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Diabetes in 2023 - Understanding the Acronyms

From GLP to SGLT2 and CGM to AGP and BeAM with TDD

MT Family Practice Annual Conference
June 23, 2023

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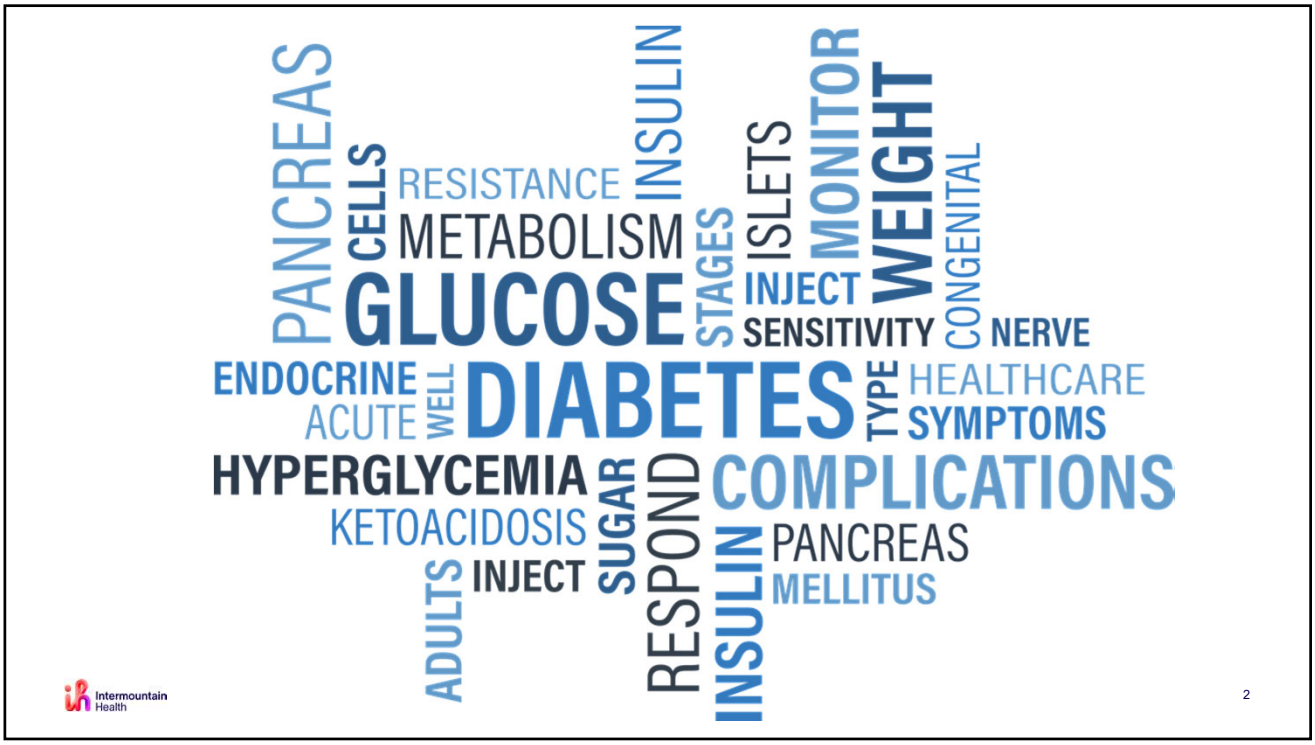

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Disclosures

Justen Rudolph, MD - None

Learning Objectives

- Identify Role & Rationale for GLP1 analogs and SGLT2 inhibitors in the treatment of type 2 diabetes
- Understand CGMs and AGP report
- Identify when and how to start mealtime insulin

