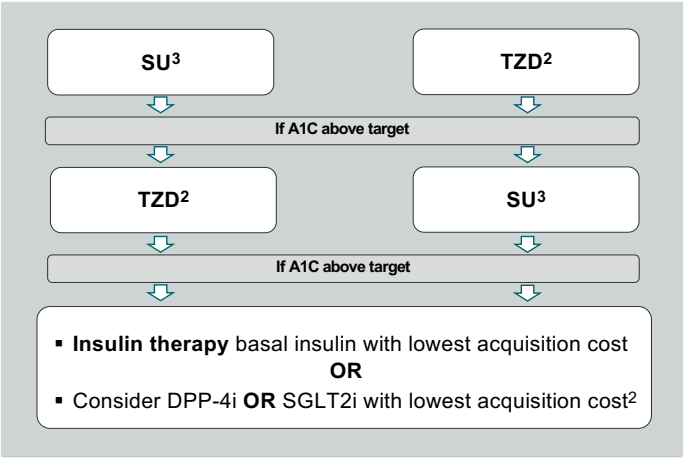
[3] Chose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i

[4] Low dose may be better tolerated though less well studied for CVD effects

Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S111-S124

9

Second-Line Therapy for T2D if Cost if a Major Issue[1,2]



[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

[4] Low dose may be better tolerated though less well studied for CVD effects

Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S111-S124

10

Case 1: 41-year-old female with a 4 year history of type 2 diabetes

- Medical history: hypertension, dyslipidemia and CAD s/p MIx2
- Family Hx: Adopted
- Notes:
  - Diabetes meds: metformin, SFU, DPP4i, TZD and basal insulin
  - Other meds: Statin, PCSK9 inhibitor, beta blocker and aspirin
  - Current A1C: 11.4% (10.6% one year ago, 10.1% two years ago)
  - Creatinine: 1.7 mg/dL, eGFR 51 mL/min/1/73 m^2, UACR 315 mg/gm

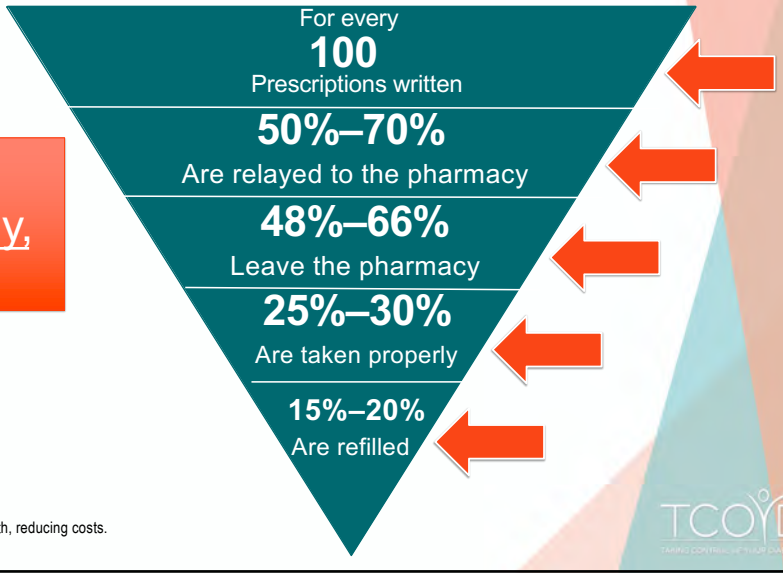
HTN, hypertension
NAFLD, non-alcoholic fatty liver disease
CAD, coronary artery disease
MI, myocardial infarction
SFU, sulfonylurea
DPP-4i, dipeptidyl peptidase-4 inhibitor
eGFR, estimated glomerular filtration rate
UACR, urine albumin creatinine ratio

What is the most likely reason this patient has not achieved his A1C goal?

A	She needs a SGLT2 inhibitor
B	She needs a GLP-1RA
C	Poor adherence with her medication
D	Her diabetes regimen is too complicated
E	She needs prandial insulin with dinner

Poor Adherence and Persistence with Type 2 Medications in the Real World

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



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

13

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

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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
- Individualize glycemic targets based on key patient factors (e.g., life expectancy, co-morbidities)
- Always address the modifiable cardiovascular risk factors (overweight and obesity, hypertension, dyslipidemia, 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

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

Metformin

- eGFR <60 to ≥45 mL/min OK to use full dose/monitor renal function
- eGFR <45 to >30 mL/min 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, not approved for this indication)
- Effective in NASH (not approved for this indication)
- Weight gain
- Be cautious in combo with insulin (fluid retention); Contraindicated in the setting of HF
- Fracture risk is increased (postmenopausal women)
- Risk of bladder cancer questionable; risk is low (~1/5000 in the general pop.)

Case 2: 38-year-old female diagnosed at age 35

- PMH: Obesity, HTN, dyslipidemia, and NAFLD
- Strong family history of CAD and T2D
- A1C 9.5% on maximum doses of metformin and SFU
- No home glucose monitoring data
- BMI 44 kg/m^2; eGFR 46 mL/min/m^2; LDL-C 176 mg/dL
- BP normally above 140/90 mmHg; on no anti-HTN meds
- No known ASCVD

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What therapeutic intervention would you change/initiate if you were evaluating this patient?

A	Add pioglitazone at the highest dose to current regimen
B	Stop SFU and start basal bolus therapy
C	Stop SFU and add an SGLT-2i
D	Continue SFU and add a SGLT-2i with lifestyle education
E	Stop SFU and add combination of DPP-4i & SGLT-2i

18

Case 2 Continued: Treatment History

- A SGLT2 inhibitor combination pill was added to her regimen in addition to having her see a dietician and diabetes educator.
- SFU was continued
- High-dose statin was also started for LDL-C target of at least <100 mg/dL
- Follow-up was arranged for 1 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
- The A1C fell from 9.5% to 7.7% after 3 months of therapy
- SBP decreased from 150 to 141 mmHg and an ARB was added

High-risk or established ASCVD, CKD or HF

Consider independently of baseline A1C of individualized A1C target

+ASCVD/Indicators of High Risk

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

Either/Or
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OR
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- DPP4i if not on GLP-1 RA
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- SU[4]

+HF

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]

+CKD

DKD and Albuminuria

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SGLT2i with primary evidence of reducing CKD progression

