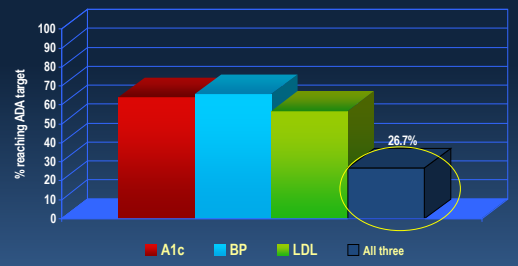
Lecture 1: 8:15 – 9:15 a.m.

William Polonsky, PhD, CDE, Presents:

Communicating the Good News
(Not Just the Bad News) About Diabetes:
How Evidence-Based Hope Can Promote Patient Engagement

Percentage of Patients Achieving ADA Treatment Targets



NHANES data: Ali et al, 2014

Number of Patients Who Avoid Sharing Information with Their HCP

	Ever Avoided Informing the Clinician, No. (%)	
Type of Information	MTurk (n = 2011)	SSI (n = 2499)
Disagreed with clinician's recommendation	918 (45.7) (n = 2010)	785 (31.4) (n = 2497)
Did not understand clinician's instructions	638 (31.8) (n = 2009)	607 (24.3) (n = 2497)
Had unhealthy diet	493 (24.5) (n = 2009)	506 (20.3) (n = 2491)
Did not take prescription medication as instructed	453 (22.5) (n = 2011)	439 (17.6) (n = 2491)
Did not exercise	446 (22.2) (n = 2008)	538 (21.6) (n = 2495)

Levy et al, 2018

HCP Attributions Regarding Poor Adherence in Diabetes

HCP top 5 complaints:

1. Patients say they want to change, but are not willing to make the necessary changes
2. Not honest/Only tells me what they think I want to hear
3. Don't listen to my advice
4. Diabetes not a priority/Uninterested in their condition/ "In denial"/Don't care/Unmotivated
5. They do not take responsibility for self-management

Edelman et al, 2012

Why Avoid Sharing Information?

Table 2. Percentage of Times a Reason Was Selected for Avoiding Telling the Clinician Collapsed Across Types of Information[a]

	% (95% CI)	
Reason	MTurk	SSI
I didn't want to be judged or get a lecture about my behavior.	81.8 (79.8-83.9)	64.1 (61.5-66.7)
I didn't want to hear how bad [insert behavior] is for me.	75.7 (73.5-78.0)	61.1 (58.5-63.8)
I was embarrassed to admit that I [insert item].	60.9 (58.9-62.9)	49.9 (47.8-52.1)
I didn't want the health care provider to think that I'm a difficult patient.	50.8 (48.7-52.9)	38.1 (36.0-40.3)
I didn't want to take up any more of the health care provider's time.	45.2 (42.6-47.9)	35.9 (33.2-38.7)
I didn't think it mattered.	38.6 (36.6-40.6)	32.9 (30.9-35.0)
I didn't want the health care provider to think that I'm stupid.	37.6 (35.7-39.6)	30.6 (28.6-32.7)

Levy et al, 2018

Real Life with Diabetes

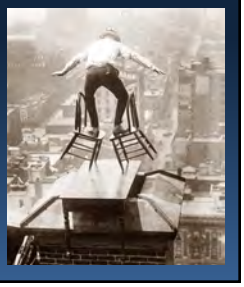
1. Living with diabetes can be tough
   - It is a time-consuming job


Estimated time required for recommended care*

Russell et al, 2005

Real Life with Diabetes

1. Living with diabetes can be tough
   - It is a time-consuming job
   - It is a balancing act that requires vigilance and an ability to deal with frustration



Motivation in Diabetes

- No one is unmotivated to live a long and healthy life
- The real problem: Obstacles to self-care outweigh possible benefits
  - And there are a TON of obstacles!
  - The underlying theme to most obstacles is a lack of "worthwhileness"

Lack of Worthwhileness

- An invisible and non-urgent disease

"Look, I'll start worrying about my diabetes as soon as something something falls off."

Lack of Worthwhileness

- An invisible and non-urgent disease
- Hopelessness

"What's the difference? This disease is going to get me no matter what I do.

Lack of Worthwhileness

- An invisible and non-urgent disease
- Hopelessness
- Discouragement

"I did everything I was supposed to, and now you're telling me I have to take even more medications?!"

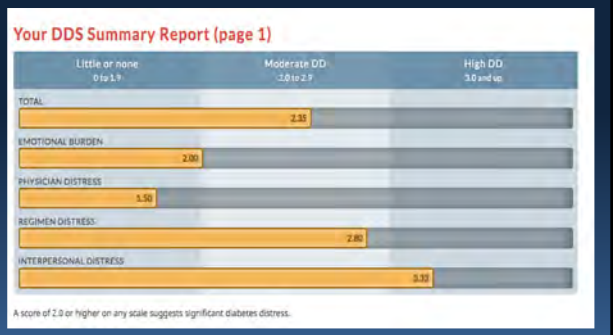
Step 1. Assess

- The informal approach:
  - "What's one thing about diabetes that's driving you crazy?"
- The formal approach:
  - Use self-report instruments

Diabetesdistress.org

- T1-DDS & DDS in English & Spanish
- Automatically scored, with printable reports

Diabetesdistress.org



A T1-REDEEM Participant

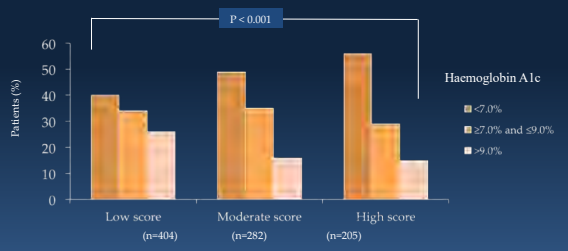
" It was totally unexpected and surprising. I have had diabetes for 35 years. In all that time no one has ever asked me what it was like for me to have diabetes and what it was about diabetes that I found most distressing. And even if they did ask, I doubt that they would have taken the time or had the interest to listen carefully to my answer."

Step 2. Respond with Empathy

- Don't try to fix your patient's difficult feelings
- Instead, acknowledge and normalize
  - "Given the nature of diabetes, feeling this way is perfectly reasonable and many other people feel the same."

Step 2. Respond with Empathy

A1c results for 891 patients, treated between 2006-2009, by levels of their HCP' empathy



Hojat et al, 2011

Step 3. Make the Invisible Visible

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*

Step 3. Make the Invisible Visible

- Be non-judgmental.
  - Fear tactics may be counterproductive:
  - "Do you want to go blind, do you?"
  - "If you don't do better, you'll end up on insulin. Is that what you want, is it?!"
  - Rather than describing numbers as "good/bad" or "high/low", use "safe/unsafe".

Step 3. Make the Invisible Visible

- Be non-judgmental.
- Offer congratulations when possible.

"Your A1C is still too high. Don't you understand the consequences? Why aren't you working harder on this?"

VS.

"Its great that you took the time to get your A1C done today. The numbers haven't moved much, which tells us that something different is needed."

Step 3. Make the Invisible Visible

- Be non-judgmental.
- Offer congratulations when possible.
- Provide a path forward.
  - "Let's work together to get these important numbers to a safe place for you".

Appealing to Fear: A Meta-Analysis of Fear Appeal Effectiveness and Theories

- 248 independent samples, n = 27,372
- Fear appeal: d=0.21
- Fear appeal + efficacy message d=0.43

Tannenbaum et al, 2015

Step 4. Share the Good News

Q. Diabetes is the leading cause of adult blindness, amputation, and kidney failure. True or false?

A. False. To a large extent, it is *poorly controlled* diabetes that is the leading cause of adult blindness, amputation and kidney failure.

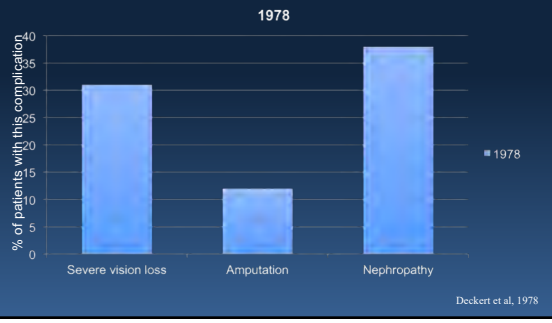
Well-controlled diabetes is the leading cause of… NOTHING!

Fact Check

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

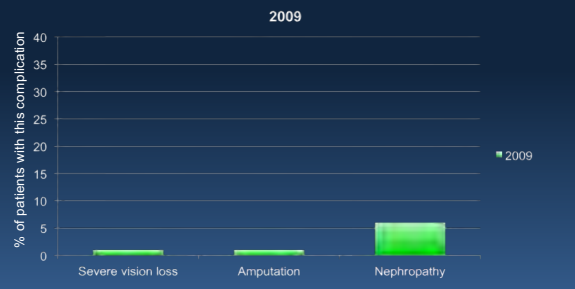
This does mean: with good care, **odds are good** you can live a long, healthy life with diabetes

T1D Complications After 30+ Years



Deckert et al, 1978

T1D Complications After 30+ Years



DCCT/EDIC Research Group, 2009

In Summary

"Historical reports of frequencies of serious complications in T1D patients are clearly outdated … rates of complications with 'intensive' treatment, or what would now be considered the standard of care, are substantially lower than in the past. This is indeed good news that should be openly shared with the newly diagnosed patient to help alleviate fears that may accompany the diagnosis.."

Nichols, 2009

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Naveed Sattar, M.D., Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Björn Zethelius, M.D., Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.

- **271,174 T2Ds, 1,355,870 matched controls**
- T2Ds "who had five risk-factor variables within target ranges appeared to have little or no excess risks of death, MIs, and stroke as compared with the general population."

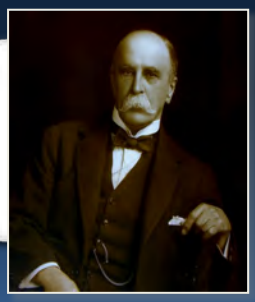
Rawshani et al, 2018

We Even Put it on Mugs!

Diabetes and Your Health

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

- Sir William Osler



Step 5. Address Discouragement

- Make behavioral success easier
  - Plan for actions must be doable
  - Focus on the behavior, not the outcome
  - Collaborative agreement and commitment

"So just to make sure we're on the same page, what's one diabetes-related action you're aiming to do over the next few months?"

Step 5. Address Discouragement

- Make behavioral success easier
- Re-frame the medication conversation

Step 5. Address Discouragement

- Make behavioral success easier
- Re-frame the medication conversation
  - Taking your meds is one of the most powerful things you can do to improve your health.
  - There are always pro's and con's; the con's are probably not as big as you think.
  - More meds doesn't mean you're sicker, fewer meds doesn't mean you're healthier.