GLP-1 Agonists – Glucose Like Peptides

GLP Analogs – Glucagon-Like Peptides

List of Drugs – Brand Names and Generic Names

- Byetta
- Bydureon
- Victoza
- Trulicity
- Ozempic
- Rybelsus (oral)
- Mounjaro (GLP/GIP)
- Exenatide
- Exenatide
- Liraglutide
- Dulaglutide
- Semaglutide
- Semaglutide
- Tirzepitide

GLP Analogs – Mechanism of Action

Pancreas/Liver

Decrease Glucagon

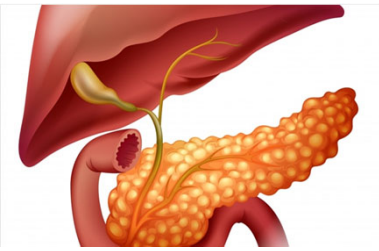
Glucose Dependent Insulin Release

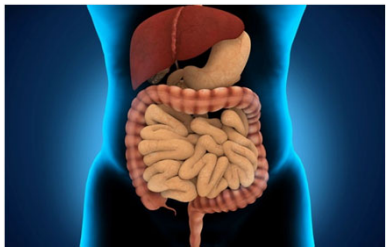
Gut

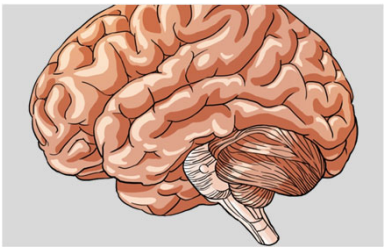
Delay Gastric Emptying

Brain

Increase Satiety







GLP Analogs – Glucagon-Like Peptides

Benefits

- Weight loss
- Feeling satiated
- Postprandial glucose control
- Easy dosing
- Low risk of hypoglycemia
- CV risk reduction

GLP Analogs – Glucagon-Like Peptides

Side Effects

- Thyroid Cancer
- Gastroparesis
- Pancreatitis ??
- Pregnancy/Breast Feeding

Contraindications

- Nausea – up to 60%
- Vomiting
- Bloating/Gas
- Diarrhea
- Constipation
- ~ 10% intolerable
- Can Dose Reduce

GLP Analogs – Glucagon-Like Peptides

Dosing - start low and go slow

- Extenatide (Byetta) – Bcise Pen - 2 mg weekly
- Lixenatide (Victoza) – start 0.6 mg daily, 1.2 and 1.8 mg dose
- Semaglutide (Ozempic)– start 0.25 mg weekly for 4 weeks, 0.5 mg, 1 mg; max 2 mg.
  - Use the 3ml pen
- Dulaglutide (Trulicity) – 0.75 mg weekly, 1.5 mg, 3 mg, 4.5 mg
- Oral Semaglutide (Rybelsus) – Start 3 mg, 7 mg, 14 mg.

GLP Analogs – Glucagon-Like Peptides

CV Outcome Trials

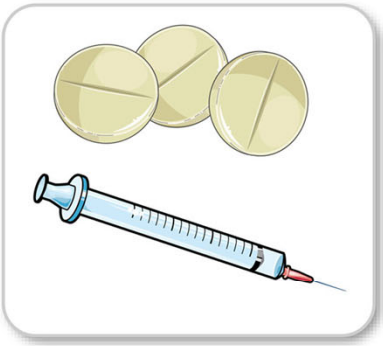
- Meta Analysis
- 8 CVOT trials
- Drugs used: Liraglutide, Dulaglutide, Semaglutide
- 14% reduction in 3 component MACE – CV death, Nonfatal MI, Nonfatal Stroke
  - NNT 65 for 12- 18 mo.

Sattar N, Lee **Lancet Diabetes Endocrinol**. 2021; 9:653–662.