OR

SGLT2i with evidence of reducing CKD progression in CVOTs

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

For patients with T2D and CKD and thus at increased risk of CV events

Either/Or
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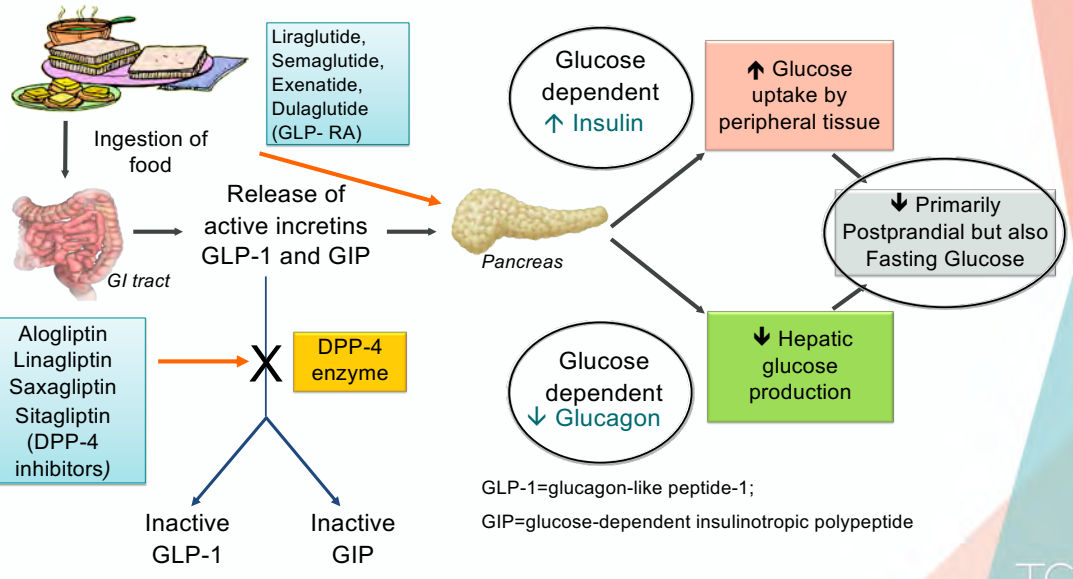
DPP-4 Inhibitors

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 ~0.5-1.0% 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 (saxa- and alo-), 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 (and some are available in combination with pioglitazone or an SGLT2i)

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 / GLP-1 RA



GLP-1=glucagon-like peptide-1;
GIP=glucose-dependent insulinotropic polypeptide

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

DPP-4 Inhibitors: Generic and Trade Names

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

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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)

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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), Fournier's Gangrene, acute kidney injury, UTI, risk of amputation (discussed later), bone fractures
Clinical Pearls	• Canagliflozin approved for renal protection; Can be used with an eGFR down to 30 cc/min • Empa- dapa- and canagliflozin showed positive CVD outcome trials (discussed later) • Reduced incidence of heart failure has ben observed with SGLT2i use • Can be added to any other oral agent or injectable • Inform women to practice good hygiene and be aware of risk of genital mycotic infections

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

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Generic and Trade Names: SGLT-2 inhibitors

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

Canagliflozin:
- Suggested starting dose: 100 mg daily before first meal of day (eGFR >30 mL/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 > 45 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 for both doses >45 mL/min)
- Increase to 25 mg daily if tolerating and need additional glycemic control

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

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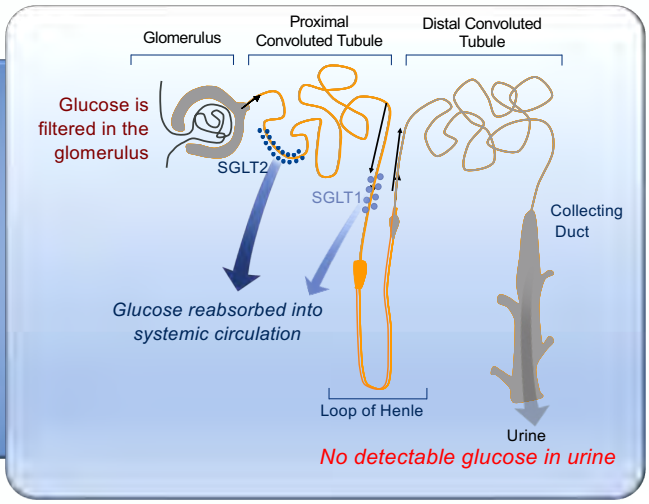
Renal Handling of Glucose in Person Without Diabetes

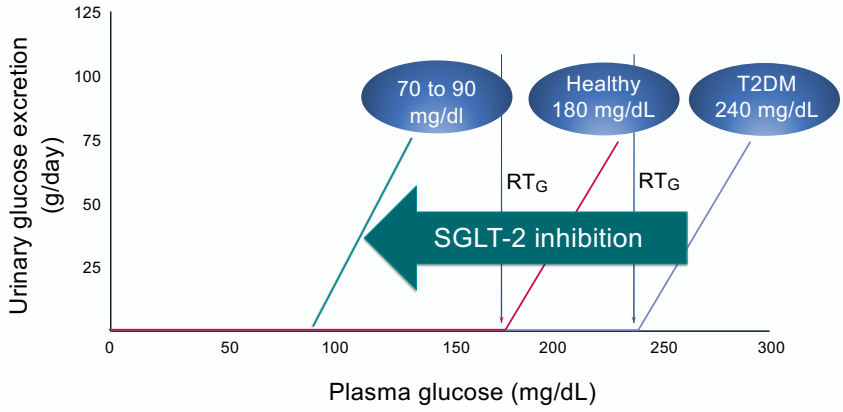
- 180 g/day/1.73 m^2 is filtered glucose load[1]
- SGLT-2 transports 90% of filtered glucose out of the tubular lumen[1-4]



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 Non-diabetic, T2D, 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

- Diabetic ketoacidosis (DKA):
  - Extremely low incidence, mostly type 1's and type 2's receiving insulin
  - Complex mechanism related to paradoxical increase in glucagon promoting ketosis in the setting of glycosuria so extreme hyperglycemia is limited (watch for "euglycemic DKA")
- Be especially cautious in women with a history of UTIs, pyelonephritis and/or genital mycotic infections
- August 2018: New warning for extremely rare but serious infection called Fournier's gangrene
- March 2020: FDA guidance on discontinuation prior to surgery
- August 2020: FDA removed *boxed warning* about amputation risk from canagliflozin label (still need to be aware of increased risk, but lower than previously described)

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

29

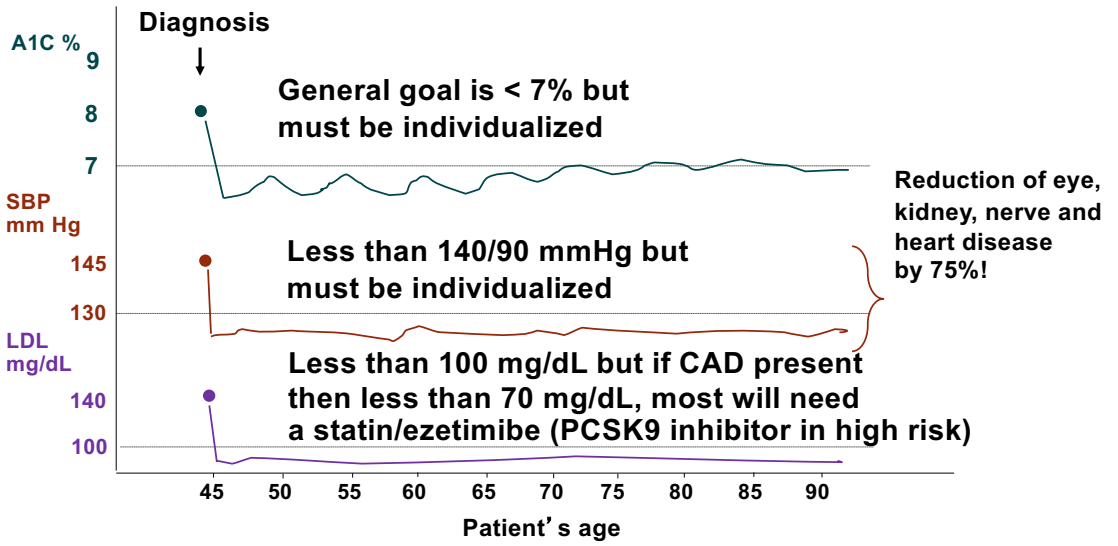
What is the most common cause of death in type 2 diabetes?