Step 5. Address Discouragement

- Make behavioral success easier
- Re-frame the medication conversation
- Provide the tools needed to be successful
  - Ongoing support

The Impact of Automated Brief Messages Promoting Lifestyle Changes Delivered Via Mobile Devices to People with Type 2 Diabetes: A Systematic Literature Review and Meta-Analysis of Controlled Trials

Carukshi Arambepola[1], MD; Ignacio Ricci-Cabello[2], PhD; Pavithra Manikavasagam[3], MBBS; Nia Roberts[2], MSc; David P French[4], PhD; Andrew Farmer[2], DM

Step 5. Address Discouragement

- Make behavioral success easier
- Re-frame the medication conversation
- Provide the tools needed to be successful
  - Ongoing support
  - Medications
  - Devices

QOL and CGM

Table 2—QOL outcomes by study arm from baseline to 24-week follow-up

	CGM group		Control group		
	Baseline	24 weeks	Baseline	24 weeks	*P* value
WHO-5	71.28 ± 14.71	70.47 ± 16.68	69.06 ± 14.89	67.32 ± 16.86	0.50
EQ-5D-5L	0.90 ± 0.11	0.89 ± 0.10	0.89 ± 0.11	0.88 ± 0.10	0.92
Diabetes distress (DDS)					
Total	1.78 ± 0.65	1.61 ± 0.48	1.69 ± 0.62	1.78 ± 0.65	0.03
Regimen	2.09 ± 0.87	1.81 ± 0.68	2.08 ± 0.99	2.05 ± 0.87	0.04
Emotional burden	2.06 ± 0.90	1.93 ± 0.80	1.91 ± 0.83	2.03 ± 0.95	0.09
Interpersonal	1.54 ± 0.81	1.43 ± 0.61	1.45 ± 0.70	1.73 ± 1.04	0.01
Physician	1.19 ± 0.63	1.09 ± 0.25	1.12 ± 0.25	1.18 ± 0.69	0.15
Hypoglycemic confidence (HCS)	3.27 ± 0.57	3.47 ± 0.55	3.15 ± 0.57	3.18 ± 0.63	0.03
Hypoglycemia fear (worry subscale of HFS-II)	15.75 ± 12.30	13.48 ± 10.63	17.30 ± 13.22	17.73 ± 14.92	0.15

Polonsky et al, 2017

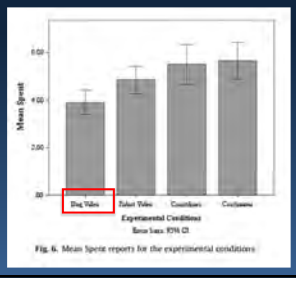
Step 6. Take Care of Yourself

- HCP burnout is much too common

Finkbeiner et al, 2016

Step 6. Take Care of Yourself

- HCP burnout is much too common



"… and although dog videos do not improve performance notably, people do report feeling better."

Finkbeiner et al, 2016

In Summary

- Assess
- Respond with empathy
- Make the invisible visible
- Share the good news
- Address discouragement
- Take care of yourself

Thanks for Listening!

www.behavioraldiabetes.org

Lecture 2: 11:30 – 12:30 p.m.

John Buse, MD, PhD Presents:

Update and Clinical Overview of the Oral Medications for Type 2 Diabetes and Their Cardiovascular Effects

Summary Of New ADA Algorithms

(see attached treatment guidelines)

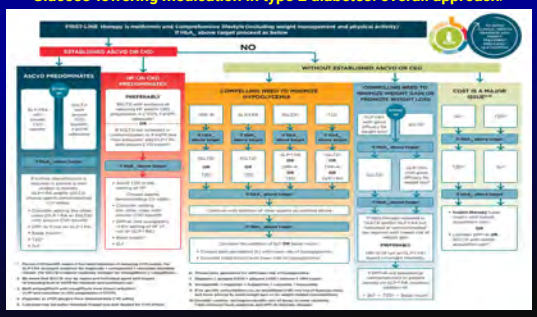
- Step 1: Start with metformin unless contraindicated
- Step 2: Decide on the main priority for your patient
- Main concern is established ASCVD or CKD: GLP1-RAs and SGLT2 inhibitors (CHF)
- Main concern is weight: avoid sulfonylureas, pioglitazone and insulin
- Main Concern is hypoglycemia: avoid sulfonylureas and insulin
- Main concern is access: use generic medication as a first priority, financial assistance programs, co-pay cards, etc.

There is overlap in the different algorithms?
Must Individualize Therapy

American Diabetes Association Dia Care 2019;39:S52-S59

TCOYD TAKING CONTROL OF YOUR DIABETES

Glucose-lowering medication in type 2 diabetes: overall approach.



American Diabetes Association Clin Diabetes 2019;37:11-34

Decision cycle for patient-centered glycemic management in type 2 diabetes.

American Diabetes Association Clin Diabetes 2019;37:11-34

Case 1: 49 year old male with type 2 diabetes for 6 years

- Other medical history: central obesity, dyslipidemia, HTN and CAD s/p MI
- Family Hx: positive for type 2 diabetes, obesity and CAD
- Notes: very few home glucose monitoring results
  - Diabetes Meds: Metformin, SFU, DPP4 inhibitor, SGLT2 inhibitor and basal insulin
  - Current A1c 11.4% (10.6% 1 year ago, 10.1% 2 years ago)
  - Creatinine 1.4 mg/dl, eGFR 65
  - LDL 112 mg/dl, Triglycerides 296 mg/dl, HDL 21 mg/dl

TCOYD TAKING CONTROL OF YOUR DIABETES

at is the most likely reason why this patient has not achieve his A1c goal?

A	He needs prandial insulin
B	Poor adherence with his medication
C	He does not exercise regularly
D	His diabetes regimen is too complicated
E	He needs a GLP-1 RA

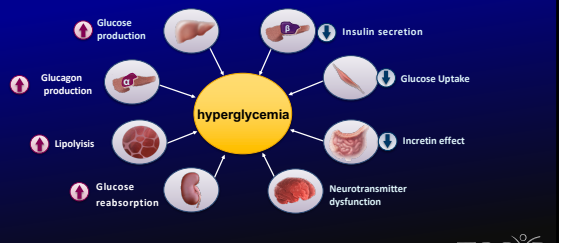
TCOYD TAKING CONTROL OF YOUR DIABETES

Glycemic Target Goals for Patients with Type 2 Diabetes

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

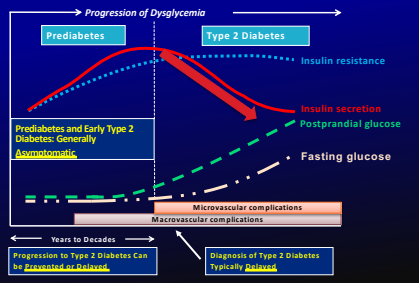
* Peak PPG; ** 2 Hr PPG
American Diabetes Association. *Diabetes Care.* 2015; 38(suppl 1):S33-S40.
Handelsman, Y., et al. (2015). Endocr Pract 21(0): 1-87.

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



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

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



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

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

- Metformin (first line therapy unless contraindicated)
- Sulfonylureas, meglitinides
- Glitazones (pioglitazone, rosiglitazone)
- DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)
- SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin , ertugliflozin)
- Bile acid sequestrant (colesevelam)*
- Dopamine receptor agonists (bromocriptine meslate)*
- Alpha glucosidase inhibitors (acarbose, miglitol)*
- ** not discussed in detail in this presentation*

http://www.fda.gov/drugs

Clinical Treatment Pearls

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

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

Edelman SV (TCOYDtv). 3 September 2015. Get Type 2 Diabetes and Live Longer Because of It (video) https://www.youtube.com/watch?v=x2AAbWrjVa8

Case 2: 69 year old centrally obese female with type 2 diabetes for 9 years

- PMH: Obesity (BMI 34), HTN, dyslipidemia, OSA, breast cancer s/p lumpectomy and hormonal therapy in remission
- Family History: Both Parents had type 2 diabetes
- Notes:
  - Creatinine 1.1 mg/dl, eGFR 75
  - A1c 8.5% (above 8% for the past two years)
  - Diabetes therapy is metformin and a SFU
  - LDL 121 mg/dl, Triglycerides 266 mg/dl, HDL 39 mg/dl

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

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

Update on metformin, SFUs and TZDs (all generic)

METFORMIN
- eGFR <60 to ≥45 OK to use full dose/monitor kidneys
- eGFR <45 to ≥30 OK to use 50% maximum dose/ monitor kidney function every 3 months
- Check B-12 levels

SFUS
- High 2ndary failure rate, however when you stop them the patient's A1c typically goes up.
- Increase risk of hypoglycemia (elderly, CKD, CAD)

TZD (PIOGLITAZONE)
- Risk of bladder cancer disproven
- Effective in prediabetes, best used early in the natural history (balance with potential side effects)
- Be cautious in combo with insulin (fluid retention)

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

TCOYD TAKING CONTROL OF YOUR DIABETES

Case 3: 62 Year Old Native American Female Diagnosed with Type 2 Diabetes Since the Age of 32.

- PMH: HTN, dyslipidemia, OSA and fatty liver
- FH: T2DM, early CAD
- A1c 7.6% on maximum doses of metformin and SFU.
- Occasional mild hypoglycemia
- No home glucose monitoring data
- Creatinine 1.3 mg/dl, eGFR 61, BMI 39
- BP normally above 140/90 mmHg; on no HTN meds

TCOYD TAKING CONTROL OF YOUR DIABETES

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

A	Add pioglitazone
B	Add a DPP-4 inhibitor
C	Add a SGLT-2 inhibitor
D	Add a GLP1-RA
E	Combination of a DPP4 inhibitor and a SGLT2 inhibitor

Case 3: continued

Treatment History

- A DPP-4/SGLT2 inhibitor combination pill was added to her regimen (once a day and one co-pay)
- Follow up was arranged for one month instead of the usual 3 to 4 months to confirm adherence
- She did well with a 10 pound weight loss and no hypoglycemia after the SFU dose was cut in half
- The A1c fell from 9.5% to 7.4%
- BP went from 150 mmHg to 141mmHg
- After 6 months she was started an ARB/statin combination pill to get her BP below 140/90 mm/Hg and her LDL <100 mg/dl
- She was resistant to starting new medications but the combo pills helped

Option #4: DPP-4 Inhibitors

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

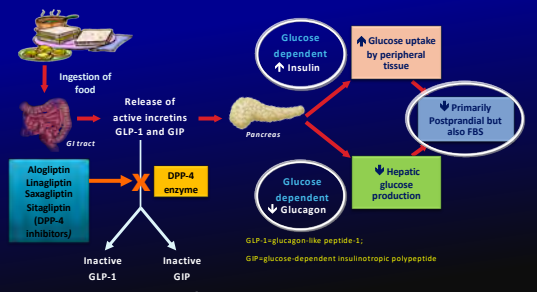
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

Generic and Trade Names

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

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

Mechanism of Action of DPP-4 Inhibitors



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.

Combination Pills With A DPP-4 Inhibitor

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

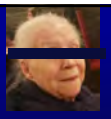
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 13th Edition. Professional Communications, Inc., Greenwich, CT. 528 pages, 2017.

Comparison of DPP-4 Inhibitors
EFFICACY VERY SIMILAR

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

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

Case 4: 70 year old obese female with type 2 diabetes for 15 years



- A1c 8.4%
- On max. doses of metformin and a DPP4-inhibitor
- Family History: Type 2 diabetes and obesity (both parents)
- Notes:
  - Very fearful of injections and gaining weight, BMI 31kg/m^2
  - HTN, osteoporosis, and CKD (creatinine 1.4/eGFR 58)
  - HGM shows FBS (147-219 mg/dl), and a few post dinner values (188 to 275mg/dl)

How would you treat patient to lower her A1c?

