Individualizing Diabetes Treatment: Case Studies

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Disclosures

- Debbie Hinnen: Speaker/consultant: Lilly, BI, Novo, Intuity: Diabetes
 - All relevant financial relationships have been mitigated.
- Jason Menges: None
- Justin Moore : None



Case Study: Fred, 61 Years Old With T2D, Obesity, Dyslipidemia, Hypertension, and History of MI

- Physical Examination
 - No apparent distress
 - Height: 5 ft 10 in
 - Weight: 246 lb (BMI: 35.3 kg/m²)
 - Blood pressure: 130/88 mm Hg. Pulse 72bpm
 - No edema noted
- Laboratory Findings
 - Fasting blood glucose: 133 mg/dL; A1C: 8.6%;
 UACR 25 mg/g; eGFR: 70 mL/min/1.73 m²
 - All other labs normal
 - PMH

- Medications
 - Atorvastatin 80 mg daily
 - Lisinopril 40 mg daily
 - Metoprolol tartrate 25 mg twice daily
 - Metformin 1000 mg twice daily
 - Aspirin 81 mg daily
- Allergies/Adverse Drug Events: GI issues when first starting Metformin
- Family Hx: Mother: dylsipidemia, MI age 68. Father HTN, Obesity
- Social
 - Lives alone, retired
 - Has BC/BS insurance

⁻MI 4 years ago



What are next steps for Fred?

- Change Metformin to XR?
- Add a GLP1?
- Add an SGLT2?
- Add an Sulfonylurea?
- Other?

- Refer to Diabetes Self Management Education and Support?
- Continuous Glucose Monitoring (CGM)?

Use of Glucose-Lowering Medications in Management of Type 2 Diabetes

To avoid therapeutic inertia, reassess and modify treatment regularly (3-6 mo)

HEALTHY LIFESTYLE BEHAVIORS, DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT, SOCIAL DETERMINANTS OF HEALTH



Cardiorenal Risk Reduction or Glycemic Lowering Needed

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Additional Cardiorenal Risk Reduction or Glycemic Lowering Needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide	Achievement and Maintenance of Weight Management Goals			
the efficacy to achieve goals Metformin OR agent(s) including	Set individualized weight management goals			
COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals	General lifestyle advice: Intensive evidence medical nutrition therapy/ based structured eating patterns/physical weight managemen activity program			
priority in high-risk individuals	Consider medication for weight loss	Consider metabolic surgery		
have greater likelihood of achieving glycemic goals Efficacy for Glucose Lowering	When Choosing Glucose-Lowering Therapies: Consider regimen with high to very high dual glucose and weight efficacy			
VERY HIGH:				
tirzepatide	Efficacy for Weight Loss			
Insulin Combination oral, combination injectable	VERY HIGH: Semaglutide, tirzepatide			
(GLP-1 RA/insulin) HIGH:	HIGH: Dulaglutide, lir	aglutide		
GLP-1 RA (not listed above), metformin, SGLT2i, sulfonvlurea, TZD	INTERMEDI GLP-1 RA (not listed a	ATE: above), SGLT2i		
INTERMEDIATE: DPP-4i	NEUTRAL: DPP-4i, metformin			

If A1C Above Target

Identify Barriers to Goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (eg, diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that affect achievement of goals

The "Ominous Octet": Multiple, Complex Pathophysiologic Abnormalities in T2D



DPP-4i = dipeptidyl peptidase-4 inhibitor; SGLT2i = SGLT2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione. Adapted from: Inzucchi SE, Sherwin RS. In: Cecil Medicine. 2011; DeFronzo RA. Diabetes. 2009;58:773-795.

GLP-1 RA Dosage Guidelines and Benefits in T2D

GLP-1 RA	Dosing Frequency	Starting Dose	Max Dose	Titration Frequency	Cardiovascular Benefit	Kidney Benefit
Exenatide BID	Twice daily	5 mcg	10 mcg	1 month		
Lixisenatide	Once daily	10 mcg	20 mcg	14 days		
Liraglutide	Once daily	0.6 mg	1.8 mg	1 week	Yes	Yes
Semaglutide PO	Once daily	3 mg	14 mg	30 days		
Dulaglutide	Once weekly	0.75 mg	4.5 mg	<u>></u> 4 weeks	Yes	Yes
Semaglutide SC	Once weekly	0.25 mg	2 mg	4 weeks	Yes	Yes
Exenatide ER	Once weekly	2 mg	2 mg	NA		

American Diabetes Association. Diabetes Care. 2022;45:S133. Dulaglutide PI. Exenatide BID PI. Exenatide ER PI. Liraglutide PI. Lixisenatide PI. Semaglutide SC PI. Semaglutide tablets PI.