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

30

Primary Objectives of Effective Management:

Important Basics…The 'ABCs"



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

31

Management of Modifiable CV Risk Factors

- The 10-year risk of a fist ASCVD event should be assessed to better stratify ASCVD risk and help guide therapy
- ACC/AHA Risk Estimator Plus (tools.acc.org/ASCVD-Risk-Estimator-Plus)

Blood Pressure Management

Individualize BP Goals:

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

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

*If it can be safely attained

Dyslipidemia Management

Individualize lipid Goals:

LDL-C < 100 mg/dL in all PWD

LDL-C<70 mg/dL if ASCVD present

Triglycerides less than 200 mg/dl

HDL as high as you can get it!

Cardiovascular disease and risk management: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S125-S150

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Use of Statins in Diabetes

Primary Prevention:

- 40-75 yo without ASCVD, moderate intensity statin
- 20-39 yo without ASCVD but with additional risk factors, may be reasonable to initiate statin therapy
- If at higher risk (50-70 yo and/or multiple CV risk factors), high-intensity statin
- 10-year ASCVD risk ≥20%, may be reasonable to add ezetimibe to maximally tolerated statin to reduce LDL-C by ≥50%

Secondary Prevention:

- High-intensity statin for all ages if DM and established ASCVD
- If LDL-C remains ≥70 mg/dL despite maximally tolerated statin, consider ezetimibe or PCSK-9 inh.

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

*Once-daily dosing. XL, extended release.

Cardiovascular disease and risk management: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S125-S150

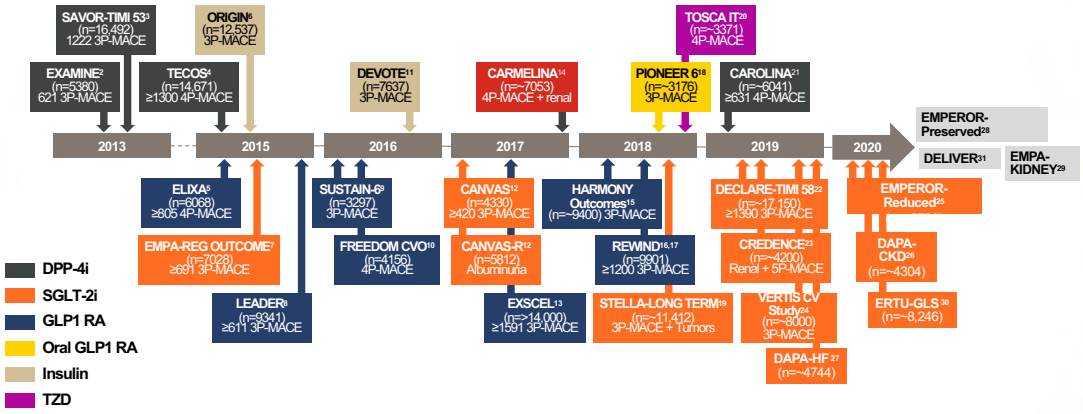
Management of Hypertriglyceridemia

- Elevated triglycerides (TGs) combined with low HDL levels are part of the insulin resistant state and metabolic syndrome
- Diet, exercise and improved glycemic control will improve but not typically normalize elevated TG levels in type 2 DM
- The goal is to get the TGs to below 200mg/dl, which in turn will elevate the HDL levels
- Fibric acid derivatives such as fenofibrate are commonly used to treat high TGs
- Icosapent ethyl is an omega-3 fatty acid that has the formal indication from the FDA to reduce MI and strokes in patient who have or are at risk for ASCVD and have TGs ≥150mg/dL*

*Icosapent ethyl is indicated as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥150 mg/dL) and established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease

N Engl J Med 2019; 380:11-22 REDUCE-IT trial

Overview of CVOTs of Glucose-lowering Drugs



Timings represent estimated completion dates as per ClinicalTrials.gov

1. Johansen OE. 2015
2. White WB et al. 2013
3. Scirica BM et al. 2013
4. Green JB et al. 2015
5. Pfeffer MA et al. 2015
6. ORIGIN. 2012
7. Zinman B et al. 2015
8. Marso SP et al. 2016
9. Marso SP et al. 2016
10. NCT01455896
11. Marso SP et al. 2017
12. Neal B et al. 2017
13. NCT01144338
14. NCT01897532
15. NCT02465515
16. NCT02065791
17. Gerstein HC et al. 2017
18. NCT02692716
19. NCT02479399
20. NCT00700856
21. NCT01243424
22. NCT01730534
23. NCT01394952
24. NCT01986881
25. NCT03057977
26. NCT03036150
27. NCT03036124
28. NCT03057951
29. NCT03594110
30. NCT03717194
31. NCT03619213

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	16,5	5	14	6	6
Results	2013	2013	June 2015	2017	2017

NEUTRAL

A Review on Cardiovascular Outcome Studies of Dipeptidyl Peptidase-4 Inhibitors: Indian J Endocrinol Metab. 2018 Sep-Oct; 22(5): 689–695.

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

Study	EMPA-REG	CANVAS	DECLARE	DAPA-HF	EMPEROR -Reduced	VERTIS-CV
SGLT-2i	empagliflozin	canagliflozin	dapagliflozin	dapagliflozin	empagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo	placebo	placebo
N	7	4	22	4	37	3
Results	Sept 2015	2017	2018	2019	2020	2020

POSITIVE POSITIVE POSITIVE POSITIVE POSITIVE NEUTRAL

Dapagliflozin was the first SGLT2 inhibitor approved by the US FDA indicated to treat patients with HFrEF (LVEF ≤ 40%). Based on results of the DAPA-HF Trial.*

* McMurray et al. N Engl J Med 2019; 381:1995-2008

Courtesy of Silvio Inzucchi MD, Yale University

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CV and Renal Risk Reduction With SGLT-2 inhibitors

Empagliflozin (JARDIANCE) (based on EMPA-REG trial data)

- To reduce the risk of CV death in adult patients with T2D mellitus and established CV disease
- *Also, FDA Fast Track designation provided to reduce the risk of CV death and hospitalization for heart failure in people with CHF (based on EMPEROR-Reduced trial)*

Canagliflozin (INVOKANA) (based on CANVAS and CREDENCE program data)

- To reduce the risk of major adverse CV events in adults with T2D and established CV disease
- To reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with T2D and diabetic nephropathy with albuminuria

Dapagliflozin (FARXIGA) (based on DECLARE and DAPA-HF program data)

- To reduce the risk of hospitalization for heart failure in adult with T2D and established CVD or multiple CV risk factors
- To reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with T2D and diabetic nephropathy with albuminuria