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

Case 4: continued

- Low dose SGLT-2 inhibitor was added to her regimen and then titrated to the maximum dose after one month
- A1c dropped to 7.3% (baseline 8.4%) and she lost 15 lbs
- She experienced a yeast infection which was easily treated with oral fluconazole and she did not want to stop the SGLT2 inhibitor
- LDL went from 100 to 108 mg/dL (8% rise) and her TGs dropped by 25%

Option #5: SGLT-2 Inhibitors

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

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

Generic and Trade Names (dose range)

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

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

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

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

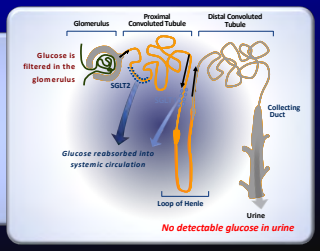
Ertugliflozin:
- Starting dose: 5 mg daily in morning with or without food (eGFR for both doses >60)
- Increase to 15 mg daily if tolerating and need additional glycemic control

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

TCOYD TAKING CONTROL OF YOUR DIABETES

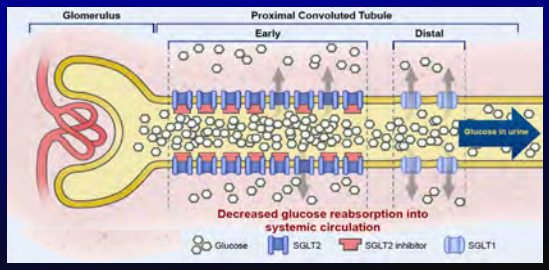
Renal Handling of Glucose in a Non-Diabetic Individual

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



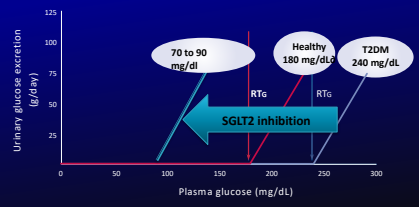
SGLT = sodium-glucose co-transporter.
1. Wright EM. *et al. J Intern Med.* 2007;261(1):32-43. 2. Kanai Y et al. *J Clin Invest.* 1994;93(1):397-404. 3. You G et al. *J Biol Chem.* 1995;270(49):29365-29371. 4. Wright EM. *Am J Physiol Renal Physiol.* 2001;280(1):F10-F18.

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



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

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



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

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

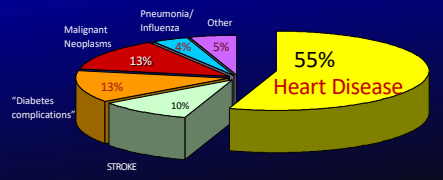
1. Extremely low incidence
2. Many but not all of the reports for DKA were in patients with LADA
3. Be especially cautious in insulin using patients (since glucagon levels go up with SGLT2s and by lowering the insulin too much an imbalance of glucagon to insulin may occur, leading to DKA)
4. Be especially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

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

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

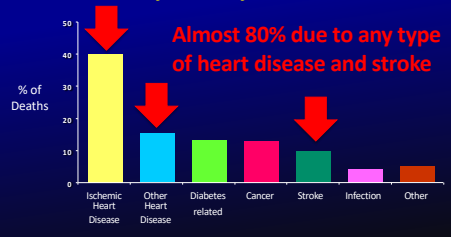
Causes of Mortality in Patients With Diabetes 20 years Ago: The Same Trend Exists Today



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

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

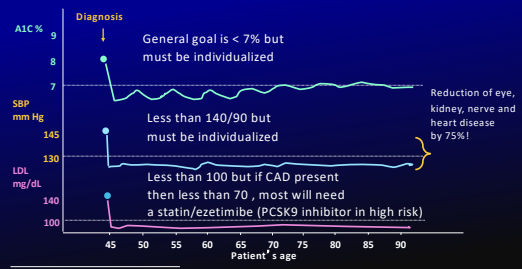
Most Common Causes of Death in People With Type 2 Diabetes: It is not eye, kidney or nerve disease!



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

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

Primary Objectives of Effective Management: These are the important basics (the ABCs)



American Diabetes Association. Diabetes Care. 2017 40(Suppl 1)

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

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

Courtesy of Silvio Inzucchi MD, Yale University

Adapted: Kendall DM , Bergenstal RM . International Diabetes Center 2009, 2015

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

Initial Trial
Long Term F/U
* in T1DM

Large Non-Insulin CVOTs in T2DM DPP-4 Inhibitors

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	sulfonylurea	placebo
N	16,50	5	14	6,000	8
Results	13	2013	June 2015	2017	2017

NEUTRAL NEUTRAL NEUTRAL NEUTRAL

Large Non-Insulin CVOTs in T2DM
SGLT-2 Inhibitors

Study	EMPA-REG	CANVAS	DECLARE	NCT01986881
SGLT-2-i	empagliflozin ✓	canagliflozin ✓	dapagliflozin ✓	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
N	7,300	7,300	17,200	3900
Results	Sept 2015 POSITIVE	2017 POSITIVE	2018 POSITIVE	2020

Courtesy of Silvio Inzucchi MD, Yale University

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

Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP1-RA	liraglutide ✓	lixisenatide ✓	semaglutide ✓	exenatide LR ✓	dulaglutide ✓
Comparator	placebo	placebo	placebo	placebo	placebo
N	9,300	6,068	3,297	14,752	8,900
Results	2016 POSITIVE	2015 NEUTRAL	2016 POSITIVE	2018 NEUTRAL	2019 POSITIVE

Courtesy of Silvio Inzucchi MD, Yale University

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

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

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

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

New FDA Indication for Diabetes Medications

- Diabetes medications FDA approved for CV risk reduction

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

- Semaglutide under review

TCOYD
TAKING CONTROL OF YOUR DIABETES

Not All CVOTs Are Created Equal

Important

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

Goutam Das, Journal of Diabetes Research & Clinical Metabolism 2015, http://www.hoajonline.com/journals/pdf/2050-0866-4-1.pdf

Courtesy of Mikail Kociborodi MD, Saint Lukes

Key Principles of Management of Type 2 Diabetes

- **Glycemic targets & glucose-lowering therapies should be individualized**
- **Diet, exercise and education are the foundations of therapy**
- **Unless contraindicated, metformin is optimal 1st line drug**
- **After metformin, consider medications according to patient needs (ASCVD, hypoglycemia, weight and financial status)**
- **Many patients over time will require insulin therapy alone or in combination with other agents to maintain glycemic control**
- **CAD is the most common cause of death and prevention strategies need to be emphasized (A1c, aspirin, blood pressure, cholesterol and diabetes drugs that reduce ASCVD/heart failure)**

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

Lecture 3: 1:15 – 2:15 p.m.

Tricia Santos Cavaiola, MD, Presents:

Practical Application of Injectable Agents:
Insulin and GLP-1 Receptor Agonists

Case 1: 60 year old male physician with type 2 diabetes for 10 years

- Currently on pioglitazone, DPP-4 inhibitor and a SGLT2 inhibitor
- Intolerant to metformin and has been resistant to taking insulin
- History of dyslipidemia, hypertension, NASH and ED
- Strong family history of type 2 diabetes
- Does not smoke but "likes to indulge in Old Fashioneds"
- A1c 8.7%
- Creatinine 1.4 eGFR 65
- HGM data: FBS average 179 mg/dl SD 35 mg/dl
- Bedtime average 210 mg/dl SD 76mg/dl

Which of the following would you recommend for This Patient?

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

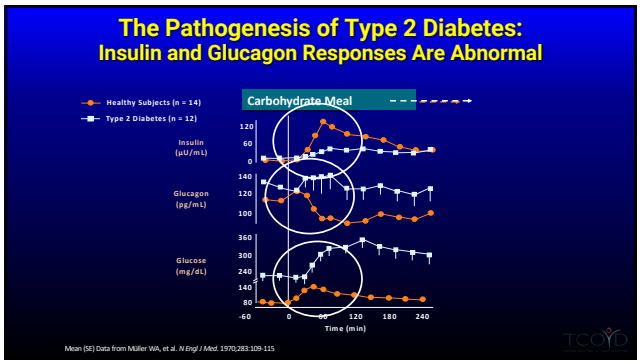
This exact question will be repeated at the end of the presentation

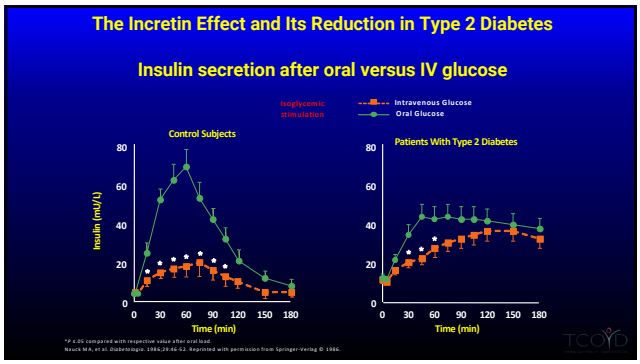
Basal Insulin vs GLP-1 RA

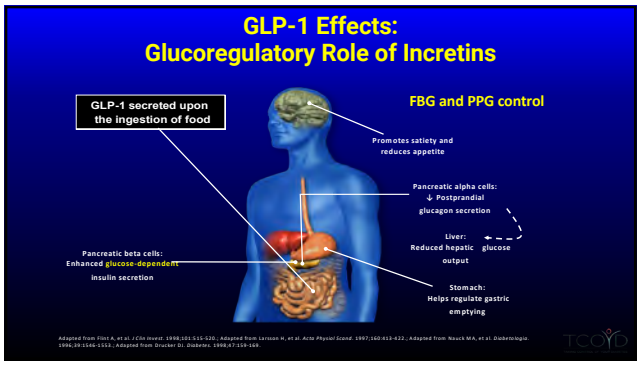
(an incretin hormone)

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

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


The Pathogenesis of Type 2 Diabetes:
Insulin and Glucagon Responses Are Abnormal
Healthy Subjects (n = 14)
Type 2 Diabetes (n = 12)
Carbohydrate Meal
Insulin (μU/mL)
Glucagon (pg/mL)
Glucose (mg/dL)
Time (min)
Mean (SE) Data from Müller WA, et al. N Engl J Med. 1970;283:109-115


The Incretin Effect and Its Reduction in Type 2 Diabetes
Insulin secretion after oral versus IV glucose
Isoglycemic stimulation
Intravenous Glucose
Oral Glucose
Control Subjects
Patients With Type 2 Diabetes
Insulin (mU/L)
Time (min)
*P ≤ .05 compared with respective value after oral load.
Nauck MA, et al. Diabetologia. 1986;29:46-52. Reprinted with permission from Springer-Verlag © 1986.