GLP-1 RA Comparative Studies: Change in A1C



**P* <0.05. ^{+}P <0.05, meeting predefined noninferiority margin.

Figure adapted from Trujillo. Ther Adv Endocrinol Metab. 2021;12:2042018821997320. Note that direct comparisons between clinical trials cannot be made. Ahmann. Diabetes Care. 2018;41:258. Blevins. J Clin Endocrinol Metab. 2011;96:1301. Buse. Lancet. 2009;374:39. Buse. Lancet. 2013;381:117. Capehorn. Diabetes Metab. 2020;46:100-109. Drucker. Lancet. 2008;372:1240. Dungan. Lancet. 2014;384:1349. Nauck. Diabetes Care. 2016;39:1501. Pratley. Lancet. 2019;394:39-50. Pratley. Lancet Diabetes Endocrinol. 2018;6:275. Rosenstock. Diabetes Care. 2013;36:2945. Wysham. Diabetes Care. 2014;37:2159. Yabe. Lancet Diabetes Endocrinol. 2020;8:377-391.

Trials of GLP-1 RAs: Changes in Body Weight



Exenatide 10 mcg BID
Exenatide 2 mg QW
Liraglutide 0.9 mg
Liraglutide 1.2 mg
Liraglutide 1.8 mg
Dulaglutide 0.75 mg
Dulaglutide 1.5 mg
Lixisenatide 20 mcg
Semaglutide 0.5 mg
Semaglutide 1.0 mg
Oral semaglutide 7 mg
Oral semaglutide 14 mg

**P* <0.05.

Figure adapted from Trujillo. Ther Adv Endocrinol Metab. 2021;12:2042018821997320. Note that direct comparisons between clinical trials cannot be made. Ahmann. Diabetes Care. 2018;41:258. Blevins. J Clin Endocrinol Metab. 2011;96:1301. Buse. Lancet. 2009;374:39. Buse. Lancet. 2013;381:117. Capehorn. Diabetes Metab. 2020;46:100-109. Drucker. Lancet. 2008;372:1240. Dungan. Lancet. 2014;384:1349. Nauck. Diabetes Care. 2016;39:1501. Pratley. Lancet. 2019;394:39-50. Pratley. Lancet Diabetes Endocrinol. 2018;6:275. Rosenstock. Diabetes Care. 2013;36:2945. Wysham. Diabetes Care. 2014;37:2159. Yabe. Lancet Diabetes Endocrinol. 2020;8:377-391.

GLP-1 RA Cardiovascular Outcomes Trials

Agent	Lixisenatide SC, Daily	Liraglutide SC, Daily	Semaglutide SC, Weekly	Exenatide ER SC, Weekly	Albiglutide SC, Weekly	Dulaglutide SC, Weekly	Semaglutide PO, Daily
Study	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER-6
Ν	6068	9340	3297	14,752	9463	9901	3183
Trial duration	25 mo	3.8 yr	2.1 yr	3.2 yr	1.5 yr	>5 yr	16 mo
Mean diabetes duration, yr	9.3	12.8	13.9	12	14	10.5	14.9
Mean age, yr	60	64	65	62	64	66	66
Female, %	30	36	39	38	30	47	32
Prior CVD, %	100	72	59	73	100	31	85
Mean BMI, kg/m ²	30	33	33	32	32	32	32
Mean A1C, %	7.7	8.7	8.7	8.0	8.7	7.3	8.2

Pfeffer. NEJM. 2015;373:2247. Marso. NEJM. 2016;375:311. Marso. NEJM. 2016;375:1834. Holman. NEJM. 2017;377:1228. Green. Am Heart J 2018;203:30. Gerstein. Diabetes Obes Metab 2017;20:42. Husain. NEJM. 2019;381:841.

Once-Weekly Tirzepatide (Mounjaro) A New Class For T2D Treatment



Terzepatide/(Mounjaro)

- Once a week auto injector
- 2.5mg/5/mg/7.5mg/10mg/12.5mg/15mg per 0.5 mL
- Works on fasting and post meal glucose
- Helps you feel full, can contribute to weight loss (13-25lb)
- Potential Side effects: Nausea/Vomiting/
 Appetite

 /Diarrhea or Constipation
 - Acute kidney diseases can occur if you get dehydrated
- Contraindicated: personal or family history of medullary thyroid carcinoma (MTC), or in patients with Multiple Endocrine neoplasia syndrome type 2 (MEN2),
- Risk of Thyroid c-cell tumors, acute pancreatitis, hypoglycemia if used with SU or Insulin (dose needs to be adjusted).
- A1c reduction 1.8% to 2.
- Cost: \$\$\$, co-pay card



Choose GLP-1 RA Before Insulin Nearly Always



ADA. Diabetes Care. 2022;45:S125.