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Renal Protection With SGLT-2 inhibitors

- **Canagliflozin (CREDENCE study):** Reduce the risk of end-stage kidney disease, doubling of the serum creatinine, CV death and hospitalization for HF in patients with T2D with nephropathy (eGRF between 30 and 90 mL/min) and albuminuria > 300 mg/gm
- **Dapagliflozin (DAPA-CKD study):** Reduced the risk of the composite of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from CV or renal cause in patients with CKD (regardless of the presence or absence of diabetes)
- **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

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	Semaglutide	Exenatide LR	Albiglutide	Dulaglutide	Oral semaglutide
Comparator	placebo	placebo	placebo	placebo	placebo	placebo	placebo*
N	16,5[illegible]	14,0[illegible]	6,0[illegible]	5,4[illegible]	9,4[illegible]	8,3[illegible]	3,1[illegible]
Results	POSITIVE [illegible]016	NEUTRAL [illegible]015	POSITIVE [illegible]016	NEUTRAL [illegible]018	POSITIVE [illegible]019	POSITIVE* [illegible]019	POSITIVE* [illegible]2019

*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

CV Risk Reduction With GLP-1 RAs

Liraglutide (based on LEADER data)

- To reduce the risk of major adverse CV events (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with T2D and established CVD

Semaglutide (based on SUSTAIN 6 data)

- To reduce the risk of major adverse CV events (MACE) including CV death, non-fatal heart attack, or non-fatal stroke in adults with T2D and established CVD

Dulaglutide (based on REWIND data)

- For the reduction of major adverse CV events (MACE) in adults with T2D who have established CV disease or multiple CV risk factors

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Not all CVOTs are Created Equal

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

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

42

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, HF, or CKD. If not, then whether hypoglycemia, weight, or financial status are dominant issues. Shared decision making is KEY!

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Key Principles of Management of T2D

- GLP-1 RA are the preferred first injectable therapy over basal insulin except in 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
- ASCVD disease is the most common cause of death and prevention strategies need to be emphasized (A1C, blood pressure, cholesterol, smoking cessation, antiplatelet therapy, and diabetes drugs with cardiorenal benefits.

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Lecture 4: 2:00 – 3:15 p.m. PST

Steven V. Edelman, MD, Presents:

Practical Application of individualized insulin strategies and a close look at the cardiovascular effects of the GLP1-RAs

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

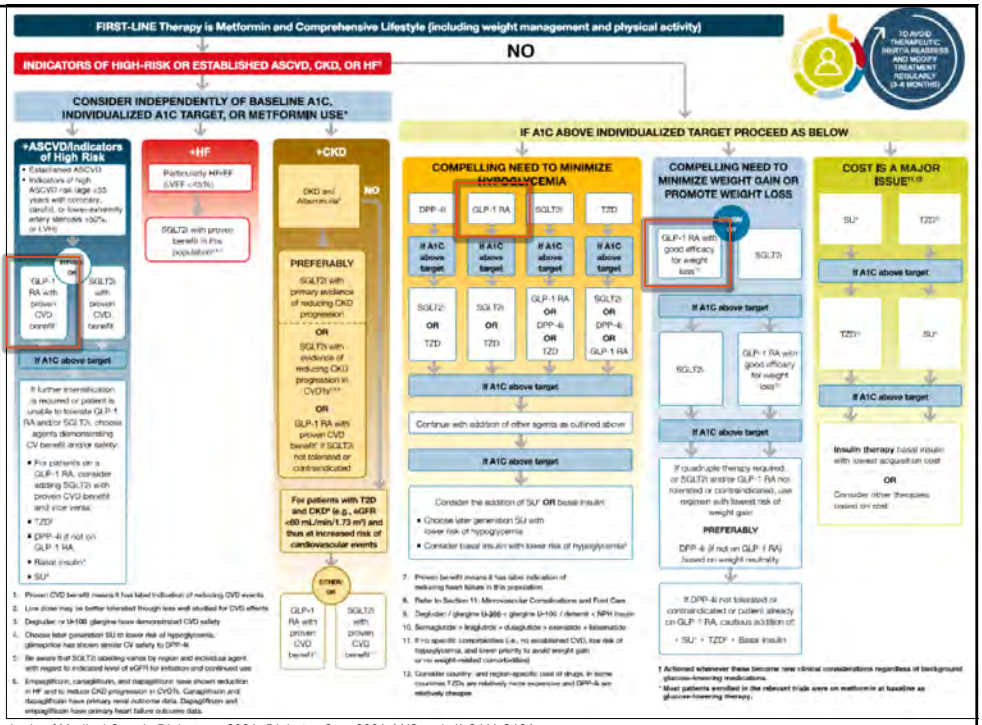
Steven V. Edelman, MD
Clinical Professor of Medicine
University of California San Diego School of Medicine
Director, Diabetes Care Clinic, San Diego VA Medical Center
Founder and Director, Taking Control Of Your Diabetes

WWW.TCOYD.ORG
Taking Control Of Your Diabetes, 501(c)3 is a not-for-profit educational organization.

1

Glucose-lowering Medication in T2D: Overall Approach

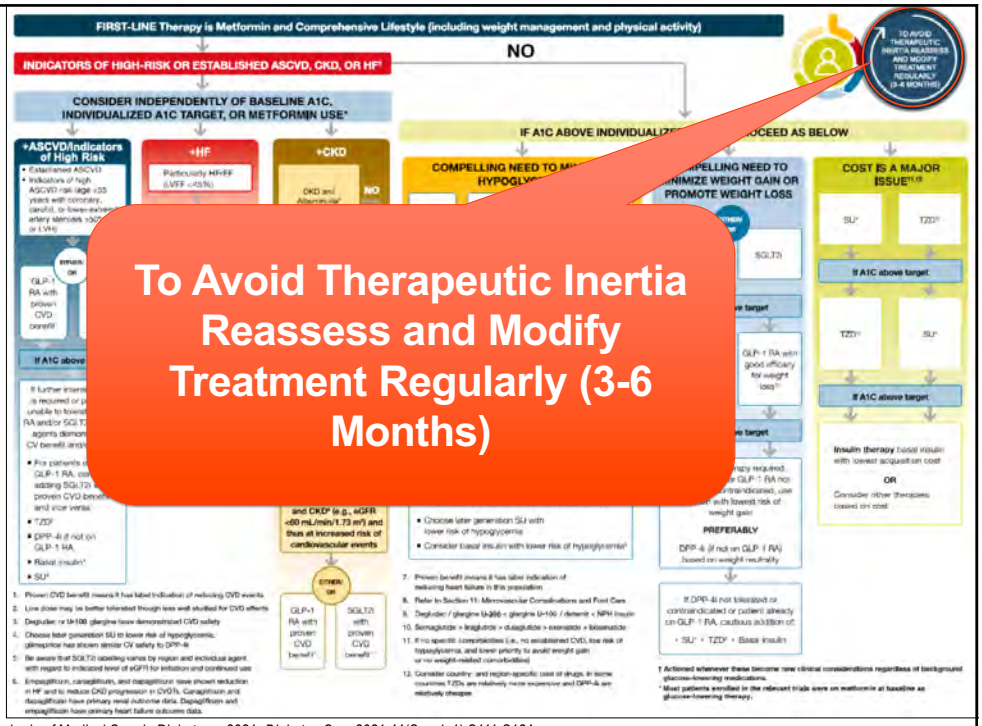
GLP-1 RAs play a prominent role as the first injectable therapy in many clinical situations in T2D



Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S111-S124

2

Glucose-lowering Medication in T2D: Overall Approach



Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S111-S124

3

Therapeutic Inertia Plays an Important Role in the Delay of Intensification of Diabetes Therapy

Substantial inertia exists at each sequential intensification step

- Patient on 1 OAD → 1.6–2.9 yrs → Adding 2nd OAD*
- Patient on 2 OADs* → 6.9–7.2 yrs → Adding 3rd OAD*
- Patient on 3 OADs* → 6–7.1 yrs → Adding insulin* → 3.7 yrs → Adding GLP-1 RA, premixed or bolus insulin**

*From time when HbA1c was ≥7.0%, ≥7.5% or ≥8.0%;
**From time when HbA1c was ≥7.5%.