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

GLP-1 Receptor Agonists

Mechanism of Action	* Mimic the effects of human GLP-1
Benefits	* Significant A1c reductions (1.0 to 3.0% depending on baseline) * Shorter acting GLP-1 RAs have greater effects on PPG * Weight loss * No hypoglycemia * Once daily, twice daily and once weekly formulations
Concerns	* GI side effects (typically nausea) * Contraindicated in patients with a personal or family history of MTC or MEN2 * Relative contraindication in patients with a history of pancreatitis (important to know the etiology)
Clinical Pearls	* Ideal choice in obese patients with poor control, especially those on large doses of insulin * "No" need to initiate or increase glucose testing * Several with positive CVOT results

Edelman SV, Henry RR: Diagnosis and management of type 2 diabetes. Eleventh Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2011

Generic and Trade Names: GLP-1 RAs

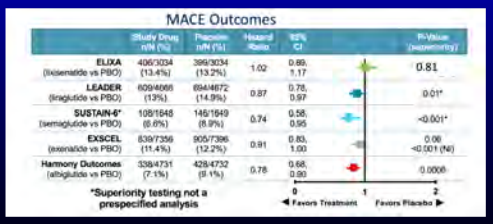
	Generic Name	Trade Name
GLP-1 Receptor Agonists	Exenatide	
	Twice-daily	Byetta
	Once-weekly	Bydureon
	Liraglutide	
	Once-daily	Victoza
	Dulaglutide	
	Once-weekly	Trulicity
	Lixisenatide	
	Once-daily	Adlyxin
	Semaglutide	
	Once weekly	Ozempic
Basal Insulin/GLP-1Receptor Agonist Fixed Combination	Glargine/lixisenatide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

Where do the GLP1-RA Class Fit in the New Treatment Guidelines?

- **GLP1-RAs are now recommended as the first injectable over basal insulin (unless glucose levels markedly elevated)**
- **Established ASCVD: GLP1-RAs are recommended immediately after metformin (SGLT2 inhibitors in CHF is the major issue)**
- **If primary concern is weight: GLP1-RAs are one of several choices preferred after metformin**
- **If primary concern is hypoglycemia: GLP1-RAs are one of several choices preferred after metformin**
- **If primary concern is access: GLP1-RAs are not generic yet, but several types of low payment plans**

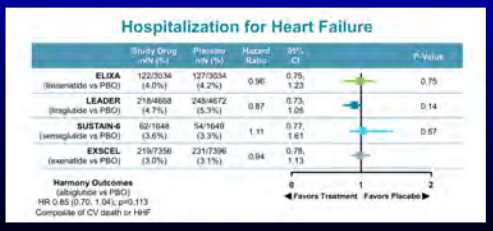
American Diabetes Association Dia Care 2018;39:552-559

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



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

CVOTs of GLP-1 RAs



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].

How Might a GLP1-RA Result in a Positive CVOT?

- GLP-1 protects against myocardial infarction in the isolated and intact rat heart. This protection appears to involve activating multiple prosurvival kinases (Diabetes 2005;54:146-51)
- Liraglutide engages prosurvival pathways in the normal and diabetic mouse heart, leading to improved outcomes and enhanced survival after MI in vivo (Diabetes 2009;58:975-83)
- Liraglutide exerts marked anti-oxidative and anti-inflammatory effects on endothelial cells with inhibition of PKC-α, NADPH oxidase, NF-κB signaling and upregulation of protective anti-oxidative enzymes (Atherosclerosis 2012;221:375-82)

ITCA 650—Medical Device To Deliver Type 2 Medication

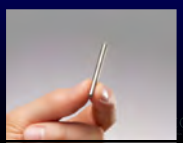
TECHNOLOGY

- Subcutaneous delivery system; short office procedure
- Small micropump
  - –maintains stability at temps ≈37°C
  - –secretes medication for ≥ 12 months

+

MEDICATION: EXENATIDE

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



Not yet approved by the FDA

Case 2: 29 year old Mexican American woman with type 2 diabetes for 3 years

- On maximal doses of metformin, SU, and a SGLT-2 inhibitor
- She adamantly does not want to take insulin for fear of weight gain
- PMH: dyslipidemia, hypertension, PCOS and obese (BMI=31)
- Both parents and two siblings have type 2 diabetes
- eGFR 75 ml/min
- Her A1c is 8.9%

FBS (mg/dl)	PPG (mg/dl)
Mean 188	Mean 265

What would you recommend now for this patient?

A	Start a DPP4 inhibitor
B	Try to convince her to start basal insulin
C	Start a GLP1-RA
D	Start pioglitazone

Case 2 continued

- She agreed to start a GLP-1RA (exenatide [once-weekly], liraglutide, dulaglutide, semaglutide or lixisenatide).
- If prescribing once-weekly GLP-1 RA, inform patient that it may take several weeks to reach equilibration and, with once-weekly exenatide, skin nodules may occur (self limited and resolve in a few days to weeks).
- She experienced no nausea or hypoglycemia. Over the next three months she lost 16 pounds and her A1c fell from 8.9% to 7.2%.

Before GLP-1*

FBS (mg/dl)	PPG (mg/dl)
Average 188	Average 265

After GLP-1*

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

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

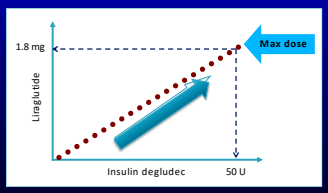
Fixed Combinations Of Basal Insulin and GLP- Receptor Agonist

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

- 1 dose step (unit) has 1 unit insulin degludec and 0.036 mg of liraglutide (max. dose is 50 iDeg/1.8mg lira)
- Injected once daily at same time each day with or without food
- 1 dose step (unit) has 1 unit insulin glargine and 0.33 mcg lixisenatide (max. dose is 60 iGlar/20 mcg lixi)
- Injected once daily within one hour prior to the first meal of the day

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

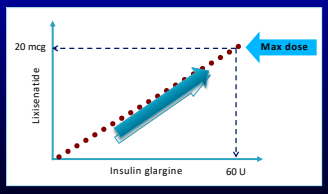
Fixed-Ratio Combination of Insulin Degludec and Liraglutide (Xultophy)



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

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

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



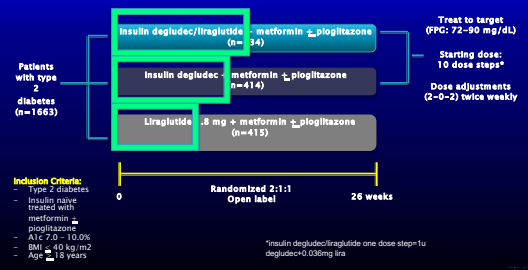
One dose step = 1 U insulin glargine and 0.33 mcg lixisenatide

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

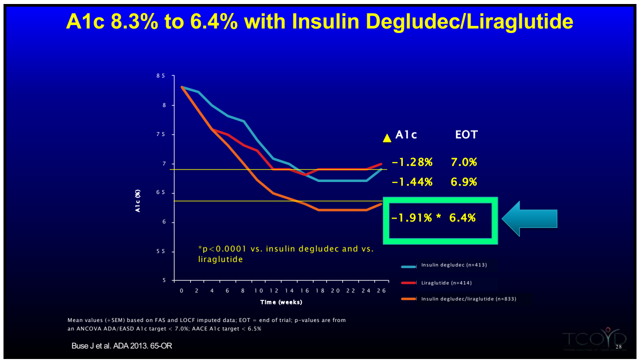
Insulin Degludec/Liraglutide vs. Insulin Glargine/Lixisenatide

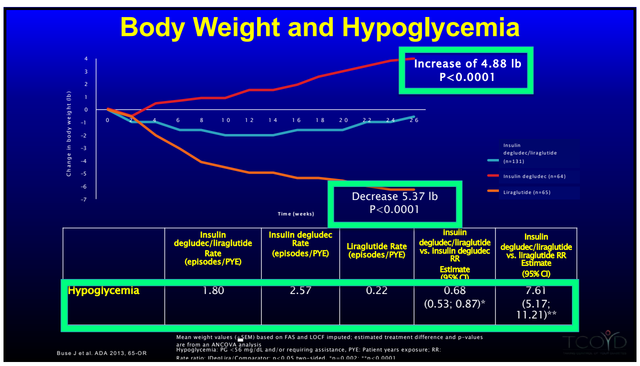
Pen dose steps (units): insulin degludec + liraglutide (Xultophy)	Pen dose steps (units): insulin glargine + lixisenatide (Soliqua)
10 dose steps=10 units insulin degludec +0.36 mgs of liraglutide 50 dose steps=50 units insulin degludec +1.8 mgs of liraglutide	15 dose steps=15 units insulin glargine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

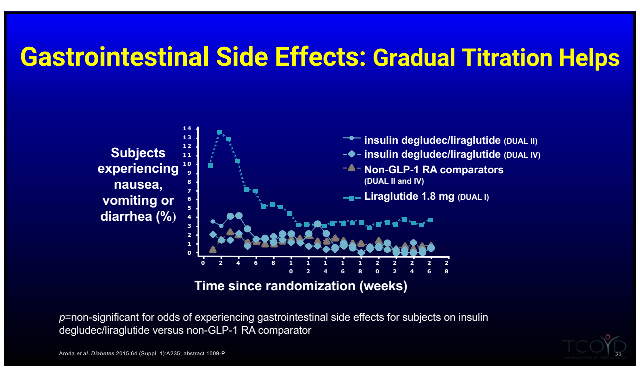
Insulin Degludec/Liraglutide in Type 2 Diabetes: Phase 3 Trial



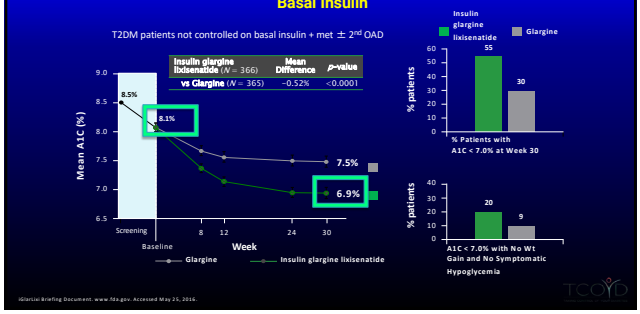
Buse J et al. ADA 2013. 65-OR; DUAL I


A1c 8.3% to 6.4% with Insulin Degludec/Liraglutide
A1c (%)
Time (weeks)
▲A1c EOT
−1.28% 7.0%
−1.44% 6.9%
−1.91% * 6.4%
*p<0.0001 vs. insulin degludec and vs. liraglutide
Insulin degludec (n=413)
Liraglutide (n=414)
Insulin degludec/liraglutide (n=833)
Mean values (+SEM) based on FAS and LOCF imputed data; EOT = end of trial; p-values are from an ANCOVA ADA/EASD A1c target < 7.0%; AACE A1c target < 6.5%
Buse J et al. ADA 2013. 65-OR
28


Body Weight and Hypoglycemia
Change in body weight (lb)
Time (weeks)
Increase of 4.88 lb
P<0.0001
Decrease 5.37 lb
P<0.0001
Insulin degludec/liraglutide (n=131)
Insulin degludec (n=64)
Liraglutide (n=65)
Insulin degludec/liraglutide Rate (episodes/PYE)
Insulin degludec Rate (episodes/PYE)
Liraglutide Rate (episodes/PYE)
Insulin degludec/liraglutide vs. insulin degludec RR Estimate (95% CI)
Insulin degludec/liraglutide vs. liraglutide RR Estimate (95% CI)
Hypoglycemia
1.80
2.57
0.22
0.68 (0.53; 0.87)*
7.61 (5.17; 11.21)**
Mean weight values (±SEM) based on FAS and LOCF imputed; estimated treatment difference and p-values are from an ANCOVA analysis
Hypoglycemia: PG <56 mg/dL and/or requiring assistance, PYE: Patient years exposure; RR:
Buse J et al. ADA 2013, 65-OR