Starting Therapies in Patients With T2D

Coverage Search App



Apple App Store <u>https://apps.apple.com/us/app/c</u> <u>overage-search/id834992816</u>

Google Play Store

https://play.google.com/store/ap ps/details?id=testformularysearc h.mmit.com.formulary&hl=en_U <u>S&gl=US&pli=1</u>

- 1. Use *Coverage Search* or another formulary search resource
 - Requires the drug, state, and insurance category to determine coverage
- 2. Review the mechanism of action and benefits of the drug (eg, A1C reductions, weight reductions, CV or renal protection)
- 3. Review the side effects and how to mitigate
 - For GLP-1 RA GI adverse effects: snack for the first few days, eat about one-half of what you usually eat, stop eating when full, follow or slow the titration schedule
 - For SGLT2i adverse effects: good genital hygiene (clean and dry), drink extra water
- 4. Show patients how to inject with demo pen or sample and supervise self injection
- 5. Call (or have an MA call) the pharmacy to verify prescription was received, run the prescription, and determine out-of-pocket cost
- 6. Print (or have an MA print) co-pay card for patients with commercial insurance



Case \rightarrow Fred

- Fred followed your advice and
 - started semaglutide at 0.25mg.
 - He was queasy, so week 2 decreased to 10 clicks. Week 3: 0.25mg, and week 4: 0.5mg
 - Weeks 5-8 and 9-12 he took 0.5mg/weekly injection
 - Weeks 13-20 he increased to 1mg/week
 - His early nausea abated with "click" titration, and after 4 months, he was able to increase to 1 mg weekly.
 - 2 months later, he was taking 2mg weekly with no further side effects
- Since originally starting a GLP-1, he has lost a total of 25 lb. He states he has more energy, and has started walking daily
- Physical Examination
 - Height: 5 ft 10 in
 - Weight: 221 lb (BMI: 31.7kg/m²)
 - Blood pressure: 128/80 mm Hg
 - Pulse: 70 beats/min
- Laboratory Findings
 - Fasting blood glucose: 108 mg/dL; A1C: 7.2%
 - All other repeat labs normal

IS THIS ENOUGH?



Case Study: Fred, 61 Years Old With T2D, Obesity, Dyslipidemia, Hypertension, and History of MI

- Physical Examination
 - No apparent distress
 - Height: 5 ft 10 in
 - Weight: 246 lb (BMI: 35.3 kg/m²)
 - Blood pressure: 130/88 mm Hg. Pulse 72bpm
 - No edema noted
- Laboratory Findings
 - Fasting blood glucose: 133 mg/dL; A1C: 8.6%;
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- Allergies/Adverse Drug Events: GI issues when first starting Metformin
- Family Hx: Mother: dylsipidemia, MI age 68.
 Father HTN, Obesity
- Social
 - Lives alone, retired
 - Has MCare with BC/BS supplement

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Role of SGLT2 Inhibitors



Nauck MA. *Drug Des Devel Ther*. 2014;8:1335-1380.

SGLT2 Inhibitor Summary

SGLT2	FDA APPROVAL FOR RISK REDUCTION			A1C	NNSF	RENAL DUSING	
INHIBITOR	CVD	HF	CKD	REDUCTION	DUUL		
Brenzavvy® (bexagliflozin)	No indication	No indication	No indication	-0.5%	20 mg/day	 <30 mL/min/1.73 m²: not recommended 	
Invokana® (canagliflozin)							



Case Summary: Fred

- Fred followed your advice and
 - started empagliflozin 10mg
 - No adverse events reported
 - No hypoglycemia
- Laboratory Findings after 3 months
 - Fasting blood glucose: 104 mg/dL; A1C: 6.9%
 - All other repeat labs normal

AND he attended diabetes education classes.

Meet Sarah, 46 y/0 F Uncontrolled DM ~ 9 years: T2, T1 or LADA?