GLP-1 receptor agonists

Effects on CV outcomes
(HR; 95%CI)

MACE	0.86 (0.80 to 0.93)
MI	0.90 (0.83 to 0.98)
Stroke	0.83 (0.76 to 0.92)
CV death	0.87 (0.80 to 0.94)



Effects on risk factors

glucose	weight	blood pressure
HbA1 ~ 1.5 %	~ 4%	~ 3 mmHg

Side effects
- GI side effect
- Local reaction at injection side
- Use with caution in patients with history of pancreatitis

Patient profile
- ASCVD
- Overweight / obese
- High risk of stroke

Treatments aspects
- Start with low dose
- Increase dose slowly
- Use ≤ 32 gauge needle
- Adjust insulin / SU dose
- Recommend small meals

Marx; Circulation. 2022;146:1882–1894

GLP Analogs – Glucagon-Like Peptides

Bottom Line

- Excellent for glucose control and weight loss
- CV Risk Reduction
- Start Low and Go Slow
- Insurance Coverage Important
- Consider Reducing other glucose lowering agents

SGLT2 Inhibitors

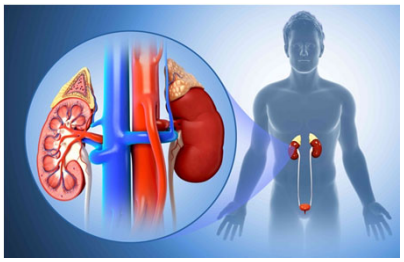
SGLT2 Inhibitors - Gliflozins

- The Triple Effect

Diabetes

Heart Disease

CKD



SGLT2 Inhibitors

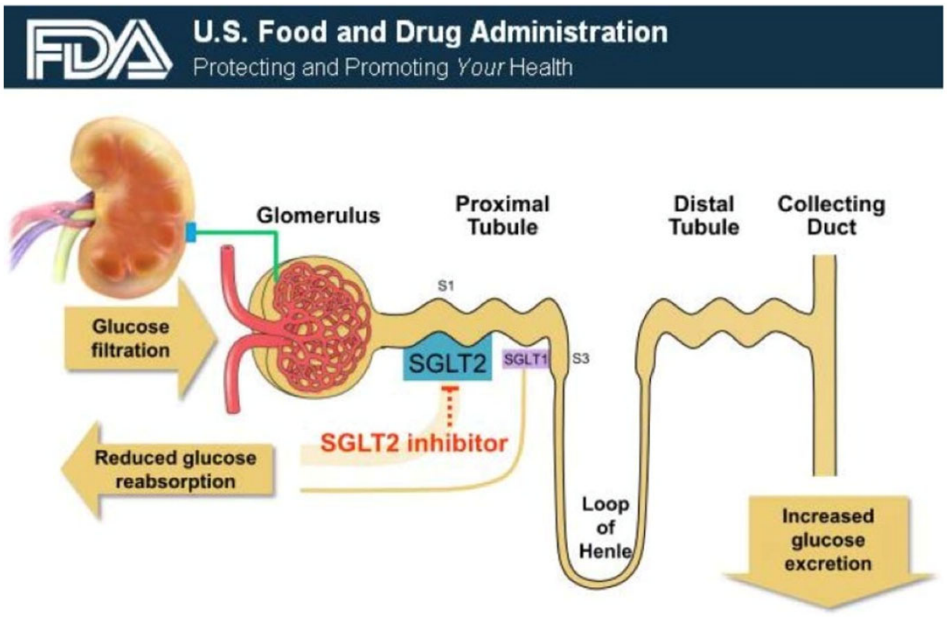
Positive Effects

- Lower Sugars
  - Without Hypoglycemia
- Lower Weight
- Lower Blood Pressure
- Lower Heart Disease
- Lower Risk Heart Failure
- Lower risk of CKD Progression

SGLT2 Inhibitors

List of Drugs – Brand Names and Generic Names

- Jardiance
- Invokana
- Farxiga
- Steglatro
- Empagliflozin
- Canagliflozin
- Dapagliflozin
- Ertugliflozin