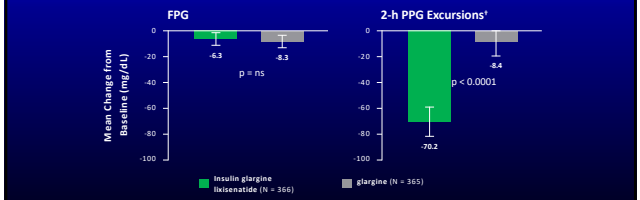

Gastrointestinal Side Effects: Gradual Titration Helps
Subjects experiencing nausea, vomiting or diarrhea (%)
insulin degludec/liraglutide (DUAL II)
insulin degludec/liraglutide (DUAL IV)
Non-GLP-1 RA comparators (DUAL II and IV)
Liraglutide 1.8 mg (DUAL I)
Time since randomization (weeks)
p=non-significant for odds of experiencing gastrointestinal side effects for subjects on insulin degludec/liraglutide versus non-GLP-1 RA comparator
Aroda et al. Diabetes 2015;64 (Suppl. 1):A235; abstract 1009-P
31

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



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

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



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

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

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

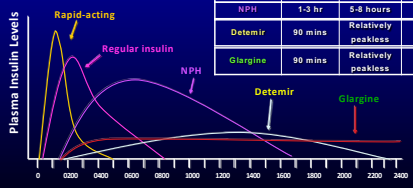
- Combined glycemic effects of GLP-1RA and basal insulin provides greater glycemic efficacy than either of its component parts.
- Dose related adverse effects of each component (nausea and weight gain) are minimized.
- No increased risk of hypoglycemia in the setting of improved glycemic control as compared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

Generic and Trade Names: Insulin

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

Time Action Profiles: Traditional Insulins

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



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

Lepore M et al. Diabetes. 2000;49:21 42-21 48; Howey DC et al. Diabetes. 1994;43:396-402; Plank J et al. Diabetes Care. 2005;28:1107-1112.; Wittlin SD et al. Insulin Therapy. Marcel Dekker, Inc.:2002:73-95.

Two New Basal Insulins Recently Added to Our List of Options

Both approved by the FDA and now available for patients

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

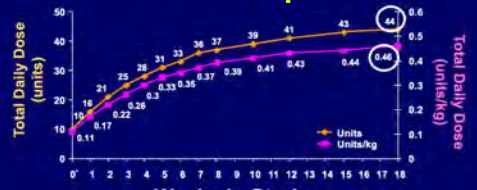
Toujeo prescribing information. Bridgewater, NJ: sanofi, US; 2015 http://products.sanofi.us/toujeo/toujeo.pdf
Tresiba prescribing information 2015. http://www.novo-pi.com/tresiba.pdf

Benefits Of U 300 Glargine And Degludec In Type 1 Diabetes

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

Riddle MC *et al. Diabetes Care*. 2014;37:2755-2762; Yki-Järvinen H *et al. Diabetes Care*. 2014; Published ahead of print: doi: 10.2337/dc14-0990
Bolli GB *et al.* Poster presented at IASD 2014: P927; Raja K. Oral presentation at CDA 2014: P14; Hono F *et al.* Abstract presented at EASD 2014: 0148
Rajaj 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

How Much Basal Insulin Will Your Patients Require?



0.5 units per Kg or
0.23 units per pound body weight

Rosenstock J, et al. ADA Annual Meeting 2001; Abstract 520-P

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

- Currently on maximum doses of 3 oral agents: metformin 1000 mg BID, SGLT2 inhibitor and a DPP4 inhibitor
- Her PCP started 10 units of glargine in the morning. After 3 months on 10 units she felt it "did not work" and she stopped it.
- A1c > 8.5% for the past 2 years, eGFR 89, LFTs normal
- Current SMBG (mg/dl) below:

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

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

A	Poor adherence
B	Initial dose was too little
C	Inadequate titration of the glargine U-100
D	Glargine U-100 should have been given at bedtime

Initiating Insulin Therapy in Type 2 Diabetes: General Concepts

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

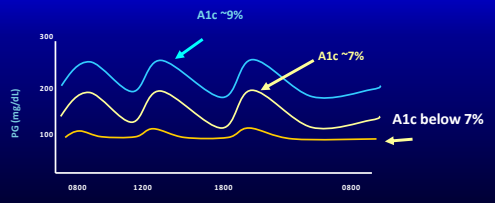
Start with basal insulin.
Titrating the dose is essential (self titration can work well).

Use a fast-acting analog as an add on to basal dose when indicated.
(may only needed to be given with the largest meal discussed later)

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.

First Goal: Correct Fasting Hyperglycemia



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

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

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

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

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

Case 4: 65 year old obese Latino with a 9 year history of type 2 diabetes

- History of CAD s/p MI 2 years ago
- Treated for 2 years with diet and exercise alone even though his A1c was above 9.5% ("did not want to take medications")
- Eventually started on metformin, sequentially followed by a sulfonylurea, DPP-4 inhibitor, and his A1c fell from 9.9% to 7.9%
- It took two years (6 clinic visits) to initiate these 3 meds and get his A1c down

Case 4: continued

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

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

Which of the following would you suggest for this patient?

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

Case 4: continued

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

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

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

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

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

Start with a long-acting basal insulin

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

Check fasting glucose daily and increase dose by:

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

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

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

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

EXAMPLE

Less than 100: decrease by 2 units

Between 100 and 150: no change

Over 150: increase by 2 units

The goal can be individualized

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

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

Gerstein HC et al. Diabet Med. 2006;23:734-742.

Self Titration Clinic Form

Starting/Adjusting Long-Acting Basal Insulin

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

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

S

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

Not Paying Attention To Bedtime Glucose Value

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

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

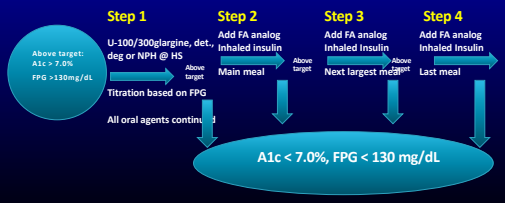
Clinical Pearls: Combination Therapy with Basal Insulin

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

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

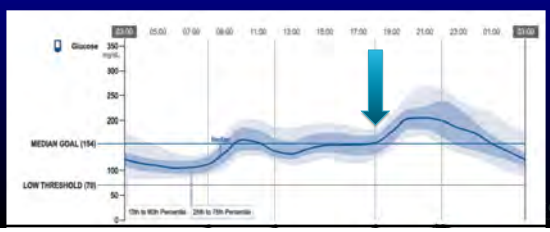
Transitioning From Basal to Basal/Bolus Insulin Therapy in Type 2 Diabetes Mellitus

(Insulin and Patch Pumps Can Improve Adherence)

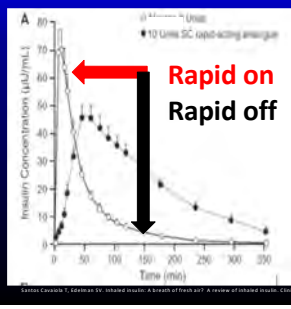


Adapted with permission from Kartl DM. Curr Diab Rep. 2004;4:152-157.

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



Inhaled Insulin: Addresses "the needle" Issue



4, 8, 12 unit insulin cartridges

- Better post meal glucose values
- Less delayed hypoglycemia

Exton-Cavalos T, Edelman SV. Inhaled insulin: A breath of fresh air? A review of inhaled insulin. Clinical Therapeutics. 2014; 36(8)

Case 1: 60 year old male physician with type 2 diabetes for 10 years

- Currently on pioglitazone, DPP-4 inhibitor and a SGLT2 inhibitor
- Intolerant to metformin and has been resistant to taking insulin
- History of dyslipidemia, hypertension, NASH and ED
- Strong family history of type 2 diabetes
- Does not smoke but "likes to indulge in Old Fashions"
- A1c 8.7%
- Creatinine 1.4 eGFR 65
- HGM data: FBS average 179 mg/dl SD 35 mg/dl
- Bedtime average 210 mg/dl SD 76mg/dl

Which of the following would you recommend for This Patient?

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

Summary

- GLP-1 RAs represent a tremendous advance in the treatment of type 2 because of significant glucose lowering in addition to weight loss and reducing the risk of hypoglycemia
- Combination therapy (adding basal insulin to daytime OHAs/GLP1-RAs) is safe, effective and easy to implement
- The fixed combination of basal insulin and a GLP-1 RA has clinical advantages in terms of efficacy, reduced side effects and ease of use
- The Basal Bolus approach in type 2 diabetes does not need to be four injections per day (pens, patch pumps and inhaled insulin to improve adherence)
- Adherence and persistence needs to be addressed at every visit

Lecture 4: 2:15 – 3:30 p.m.

Steven V. Edelman, MD, Presents:

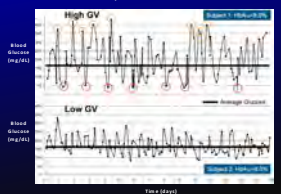
Addressing the Therapeutic Strategies and
Unmet Needs in Type 1 Diabetes

Unmet Needs in Type 1 Diabetes

- Reducing glycemic variability (GV)
- Increasing time in range (TIR)
- Reaching A1c goal without hypoglycemia
- Preventing and controlling weight gain
- Addressing cardiovascular risk factors
- Emotional burden of living with type 1 diabetes for the individual and his/her family

Glucose Variability has Important Impact on Patients with T1D: Both Patients Have the Same A1c

Fluctuations in Daily Glucose Levels in Two Different Patients[5]



- Measuring A1c alone gives no information on variability
- Importance of avoiding extreme hyperglycemia and dangerous hypoglycemia
- Improvement in time in range significantly reduced retinopathy and nephropathy[5]

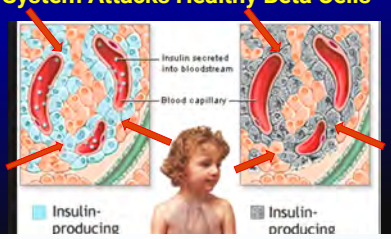
1. Kovatchev B et al, 2016; 2. Suh S et al, 2015; 3. Bergenstal RM, 2015; 4. Evans M et al, 2017;

Prevalence of T1D Increasing in US

- 1.3 million adults currently have T1D[1]
  - 1 million adults ≥ 20 years; not a childhood disease anymore
- 21% increase in prevalence of T1D in people < 20 years between 2001-2009[2]
- 40,000 people diagnosed each year in U.S.[2]
- 5 million people in U.S. expected to have T1D by 2050[2]

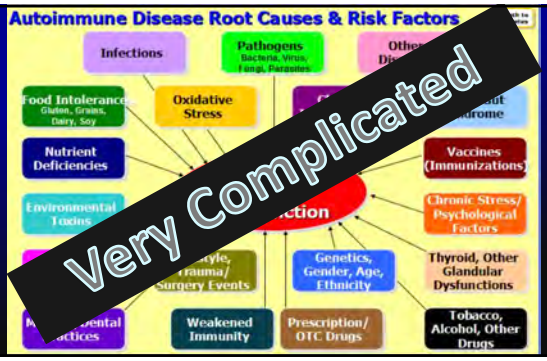
1. T1D Exchange T1D prevalence based on estimates 2;