Khunti K, et al. *Diabetes Care* 2013;36:3411–7
Khunti K, et al. *Diabetes Obes Metab* 2016;18:401–9

TCOYD TAKING CONTROL OF YOUR DIABETES

4

Case 1: 69-year-old female with type 2 diabetes for 22 years

- History of central obesity, dyslipidemia, hypertension, and pancreatitis from elevated triglycerides
- Recent myocardial infarction s/p CABG
- On metformin, SFU, TZD and a DPP4 inhibitor for over 5 years
- A1C 8.6%
- Creatinine 1.4 mg/dL, eGFR 56 mL/min
- SMBG data: tests in the morning and occasionally at bedtime, all values over 200 mg/dl

5

Which of the following would you recommend for this patient?

(currently on metformin, SFU, TZD and DPP4i)

A	Initiate an SGLT-2 inhibitor
B	Initiate a GLP-1 Receptor Agonist (RA)
C	Initiate premixed insulin (70/30) BID
D	Initiate basal insulin
E	Initiate a fixed combination of a basal insulin and a GLP-1 RA

6

High-risk or established ASCVD, CKD or HF

Consider independently of baseline A1C of individualized A1C target

+ASCVD/Indicators of High Risk

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

Either/Or

GLP-1 RA with proven CV benefit[1]

OR

SGLT2i with proven CVD benefit[1]

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 and vice versa[1]
- TZD[2]
- DPP4i if not on GLP-1 RA
- Basal insulin[3]
- SU[4]

+HF

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]

+CKD

DKD and Albuminuria

NO

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

OR

SGLT2i with evidence of reducing CKD progression in CVOTs

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

For patients with T2D and CKD and thus at increased risk of CV events

Either/Or

GLP-1 RA with proven CV benefit[1]

OR

SGLT2i with proven CVD benefit[1,7]

Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. *Diabetes Care* 2021;44(Suppl. 1):S111-S124

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

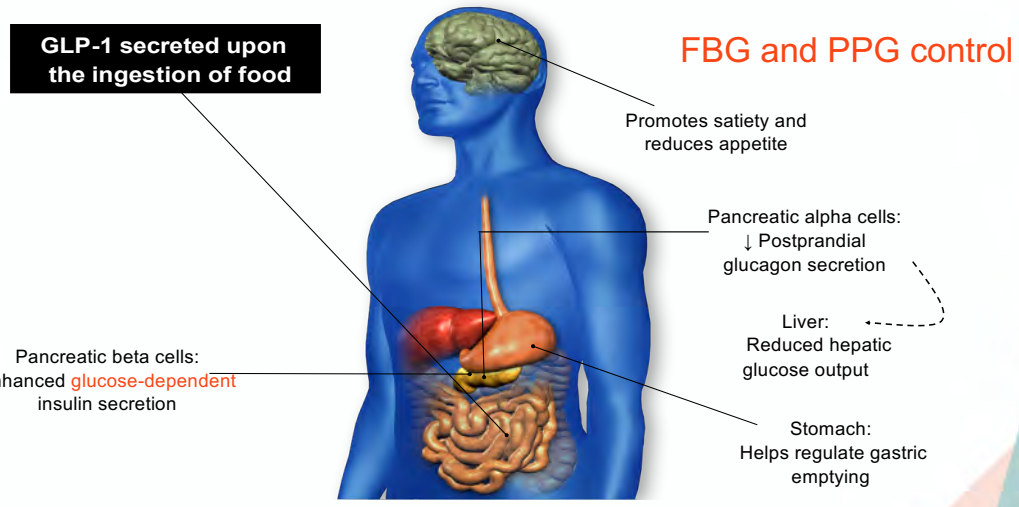
7

Basal Insulin	GLP-1 RA
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	Escalate does to the highest tolerated dose
Need to institute SMBG	SMBG not absolutely necessary
Need frequent follow up when initiating basal insulin (days to weeks)	Short-term follow up not as crucial
Weight gain	Weight loss
Hypoglycemia risk	No to minimal hypoglycemia risk
No GI side effects	GI side effects relatively common

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

8

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.

9

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 A1C) • Shorter-acting GLP-1 RAs have greater effects on PPG • Weight loss • No hypoglycemia (unless used with insulin or SFU) • Once daily, twice daily and once weekly formulations
Concerns	• GI side effects (typically nausea; most mild to moderate in severity) • 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 • Two GLP-1 RAs (liraglutide and lixisenatide) are available in a once-daily fixed-ratio combination with basal 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.

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GLP-1 RAs: Generic and Trade Names

	Generic Name	Trade Name
GLP-1 Receptor Agonists	**Exenatide** Twice-daily Once-weekly	 Byetta Bydureon
	Liraglutide Once-daily	 Victoza
	Dulaglutide Once-weekly	 Trulicity
	Lixisenatide Once-daily	 Adlyxin
	Semaglutide Once weekly	 Ozempic
	Oral Semaglutide Once daily	 Rybelsus

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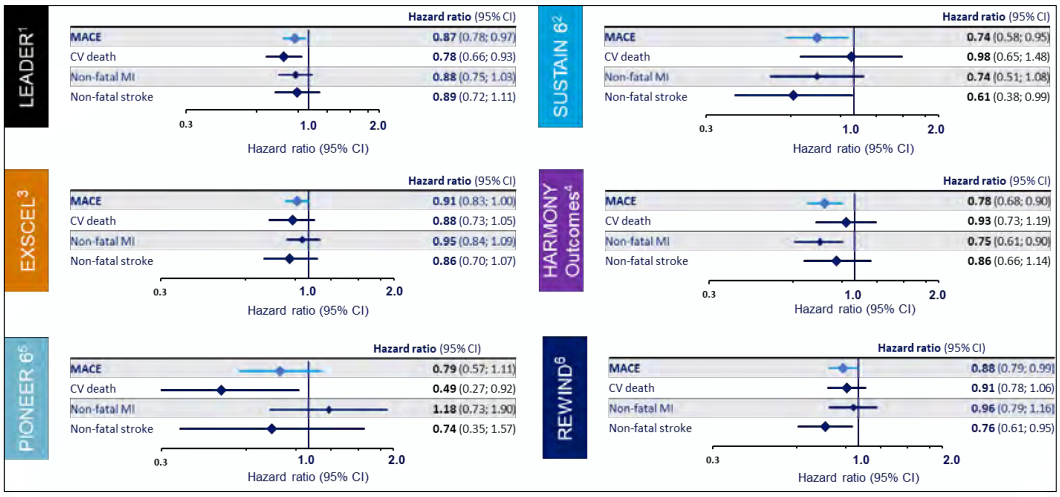
GLP-1 RAs: Generic and Trade Names (cont.)