SGLT2 Inhibitors - Gliflozins

CVOT Data

Table 1. Cardiovascular Outcome Trials Involving Patients with Type 2 Diabetes.*

Variable	EMPA-REG OUTCOME	CANVAS Program	CREDENCE	DECLARE–TIMI 58	VERTIS CV	SCORED	All
Drug	Empagliflozin	Canagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Sotagliflozin	
No. of patients	7020	10,142	4401	17,160	8246	10,584	57,553
Atherosclerotic cardiovascular disease — % of patients	100	65.6	50.4	40.6	100	48.6	63.0
History of heart failure — % of patients	10.1	14.4	14.8	10.0	23.7	31.0	17.0
Outcomes — hazard ratio (95% CI)†							
Major adverse cardiovascular events	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.80 (0.67–0.95)	0.93 (0.84–1.03)	0.99 (0.88–1.12)	0.77 (0.65–0.91)	0.89 (0.84–0.94)
Cardiovascular death	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.78 (0.61–1.00)	0.98 (0.82–1.12)	0.92 (0.77–1.10)	0.90 (0.73–1.12)	0.86 (0.79–0.93)
Hospitalization for heart failure	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.61 (0.47–0.80)	0.73 (0.61–0.88)	0.70 (0.54–0.90)	0.67 (0.55–0.82)	0.68 (0.62–0.75)

* Data sources for the individual trials are as follows: EMPA-REG OUTCOME, Zinman et al.[14]; CANVAS Program, Neal et al.[15]; CREDENCE, Perkovic et al.[16]; DECLARE–TIMI 58, Wiviott et al.[17]; VERTIS CV, Cannon et al.[18]; and SCORED, Bhatt et al.[19] Data are also based on a meta-analysis by McGuire et al.[20]
† Hazard ratios are based on a time-to-first event analysis, except for SCORED, which estimated hazard ratios for major adverse cardiovascular events and hospitalization for heart failure on the basis of a total-event analysis. CI denotes confidence interval.

Braunwald, N Engl J Med 2022; 386:2024-2034

SGLT2 Inhibitors - Gliflozins

CKD Data

- CREDENCE Trial – Canagliflozin
  - 4401 pts with Type 2 dm and albuminuric CKD GFR 30 – 90, on ACE or ARB
  - Primary Endpoint – composite ESRD, Doubling Cr, or Death d/t CV or Renal
  - 100 cana vs placebo
  - Stopped early at 2.6 yrs due to efficacy
    - 30% reduction in primary outcome (43 events/1000 pt-yrs vs 61)

Perkovic. N Engl J Med 2019; 380:2295-2306

SGLT2 Inhibitors - Gliflozins

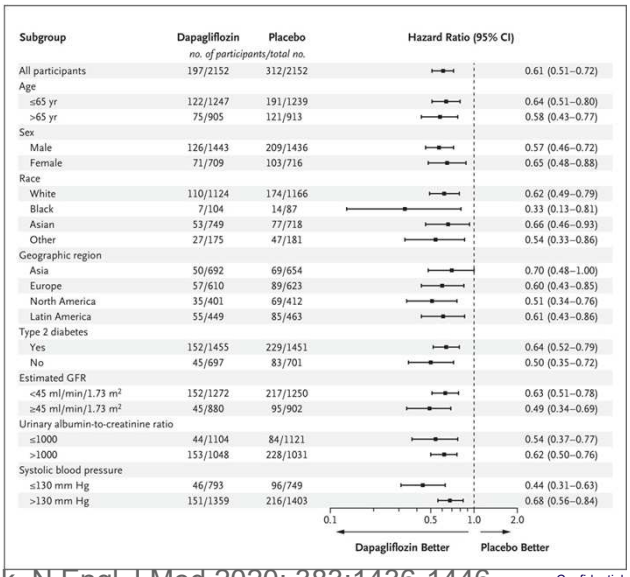
CKD Data

- DAPA-CKD Trial Dapagliflozin
  - – 4304 pt with GFR 25-75 and ACR 200 – 5000, on ACE or ARB
    - 68% with Type 2 DM
  - – Primary Outcome – sustained decline in GFR of 50%, ESRD, death from renal or CV cause
  - – 10 dapa vs placebo
  - – Results: Stopped early 2.4 yrs due to efficacy
    - 37% reduction in primary outcome (9.2% dapa vs 14.5% placebo)
    - NNT 19