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



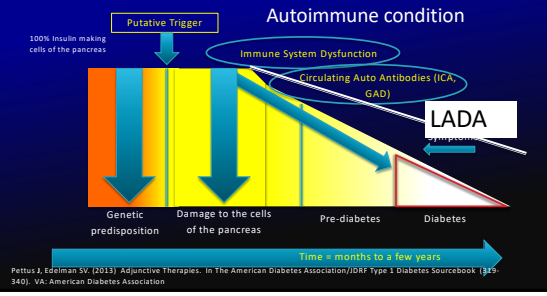
Natural Progression is <u>months</u> to a <u>few years</u>

Autoimmune Disease Root Causes & Risk Factors



Very Complicated

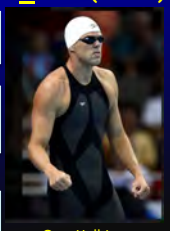
Natural History and Cause of Type 1 Diabetes



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

Latent Autoimmune Diabetes in Adults (LADA)

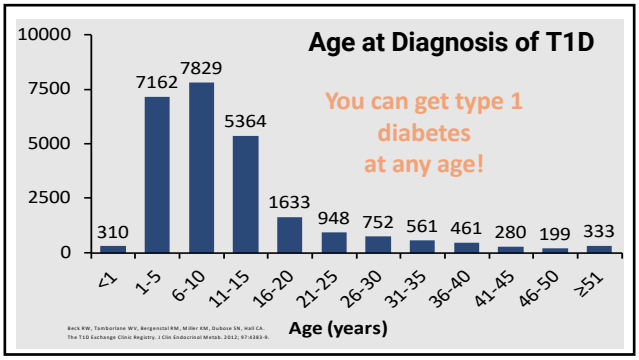
- The most missed diagnosis in diabetes
- Type 1 diabetes can occur at any age
- Slower beta-cell destruction (may respond briefly to oral agents)
- Typically does not have features of the Metabolic Syndrome
- Blood test positive for type 1 diabetes (GAD auto antibodies)



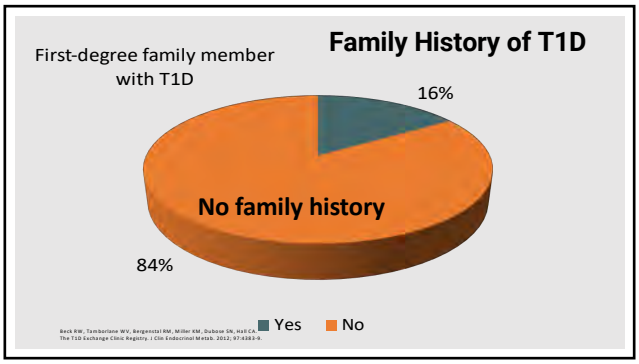
Gary Hall Jr.
Olympic Gold Medalist
World Record Holder

Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fourth Edition Professional Communications Inc., Greenwich, CT. 144 pages, 2013.

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



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

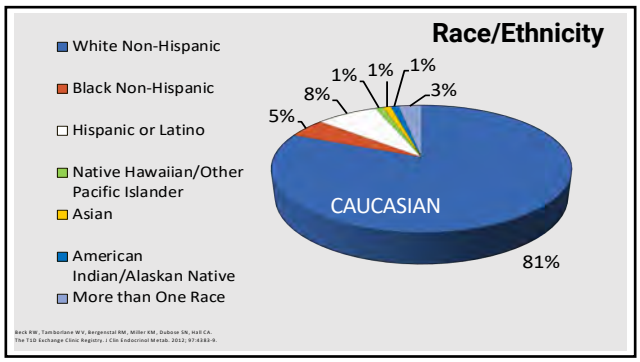


Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

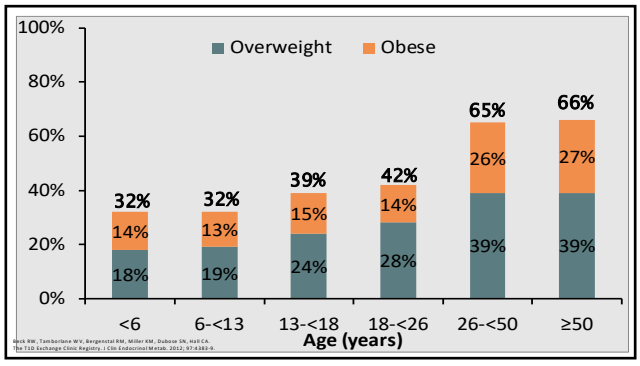
Risk of Developing Type 1 vs Type 2

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

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



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



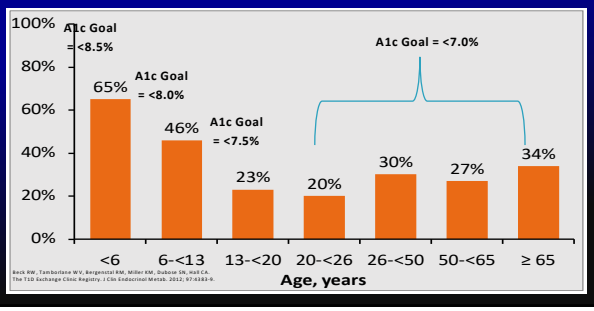
Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, DuBose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

Consequences of Weight Gain

- The leading cause of death in type 1 diabetes is from heart disease
- Excess weight gain associated with risk factors for cardiovascular disease, including increased
  - Lipid levels
  - Blood pressure levels
  - Waist circumference
  - BMI

Pursell JQ et al. Circulation. 2013

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

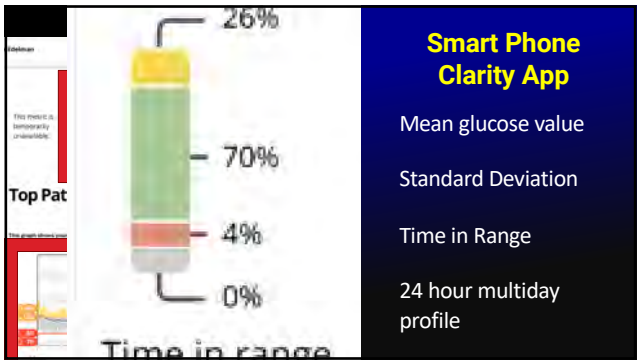


Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA. The T1D Exchange Clinic Registry. J Clin Endocrinol Metab. 2012; 97:4383-9.

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

1. 1st priority is getting a CGM and educate your patients to respond to the trend arrows.
2. Bolus calculations are more than just the carbohydrates and static glucose readings
3. In addition to getting the A1c below 7%, try to reduce the daily glucose fluctuations in your patients (hyper- and hypoglycemia)
4. The insulin regimen should mimic what happens in a non-diabetic state

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



Smart Phone Clarity App

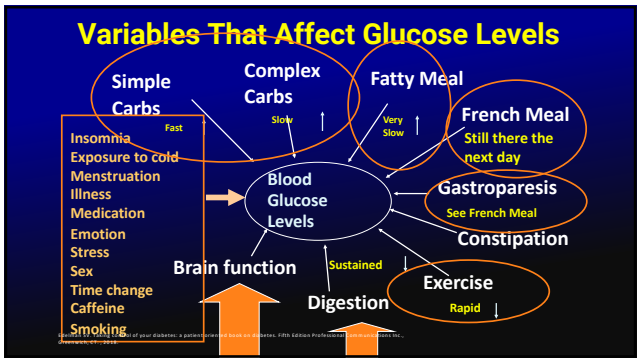
Mean glucose value

Standard Deviation

Time in Range

24 hour multiday profile

Variables That Affect Glucose Levels



Despite Following All of the Rules

1. Unexpected highs
2. Unexpected lows
3. Carb:Insulin ratio not working consistently
4. Correction Factor not working consistently
5. Not responding to insulin and exercise consistently

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

G6

- No calibration required
- 10 day sensor life
- Predictive low alerts
- No interference with acetaminophen
- Auto inserter
- Medicare Approve

Eversense

Implantable Continuous Glucose Monitor

Sensor

Sensor lasts up to 90 days
No weekly sensor insertion
No open wound

Smart Transmitter

Removable and rechargeable
On-body vibe alerts
Gentle, daily adhesive patch

Mobile App

No extra device to carry
iOS and Android platform
Alarm settings & reports

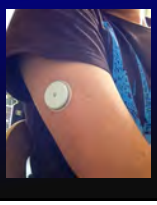
GUARDIAN CONNECT

- Predictive high alerts
- Predictive low alerts
- Requires calibration
- 6-day wear
- Need to confirm with fingerstick when dosing

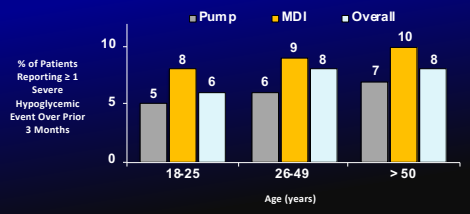
Freestyle Libre Flash IS or Intermittent Sensing

- 1 hour warm-up time
- Lasts 14 days
- Swipe to get a number
- Trend arrows

- No calibration
- No alerts or alarms
- No sharing features



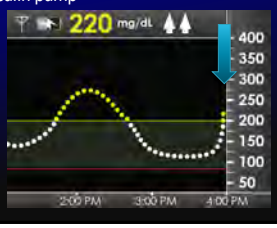
Severe Hypoglycemia Due to Too Much Insulin: 5 to 10% of all deaths in T1D



Miller KM, et al. Diabetes Care. 2015

Case

- 25 year old female with type 1 diabetes for 5 years
- CHO to insulin ratio 15:1
- CF 1:50 goal 100 mg/dl
- Wears an insulin pump



Case (continued)

- Patient uses her bolus calculator to determining her correction dose
  - Correction factor 1:50
  - Target glucose 100 mg/dL
  - 220-100/50 = 2.4 units

Which option below is the best suggestion for her to follow now?

A	Watch and wait (give no additional insulin)
B	Use her standing desk instead of sitting
C	Give a correction dose of at least 4 units
D	Give a correction dose of 2.4 units

A Single BS at one Point In Time Lacks Important Information

Pump and meter software suggests the same either way

No insulin. Watch and maybe get some carbs

Take a larger than usual dose

Trend Arrows Give Important Information To The User For Treatment Decisions

Hermanides K, Fryis LP, Edelman SV, Lutz K, Chen S, Maggs D, Esterman DS. Frankstein improved measures of glycemic control and body weight in patients with type 1 diabetes mellitus undergoing continuous subcutaneous insulin infusion therapy. Postgraduate Medicine. 123(1), 2011.