	Generic Name	Trade Name
Basal insulin + GLP-1 RA Fixed-Ratio Combinations	iGlarLixi (insulin glargine U-100 + lixisenatide)	Soliqua
	IDegLira (insulin degludec + liraglutide)	Xultophy

12

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



ELIXA with lixisenatide showed CV safety

CV, cardiovascular; MI, myocardial infarction; MACE, major cardiovascular events

1. Marso SP et al. N Engl J Med 2016;375:311–322; 2. Marso SP et al. N Engl J Med 2016;375:1834–1844; 3. Holman RR et al. N Engl J Med 2017;377:1228–1239;
4. Hernandez AF et al. Lancet 2018;392:1519–1529; 5. Husain M et al. N Engl J Med 2019; DOI:10.1056/NEJMoa1901118; 6. Gerstein HC et al. Lancet 2019; S0140-6736:31149-31153

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

0 1 2
◀ Favors Treatment Favors Placebo ▶

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).

Case 2: 72-year-old woman with T2D for 23 years

- On maximal doses of metformin, SFU, 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 kg/m^2)
- eGFR 65 mL/min
- Her A1C is 8.8 % (goal for this patient at least less than 8.0%)
- Average FBS is in the 180 mg/dL range (does not test at other times)

15

What would you recommend now for this patient?
(currently on metformin, SFU and SGLT2i)

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

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Case 2 continued

- She agreed to start a once weekly GLP-1 RA (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 mild nausea that resolved after 2-3 weeks
- She had several episodes of mild hypoglycemia which resolved when SFU was discontinued
- Over the next three months she lost 8 pounds and her A1C fell from 8.8% to 7.2%

Before GLP-1 RA*

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

After GLP-1 RA*

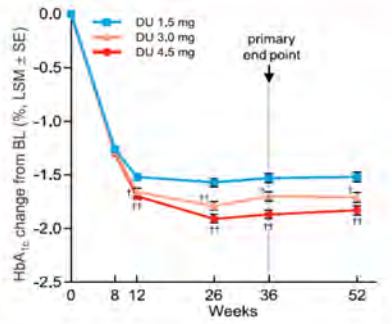
FBS (mg/dl)	PPG (mg/dl)
Average 139	Average 167

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

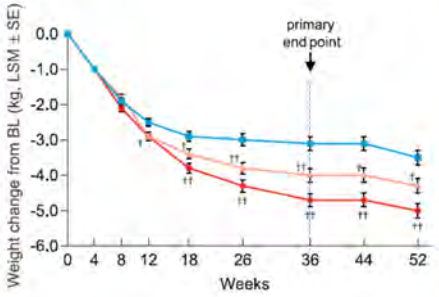
17

Higher-Dose Dulaglutide (3.0 and 4.5 mg QW): Significantly Greater A1C and Body Weight Reduction

Change in A1C at 36 and 52 Weeks



Change in Weight at 36 and 52 Weeks



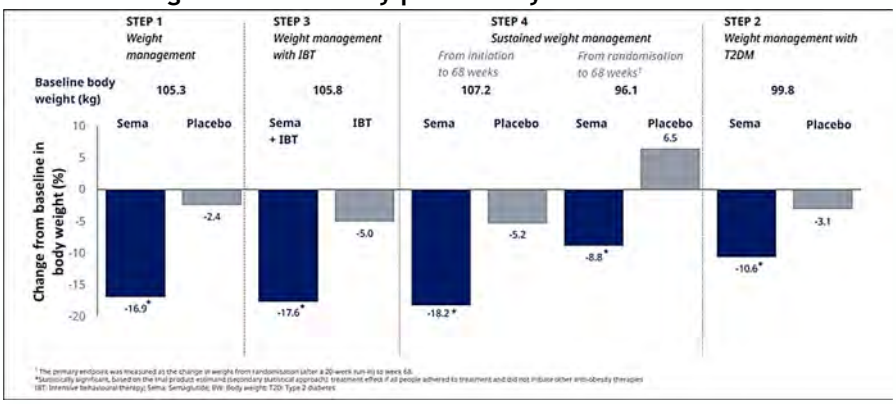
- Higher dose dulaglutide had similar safety profile compared with 1.5 mg dose
- Expanded doses recently approved by FDA and added to product label
- Allows intensification of therapy in patients treated with dulaglutide who need additional A1C or body weight control (without having to change medication)

Frías JP, Bonora E, Nevarez Ruiz L, et al. Diabetes Care. 2021 Jan 4 Epub ahead of print.
TRULICITY (dulaglutide) US Package Insert, Eli Lilly and Company, Accessed February 5, 2021

18

Higher Doses of Semaglutide Have Been Assessed in T2D (2.0 mg QW) and Obesity (2.4 mg QW) (pending FDA review)

STEP Trials:
Phase 3 semaglutide for obesity preliminary results



https://investor.novonordisk.com/q2-2020-presentation. Accessed September 18, 2020
https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=43581

19

Fixed-Ratio Combinations of Basal Insulin and GLP-1 RA

IDegLira (XULTOPHY)
(insulin degludec + liraglutide)

- 1 unit IDegLira contains 1 unit insulin degludec and 0.036 mg liraglutide
- Dosed just like any basal insulin (based on patient's individualized fasting glucose target
- Maximum dose is 50 units (50 units insulin degludec and 1.8 mg liraglutide)
- Injected once daily at same time each day with or without food

iGlarLixi (SOLIQUA)
(insulin glargine U-100 + lixisenatide)

- 1 unit iGlarLixi contains 1 unit insulin glargine U-100 and 0.33 mcg lixisenatide
- Dosed just like any basal insulin (based on patient's individualized fasting glucose target
- Maximum dose is 60 units (60 units insulin glargine and 20 mcg lixisenatide)
- Injected once daily within one hour prior to the first meal of the day

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Fixed-Ratio Combinations: IDegLira vs iGlarLixi