 Heerspink. N Engl J Med 2020; 383:1436-1446

SGLT2 Inhibitors - Gliflozins

DAPA-CKD Prespecified Subgroup Analysis



Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of participants/total no.		
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Age			
≤65 yr	122/1247	191/1239	0.64 (0.51–0.80)
>65 yr	75/905	121/913	0.58 (0.43–0.77)
Sex			
Male	126/1443	209/1436	0.57 (0.46–0.72)
Female	71/709	103/716	0.65 (0.48–0.88)
Race			
White	110/1124	174/1166	0.62 (0.49–0.79)
Black	7/104	14/87	0.33 (0.13–0.81)
Asian	53/749	77/718	0.66 (0.46–0.93)
Other	27/175	47/181	0.54 (0.33–0.86)
Geographic region			
Asia	50/692	69/654	0.70 (0.48–1.00)
Europe	57/610	89/623	0.60 (0.43–0.85)
North America	35/401	69/412	0.51 (0.34–0.76)
Latin America	55/449	85/463	0.61 (0.43–0.86)
Type 2 diabetes			
Yes	152/1455	229/1451	0.64 (0.52–0.79)
No	45/697	83/701	0.50 (0.35–0.72)
Estimated GFR			
<45 ml/min/1.73 m²	152/1272	217/1250	0.63 (0.51–0.78)
≥45 ml/min/1.73 m²	45/880	95/902	0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)
Systolic blood pressure			
≤130 mm Hg	46/793	96/749	0.44 (0.31–0.63)
>130 mm Hg	151/1359	216/1403	0.68 (0.56–0.84)

 Heerspink. N Engl J Med 2020; 383:1436-1446

SGLT2 Inhibitors - Gliflozins

ADA Statement 2023 Guidelines

"In sum, for people with type 2 diabete and diabetic kidney disease, use of an SGLT2 in hibitor is recommended to reduce CKD progression and cardiovascular events in people with an eGFR ≥ 20ml/min/1.73m^2."

ElSayed. *Diabetes Care* 2023;46(Supplement_1):S191–S202

SGLT2 Inhibitors - Gliflozins

Side Effects and Contraindications

- UTI & Yeast Infections
- Dehydration and AKI
- Euglycemic DKA – especially in Type 1 (not indicated for however)