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

3.0 units

6.8 units

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

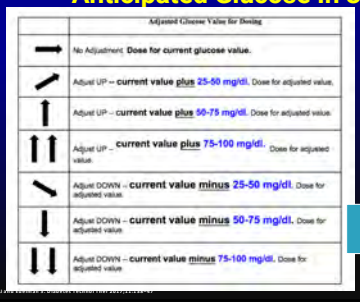
How CGM and Trending Information Can Affect Dosing Decisions

No change in calculation

140% Mean Increase

48% Mean Decrease

Adjust Correction Insulin Dose Based On Anticipated Glucose In 30 Minutes

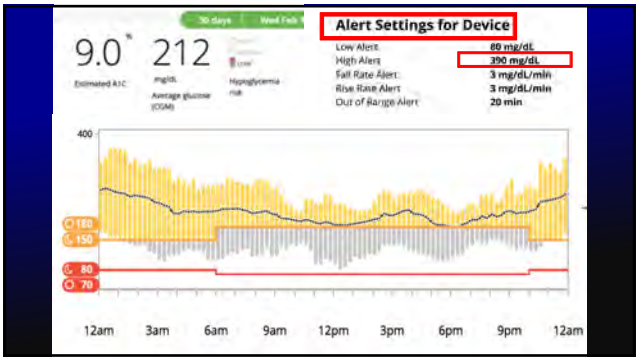


Add 50 mg/dl

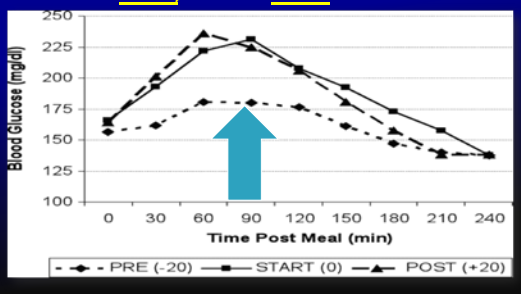
Add 75 mg/dl

Add 100 mg/dl

Wait until trend arrow becomes horizontal



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



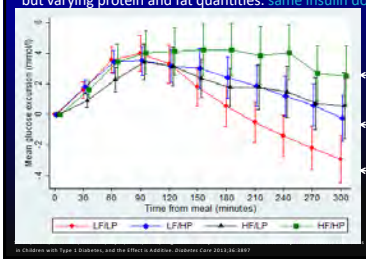
Cobry et al, Diab Tech Therap 2010;12: 173-177

How much fast acting insulin would you recommend to a patient eating a meal with 60 grams of carbohydrates (Insulin to Carb ratio is 1 to 10), an 8 oz Filet and a salad with olives and avocado slices?

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

BOTH DIETARY FAT AND PROTEIN INCREASE POST MEAL GLUCOSE CONCENTRATIONS

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

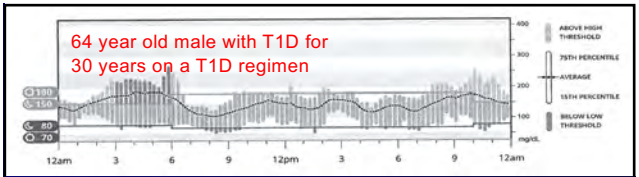


High fat/high protein

High fat/low protein

Low fat/high protein

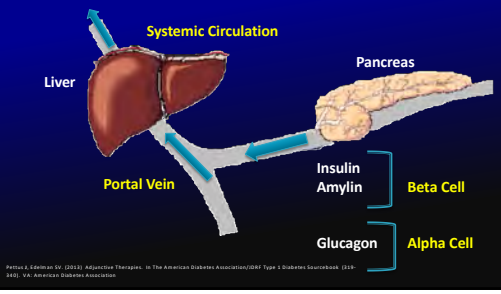
Low fat/low protein



What is/are the possible causes of this patients glucose profiles overnight?

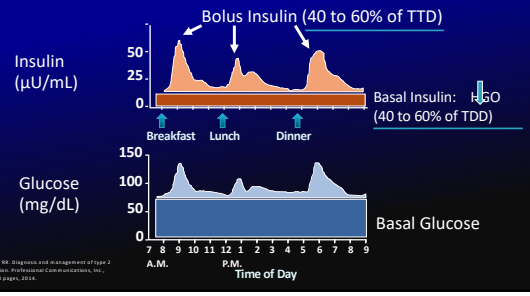
A	Needs more basal insulin
B	Needs to be more consistent in his dinner meals/times
C	He has gastroparesis
D	All of the above

Physiologic Insulin, Glucagon and Amylin Secretion



Pettus J, Edelman SV. (2013) Adjunctive Therapies. In The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook (319-343). VA: American Diabetes Association

Physiologic Insulin Secretion and Glucose Levels In Healthy Subjects



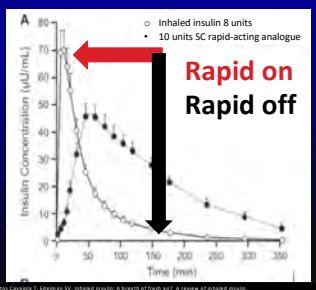
Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2014.

Generic and Trade Names: Insulin

	Generic Name	Trade Name
Fast-Acting Insulin	Regular	Humulin R, Novolin R
	U-500 Regular	Humulin R U-500
	Aspart	NovoLog
	Faster Acting Aspart	Fiasp
	Glulisine	Apidra
	Lispro (U-100 and U-200)	Humalog
	Follow on biologic lispro	Admelog
	Inhaled Insulin	Afrezza
Basal Insulin	Intermediate-Acting:	
	NPH	Humulin N
		Novolin NPH
	Long-Acting:	
	Detemir	Levemir
	Glargine (U-100)	Lantus
	Glargine (U-300)*	Toujeo*
	Degludec (U-100/200)*	Tresiba*
	Follow on biologic glargine (U-100)	Basaglar

Information taken from the PDR Guide and Package Inserts

Inhaled Insulin



- Inhaled insulin 8 units
- 10 units SC rapid-acting analogue

Rapid on
Rapid off

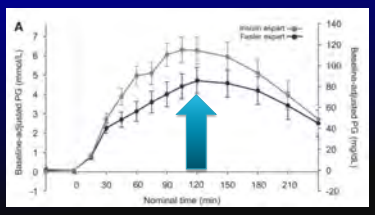
- Better post meal glucose values
- Less delayed hypoglycemia

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

Faster-Acting Aspart or Fiasp

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

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



Bode et al DTT Vol 18 2017

Two New Basal Insulins Recently Added to Our List of Options

Both approved by the FDA and now available for patients

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

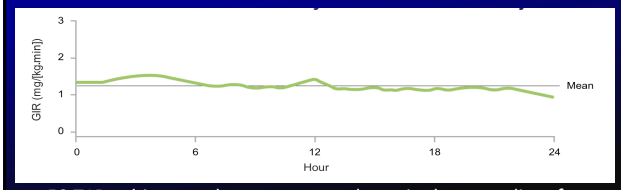
Toujeo prescribing information. Bridgewater, NJ: sanofi, US; 2015 http://products.sanofi.us/toujeo/toujeo.pdf
Tresiba prescribing information 2016. http://www.novo-pi.com/tresiba.pdf

Benefits Of U 300 Glargine and Degludec in Type 1 Diabetes

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

Riddle MC *et al. Diabetes Care.* 2014;37:2755-2762; Yki-Järvinen H *et al. Diabetes Care.* 2014; Published ahead of print: doi: 10.2337/dc14-0990
Bolli GB *et al.* Poster presented at EASD 2014: P967; 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: P-12; Matsushita M *et al.* Poster presented at EASD2014: P975; Terauchi Y *et al.* Poster presented EASD 2014: P974.

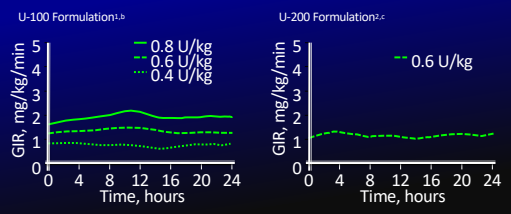
Glucose Infusion Rate In Subjects With Type 1 Diabetes Insulin Glargine U-300



50 T1D subjects underwent two euglycemic clamp studies after six days of receiving insulin glargine U-300

Becker RHA, *et al. Diabetes Obes Metab.* 2015; 17(3): 241-247

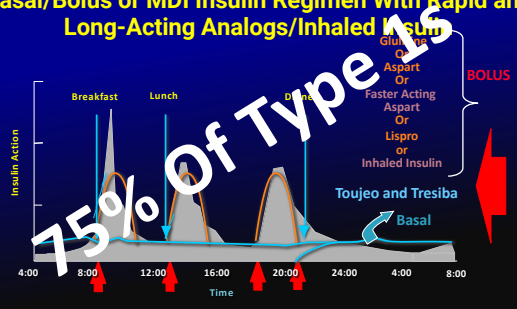
Pharmacodynamics of Insulin Degludec[a] U-100 and U-200 in Patients with T2DM: Same time course of action



[A,B]Glucose clamp study in patients with T2DM (n = 49).
[C]Glucose clamp study in patients with T2DM (n = 16).

1. Heise T, *et al. Diabetes Obes Metab.* 2012;14:944-950.
2. Heise T, *et al. Diabetes.* 2012;61(suppl 1):A91 [abstract 349-OR].

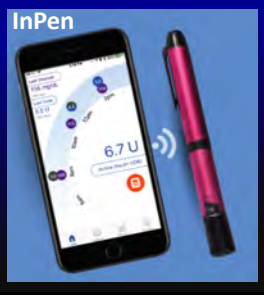
Basal/Bolus or MDI Insulin Regimen With Rapid and Long-Acting Analogs/Inhaled Insulin



75% Of Type 1's

Adapted with permission from Leahy J. In: Leahy J, Cefalu W, eds. *Insulin Therapy*. New York: Marcel Dekker; 2002:87-112. Nathan DM. *N Engl J Med* 2002;347:1342-1349.

Smart Pens: Software Programs As Pumps



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

Let Your Patients Pick the Pump

- Animas Vibe G4 (Discontinued)
- t:slim G6/X2
- 630/670G/530G
- OmniPod

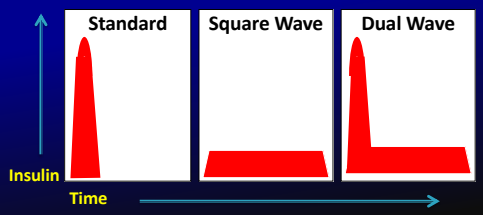
Edelman SV. Taking control of your diabetes: a patient oriented. book on diabetes. Fourth Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2012.

Insulin Pumps: Advantages

- Improved glycemic control
  - More precise, physiologic insulin delivery
  - **Greater ability to handle dawn phenomenon, stress and other conditions that alter insulin requirements**
  - "Smart features" help to estimate insulin doses and reduce errors, i.e. stacking insulin
- In some situations (but not all) freedom and flexibility in lifestyle
  - Eliminate multiple daily injections (1 stick every 3 days)
    Very easy to respond to CGM results
  - Reduce restrictions on eating, exercise and sleeping patterns; could have the same benefits with MDI
  - Greater flexibility with sports, travel, work schedule and other activities (not with water sports)

Edelman, Taking Control Of Your Diabetes 4th edition. 2013 and Walsh JA, Roberts R. Pumping Insulin 5th edition. 2011.

Bolus Options With Pump Therapy



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

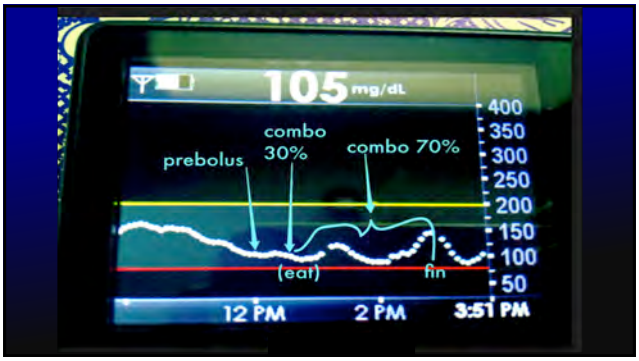
Edelman SV. Taking control of your diabetes: a patient oriented book on diabetes. Fourth Edition Professional Communications Inc., Greenwich, CT. 544 pages, 2013.