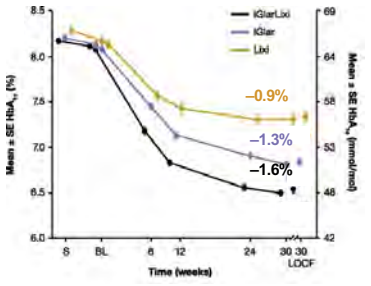
IDegLira (insulin degludec + liraglutide)	iGlarLixi: (insulin glargine + lixisenatide)
• **10 U** = 10 U insulin degludec + 0.36 mg liraglutide • **50 U** = 50 U insulin degludec + 1.8 mg of liraglutide	• **15 U** = 15 U insulin glargine + 5 mcg lixisenatide • **30 U** = 30 U insulin glargine + 10 mcg lixisenatide • **60 U** = 60 U insulin glargine + 20 mcg lixisenatide
STARTING DOSE: 16 U (which has 16 U insulin degludec + 0.58 mgs liraglutide)	**STARTING DOSE:** **If patient on oral agents or GLP-1 RA:** Start with 15 U (15 U insulin glargine + 5 mcg lixisenatide **If patient on basal insulin:** If basal insulin dose is <30 U, start at 15 U (15 U insulin glargine + 5 mcg lixisenatide) If basal insulin dose is ≥30 U, start at 30 U (30 U insulin glargine + 10 mcg lixisenatide)
Titrate according to FBG, as if you were using basal insulin alone, generally 2 U at a time, usually every 3-4 days	Titrate according to FBG, as if you were using basal insulin alone, generally 2-4 U at a time, usually weekly
Maximum dose is 50 U (50 U insulin degludec and 1.8 mg liraglutide)	Maximum dose is 60 U (60 U insulin glargine and 20 mcg lixisenatide)

PDR (PI for both) 2017

21

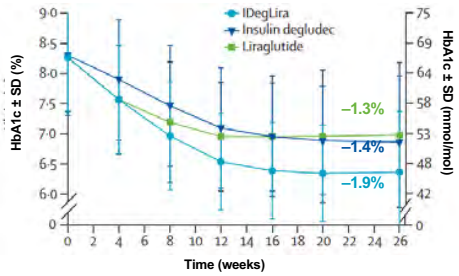
Both Fixed-Ratio Combinations Significantly Reduced A1C vs Individual Components in Patients with T2D Suboptimally Controlled on Oral Agents

LixiLan-O[1]



iGLarLixi was non-inferior to iGlar (p<0·0001) and superior to lixisenatide for change in HbA1c (p<0.0001)

DUAL I[2]



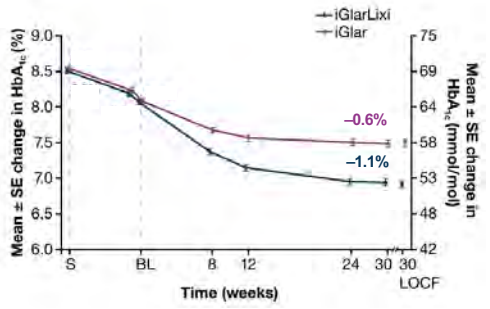
IDegLira was non-inferior to IDeg (p<0·0001) and superior to liraglutide for change in HbA1c (p<0.0001)

1. Rosenstock J, et al. Diabetes Care 2016;39:2026–35
2. Gough SC, et al. Lancet Diabetes Endocrinol 2014;2:885–93

22

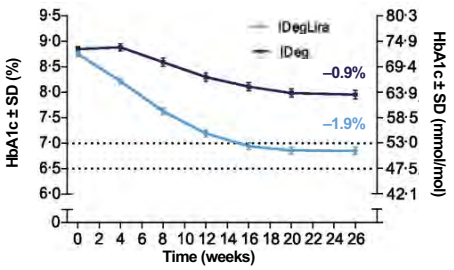
Both Fixed-Ratio Combinations Significantly Reduced A1C vs Basal Insulin Alone in Patients with T2D Suboptimally Controlled on Basal Insulin (± Oral Agents

LixiLan-L[1]



iGLarLixi was superior to iGlar for change in HbA1c (p<0.0001)

DUAL II[2]



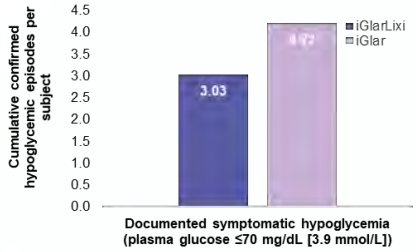
IDegLira was superior to IDeg for change in HbA1c (p<0.0001)

1. Aroda V, et al. Diabetes Care 2016;39:1972–80
2. Buse JB, et al. Diabetes Care 2014;37:2926–33

23

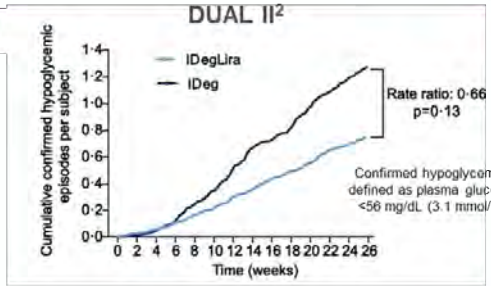
Hypoglycemia Events Were Lower With Fixed-Ratio Combination, Despite Better A1C Control

LixiLan-L[1]



Number of hypoglycemic events per patient year was lower with iGlarLixi versus iGlar

DUAL II[2]



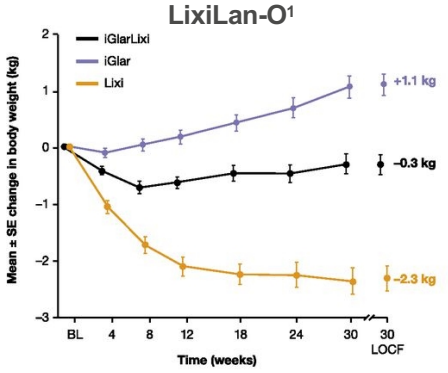
Rate of confirmed hypoglycemic episodes was numerically lower with IDegLira versus IDeg

1. Aroda V, et al. Diabetes Care 2016;39:1972–80
2. Buse JB, et al. Diabetes Care 2014;37:2926–33

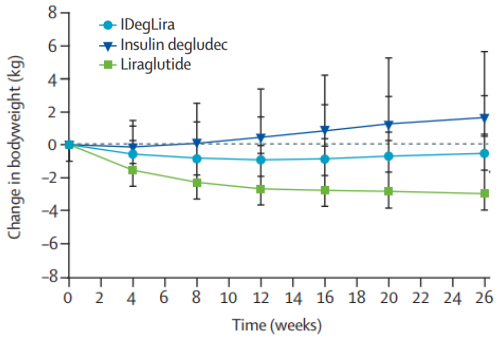
24

Mitigation of Weight Gain Typically Seen With Insulin With Use of Fixed-Ratio Combination

LixiLan-O[1]



DUAL I[2]

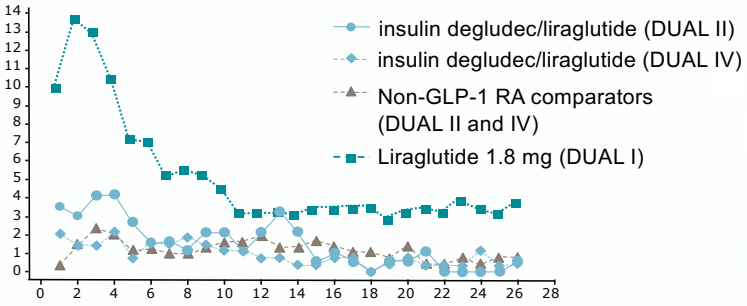


1. Aroda V, et al. Diabetes Care 2016;39:1972–80
2. Buse JB, et al. Diabetes Care 2014;37:2926–33

25

Gradual Dose Escalation of GLP-1 RA With Fixed-Ratio Combination Reduces GI Side Effects