SGLT2 Inhibitors - Gliflozins

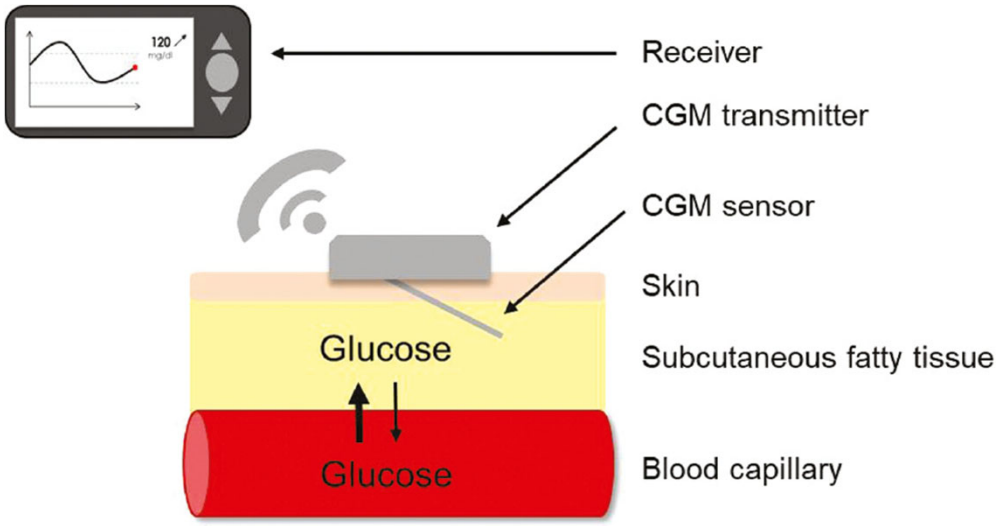
Practical Tips

- Stop 3 days prior to surgery
- Don't fret about > 1000 glucose on UA
- Drink Fluids
- Use in Heart Failure Patients & CKD
- Avoid using with recurrent UTIs
- Glucose lowering effects less if GFR < 45
- Cardiology and Nephrology may be prescribing
- Avoid with Type 1 Diabetes

CGM

Continuous Glucose Monitors

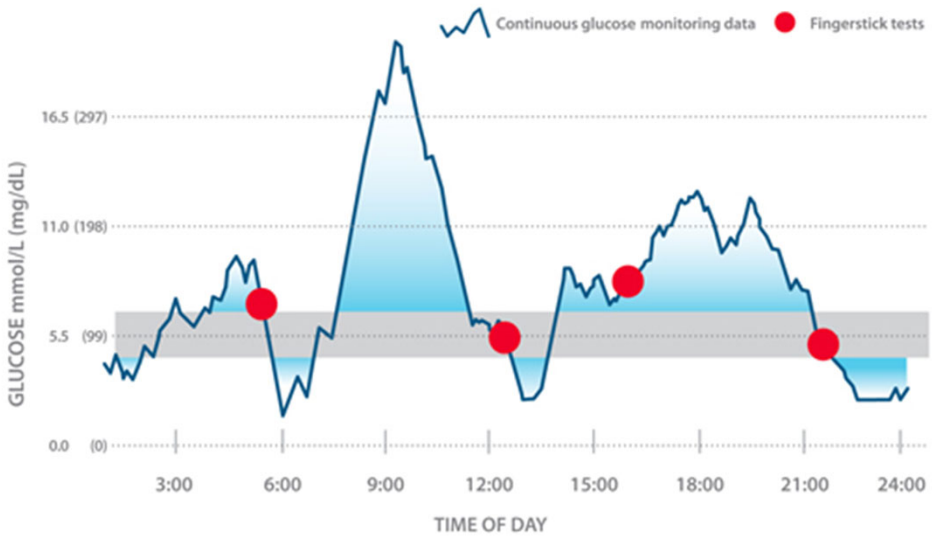
CGM Explained



Freckmann, Guido. "Basics and use of continuous glucose monitoring (CGM) in diabetes therapy" *Journal of Laboratory Medicine*, vol. 44, no. 2, 2020, pp. 71-79. https://doi.org/10.1515/labmed-2019-0189

CGM Types

CGM Data



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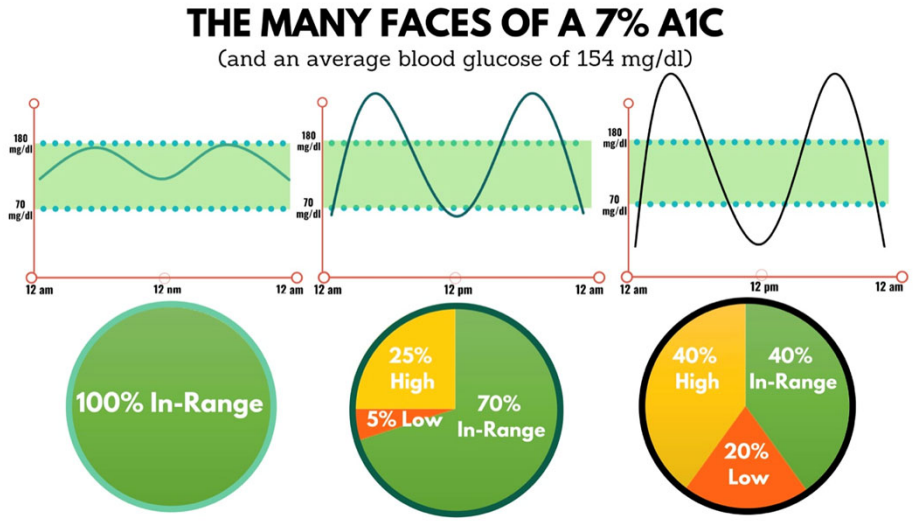
Beyond A1c