Variable Basal Rate Capability

- More precise, physiologic insulin delivery
- Greater ability to handle dawn phenomenon, stress and other conditions that alter insulin requirements
- Able to suspend and reduce basal rates to avoid hypoglycemia

Variable Basal Rate Capability

- Able to set a higher basal rate for illnesses and medications
- Able to program different sets of basal rates for different situations, ie. Work days versus weekends.



What adjustment would you suggest with this patient on a pump?

	B	L	D	HS	~3 am
Day 1	227	121	143	164	142
Day 2	203	152	144	144	161
Day 3	198	124	132	135	133
Day 4	188				

A	Increase the insulin to carbohydrate ratio at dinner time
B	Increase the correction factor at breakfast time
C	Increase the basal rate by 20% starting at 10pm to 7am
D	Increase the basal rate by 20% starting at 3am to 7am

Testing the Basal Rate in Type 1 Diabetes

Testing Overnight

1. Ask the patient have an early dinner, make sure the post prandial BS is between 140 and 180mg/dl (may need a correction dose) with a horizontal trend arrow
2. Fast until the next morning
3. If not on a CGM then he/she needs to test the BS every few hours

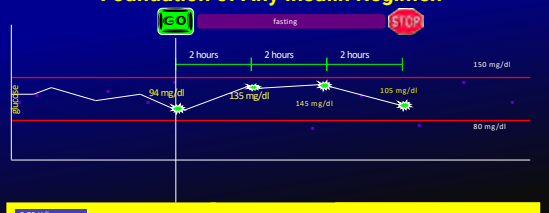
Testing During The Day (different day than testing pm)

1. Ask the patient if he/she can skip breakfast and fast as long as possible.
2. If patient wants to eat a small breakfast then make sure the post breakfast BS is between 140-180mg/dl with a horizontal trend arrow

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

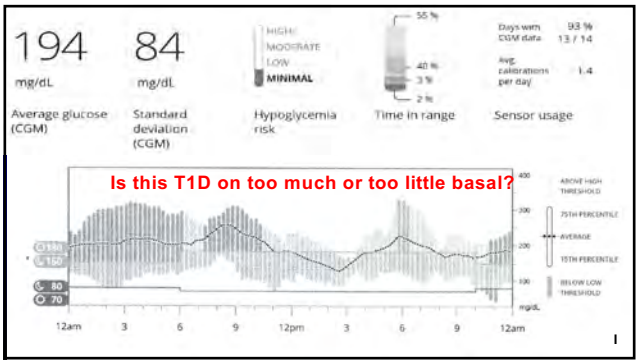
Testing a Basal Segment in T1D:

Foundation of Any Insulin Regimen

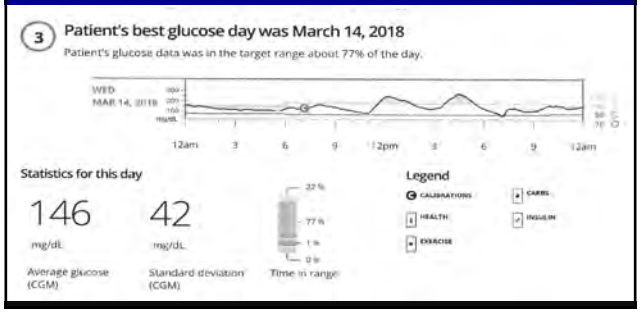


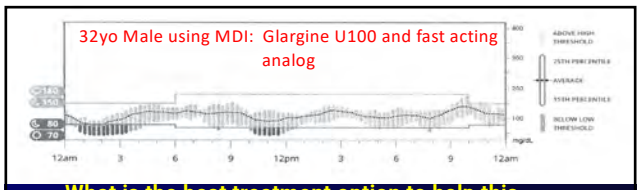
https://myvuqo.com/basal-rate-testing/

5



Same pt. Fasting from 9pm until 7am





What is the best treatment option to help this patient with his overnight values?

A	Decrease the basal insulin
B	Switch the U-100 glargine for U-300 glargine or degludec
C	Have a larger bedtime snack
D	Do not exercise after 7pm

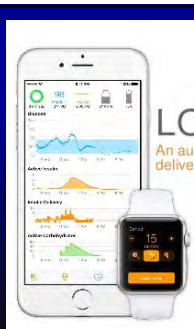
Pump vs. Multiple Daily Injections?

Sensor Augmented Pumps With Newer Features May Change The Way Patients Choose

It Comes Down To Personal Choice

Medtronic 670G: Hybrid Closed Loop

- This is a basal rate modulator
- Works well overnight
- Still requires meal and correction boluses
- 4 or more fingersticks a day to stay in auto move
- Diabetes tasks during the day are not decreased
- There are more alarms
- No sharing capabilities
- Fingerstick required/boluses

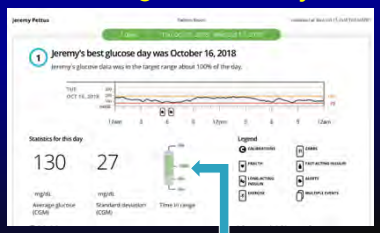


NOT FDA APPROVED YET

DIY: Do It Yourself
Hybrid closed loop

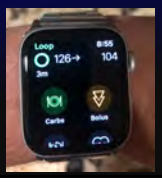
Old Medtronic pump/Omnipod
Smart phone/Apple Watch
Riley link hacking device
Dexcom G6
Always in auto mode
No fingersticks
Formal studies underway

Tracing from Jeremy Pettus L.L.C



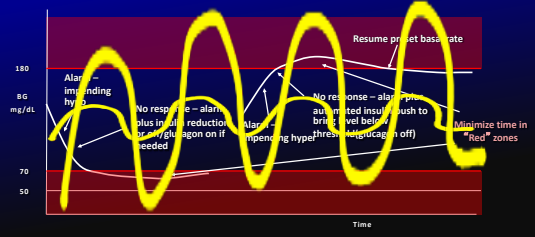
Time in range
"about 100%"

Looping
Low
Carbs



An Artificial Pancreas Will Bridge The Gap Until There Is A Cure

iLet • BigFoot • Tandem • Insulet • Lilly • Medtronic • DIY Loop

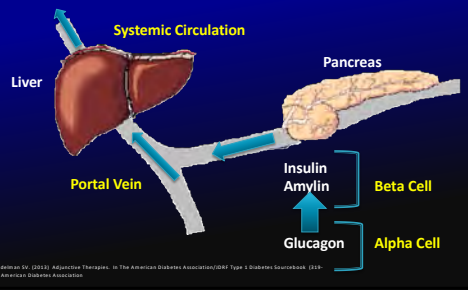


Adjunctive Therapies for People with Type 1 Diabetes

- Amylin Analog (Pramlintide)
- Incretins (GLP-1 RA) *
- SGLT-2 Inhibitors*
- DPP4 Inhibitors*
- Metformin*

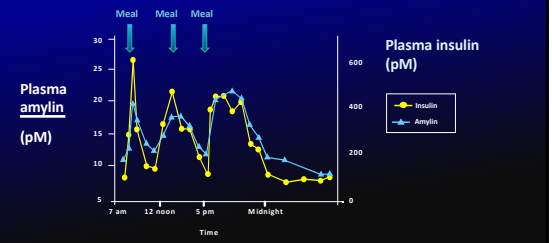
*Medications FDA approved only in type 2 diabetes at the current time

Physiologic Insulin, Glucagon and Amylin Secretion



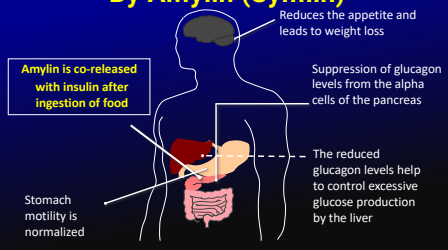
Pettus J, Edelman SV. (2013). Adjunctive Therapies. In The American Diabetes Association/JDRF Type 1 Diabetes Sourcebook (319-340). VA: American Diabetes Association

Physiologic Insulin and Amylin Secretion After Meals



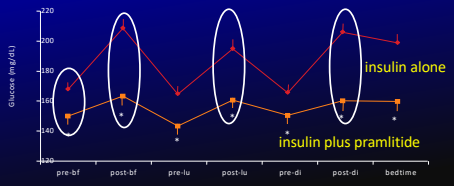
Koda et al, Diabetes. 1995; 44 (s1): 238A.
Weyer et al. Curr Pharm Des. 2001;7:1353-1373

Regulation of Blood Glucose Levels After Meals By Amylin (Symlin)



Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. Eleventh Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2011.

Pramlintide Reduces FBG, PPG and Glucose Fluctuations



Clinical Practice Study, 120 µg SYMLIN
bf, breakfast; lu, lunch; di, dinner
N=166; *p-values for all data points <0.05
Data on file, Amylin Pharmaceuticals, Inc.

Edelman, S., Luth, C., Kesty, N., Burns, C., Weyer, C., Frias, J.: Progressive Reduction in Body Weight with Pramlintide Therapy in Obese Subjects with Type 2 Diabetes Treated with Diet and Exercise and/or Metformin. Diabetes. 56 (Suppl 1):1626-P.

DPP4 Inhibitors In T1D

- No statistically significant differences compared to placebo

Metformin In T1D

- No statistically significant differences compared to placebo in A1c, hypoglycemia and DKA
- Slight reduction in weight and insulin dose

Petrie et al. Lancet DE 2017; 5:597-609
Garg et al. Endocrine Practice, 2013

GLP1-RA in T1D

- There were small very early studies with exenatide
- One large well controlled study looking at liraglutide
- Many of the clinical effects in type 1 are similar to what is seen with SGLT ½ inhibitors
- No agent is actively being studied for FDA approval in type 1 diabetes

SGLT 1/2 Inhibitors in T1D

- There are 3 different drugs being studied in type 1 diabetes (empagliflozin, dapagliflozin and sotagliflozin)
- Sotagliflozin is the furthest along in development and will review the clinical trial data in detail
- If any are approved it would be the first oral agent for type 1 diabetes

Summarize Findings From All SGLT -1/2 Inhibitors

(difficult to make precise efficacy comparisons across trials due to design and analysis differences)

Efficacy (placebo adjusted)	Highest dose*
A1C reduction	~0.4%
Time in Range (blinded CGM)	~3 hour increase
Time in Hypoglycemia (CGM)	No change or some reduction
Insulin dose	10-15% reduction
Weight	~2-3 kg reduction
Systolic blood pressure	~3-4 mm Hg reduction
Patient reported outcomes	Improved

Clinically relevant adverse events include genital mycotic infections (primarily In women 12 to 15%) and DKA (3 to 4%), sometimes euglycemic DKA

* Lower doses retain much of the glycamic efficacy with lesser effect on weight and blood pressure

Summary

- The important unmet needs in T1D include improved glycemic variability (GV), increased time in range (TIR)
- Reaching A1c goal without hypoglycemia
- CGM is the standard of care for T1D
- Pumps and the newer ultra rapid and basal insulins can help improve TIR
- Adjunctive therapies can address some of the unmet needs