Subjects experiencing nausea, vomiting or diarrhea (%)



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

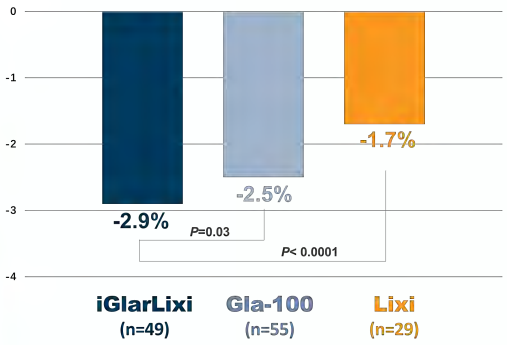
26

LIXILAN-O

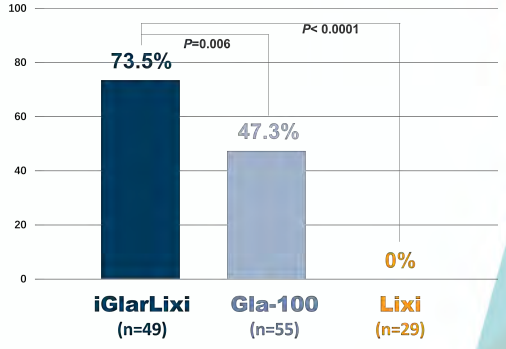
Change in HbA_{1c} at Week 30 Stratified by Baseline A1C

Mean HbA_{1c} at Baseline = 9.4%

Change in HbA_{1c} from baseline (%)



% of patients achieving HbA_{1c} <7% at Week 30



With iGlarLixi: A1C reduced from 9.4% to 6.8%, and 73.4% reached the goal of <7.0%

Davies MJ, et al. *Diabetes Obes Metab.* 2019;21:1967-1972

27

Summary: Benefits of Fixed-Ratio Combinations of Basal Insulin and a GLP-1 RA

- Combined glycemic effects of GLP-1 RA and basal insulin provides greater glycemic efficacy than either of its individual components
- Dose-related adverse effects of each component (GI side effects 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 or switching to pre-mixed insulin
- Fixed-ratio combinations are simple for the patient (one injection daily which contains both basal insulin and a GLP-1 RA)

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Generic and Trade Names: Insulin

	Generic Name	Trade Name
Fast-Acting Insulin	regular U-500 regular aspart Faster-acting aspart Faster-acting lispro glulisine lispro (U-100 and U-200) Follow on biologic lispro inhaled insulin	Humulin R, Novolin R Humulin R U-500 NovoLog Fiasp Lyumjev 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

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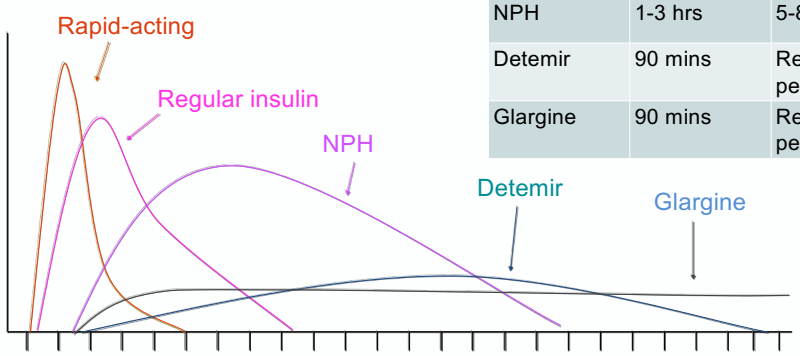
Time Action Profiles: Traditional Insulins

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.

30

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 insulin 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

31

Case 3: 66-year-old obese female diagnosed with T2D 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-1 RAs
- 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 mL/min, 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	---

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

(On metformin, SFU, and a SGLT2i prior to stating 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

33

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

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

34

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.

35

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
- Obesity, HTN, dyslipidemia, OSA , NAFLD, and h/o pancreatitis
- Currently treated with low-dose metformin, SFU, DPP4 inhibitor and canagliflozin (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		

36

Which of the following would you suggest for this patient?

(currently on metformin, SFU, DPP4i and a SGLT2i)

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

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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

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Clinical Pearls: Combination Therapy with Basal Insulin

- Start with 10 to 20 units (based on FBS, weight)
- The key to success is frequent follow up after initiation to avoid “failure” (most patients with T2D will need 40 to 70 units/day)
- 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
- You can usually limit SMBG to only once a day in the morning but check at bedtime periodically 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.

39

Second Pitfall in Initiating/Titrating Basal Insulin

(First one is too slow titration after starting)

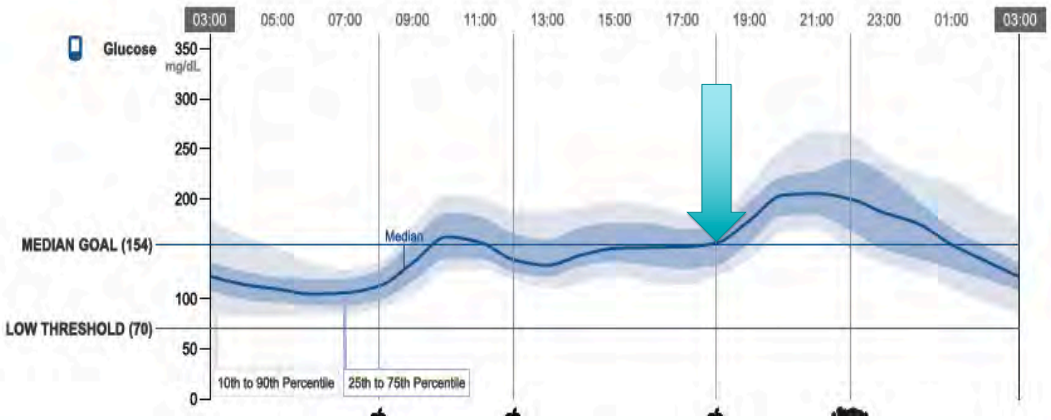
Not Paying Attention To
Bedtime Glucose Value So You Avoid Overbasalinization

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.

40

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



41

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

Above target*:
A1c >7.0%
FPG >130mg/dL

*Individualize targets

Step 1
Glargine (U100 or U300), degludec, detemir or NPH

Titration based on FPG
All oral agents continued

Above target

Step 2
Add FA analog or Inhaled insulin

Main meal

Above target

Step 3
Add FA analog or Inhaled insulin

Next largest meal

Above target

Step 4
Add FA analog or Inhaled insulin

Last meal

A1c <7.0%, FPG< 130 mg/dL

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

42

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 T2D** because of significant glucose lowering in addition to weight loss, reducing the risk of hypoglycemia, and cardio-protection
- **Higher doses of GLP-1 RAs** have been assessed in clinical trials (e.g., dulaglutide, semaglutide) for enhanced glycemic and body weight control
- **Combination therapy** (adding basal insulin to daytime OHAs/GLP1-RAs) is safe, effective and easy to implement
- The **fixed-ratio combinations** 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** is critical!