DX:

- peripheral neuropathy,
- hyperlipidemia,
- iron deficiency anemia
- persistently elevated A1C
- BMI 30.78 (wt 185, ht 65 inches)

MEDS:

- She is currently on 54 units of Glargine (lantus) at bed time,
- 1.8mg Liraglutide (Victoza) injection daily,
- Metformin 1000mg twice a day and
- Dapagliflozin (Farxiga) 10mg daily.

PMH:

- She has a strong family history of diabetes
- hx of gestational diabetes when she was pregnant some ago. LABS:
- Her sugars range from 70-400mg/dl and she complains of daily nausea and dyspepsia.
- GAD 65 (results +) and other labs ordered to evaluate for type 1
- eGFR 52
- •

Questions about Sarah's case....

- 1. Does she have late onset T1 diabetes?
- 2. Since GAD65 was positive, do we need to test other antibodies? What are they?
- 3. If LADA, should she continue other meds or just insulin?
 - 1. Dapagliflozin? Other renal protection?
 - 2. Metformin?
 - 3. Insulin? Adjust current 54u glargine (basal)?
 - 1. How do you switch to Multiple daily insulin (MDI)? How to titrate basal/bolus
 - 4. When should she do Blood glucose testing? What about a CGM? Insulin Pump?
 - 5. What other auto immune issues should be checked?
 - 6. Other?

Units of pre-meal rapid-	Units of peakless insulin		
acting analog	glargine (Lantus)		
c lispro (Humalog)	c Before breakfast		
c aspart (Novolog)	c Before bedtime		
c glulisine (Apidra)			
8	24		
10	24		
10	30		
12	30		
12	36		
14	36		
14	42		
16	42		
16	48		
18	48		
18	54		
20	54		
20	60		
22	60		
22	66		
24	66		
24	72		
26	72		
26	78		
28	78		
28	84		
30	84		
30	90		
32	90		
32	96		
	Units of pre-meal rapid- acting analog c lispro (Humalog) c aspart (Novolog) c glulisine (Apidra) 8 10 10 12 12 12 14 14 16 16 18 20 20 20 22 22 22 24 24 26 28 30 30 32 32 32		

While we are trying to discover the amount of insulin that you need, please eat

(c gm) (c servings) of carbohydrate at every meal. The instruction to eat the same amount at each meal is a temporary restriction. Our goal is to discover the amount of insulin that is needed to get good results for a certain amount of carbohydrate. Then, once we discover the matching rule, you will be free to change the amount that you eat from meal to meal.

Call me if you begin to show any readings under 80 or if you have symptoms of hypoglycemia. If you begin to show some blood glucose readings before meals that are in the target range of ______ to

mg/dL, please hold with the dose you are taking, make no further changes of insulin dose, and come in to visit me to review your logbook. Be sure to carry in your meter and one week of log-

Moore. University of Kansas, endocrinology. 2023

Time Action of Insulins

Insulin	Starts (m-hr)	Peak (hr)	<i>Duration</i> (hrs)
Aspart,Lispro,Gulisine Novolog, Humalog, Apidra	10-15m	1–1.5	3-4
Lyumjev, FiAsp Ultra fast	1-5 m	30-90m	3
Afrezza(inhaled rapid)	12-15	53min	180min
Regular	30+m	2–3	4–6
NPH (Walmart \$25 no Rx)	2–4h	6–8	10–12
Glargine (Lantus) u-100	2+h	~Flat	24+/-
(Toujeo) - U300		VERY flat	32 hr
Detemir (Levemir)	2+h	6+/-	20-24
Degludec (Tresiba)	2+ hr	very flat	42 hr

Impaired Insulin Secretion





 a Results shown for individuals with T1DM; b Individuals with and without T1DM; c U-200 degludec curve is similar. 3

1. Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/daf/. 2. Google Patents. http://www.google.com/patents/US20120122774. 3. Heise T, et al. *Diabetes*. 2012;61(suppl 1):A91 [abstract 349-OR].



Pumps *PLUS* CGM *automated insulin delivery*



Summary

- You can now *Treat* Diabetes, not just *Chase* Glucose
- SGLT2s and GLP's offer simplicity in treatment, Glucose improvement with additional weight loss and very low hypoglycemia risk
- SGLT2s and GLP's also offer Renal, Cardiac, and Stroke protection. (The big uglies if diabetes is out of control long term)
- Help your PWD get the best they can afford: Check the formulary, other resources. It might require a PA
- New technology is empowering. CGMs, Pumps, communication back and forth...
- Ultra long acting insulins are like I-70 through W Ks. Plus: Less hypoglycemia, intra patient, intra day variability
- You Can Do It!