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Adapted from https://diatribe.org/foundation/beyonda1c. 3/2023

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CGM Uses and Insurance

Uses and Insurance

- Type 1 Diabetes
- Pregnancy
- Type 2 diabetes
  - Medicare 2023 Guidelines – DME coverage
    - One or more shots of insulin a day
    - "problematic hypoglycemia"
  - Commercial - Pharmacy benefit – eRx
- Athletes ??

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CGM Uses and Insurance

Medicare Guidelines

- To be eligible for coverage of a CGM and related supplies, the beneficiary must meet all of the following initial coverage criteria (1)-(5):

1. The beneficiary has diabetes mellitus
2. The beneficiary's treating practitioner has concluded that the beneficiary (or beneficiary's caregiver) has sufficient training using the CGM prescribed
3. The CGM is prescribed in accordance with its FDA indications for use
4. The beneficiary for whom a CGM is being prescribed, to improve glycemic control, meets at least one of the the criteria:
   a. The beneficiary is insulin-treated; OR
   b. the beneficiary has a history of problematic hypoglycemia with documentation of at least one of the following:
      a. Recurrent (more than one) level 2 hypoglycemic events (glucose <54mg/dL (3.0mmol/L)) that persist persist despite multiple (more than one) attempts to adjust medication(s) and/or modify the diabetes diabetes treatment plan; or,
      b. A history of one level 3 hypoglycemic event (glucose <54mg/dL (3.0mmol/L)) characterized by altered altered mental and/or physical state requiring third-party assistance for treatment of hypoglycemia
5. Within six (6) months prior to ordering the CGM, the treating practitioner has an in-person or Medicare-approved telehealth visit with the beneficiary to evaluate their diabetes control and determined that criteria (1)-(4) above are met.

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American Diabetes Association.

From: **Standards of Care in Diabetes—2023 Abridged for Primary Care Providers**

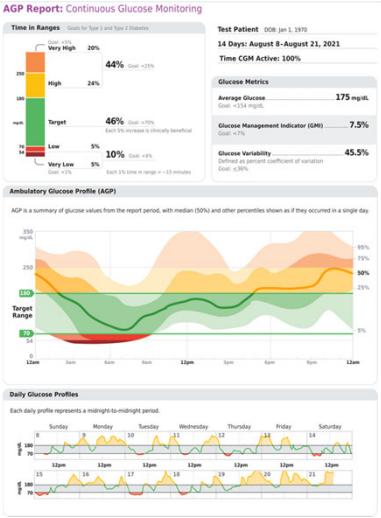

Figure Legend:

Key points included in standard AGP report. Reprinted from Holt RIG, DeVries JH, Hess-Fischl A, et al. Diabetes Care 2021;44:2589–2625.

Clin Diabetes. 2022;41(1):4-31. doi:10.2337/cd23-as01

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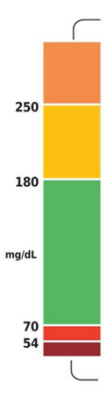
AGP Report: Continuous Glucose Monitoring

Time in Ranges Goals for Type 1 and Type 2 Diabetes



Very High	20%	
High	24%	44% Goal: <25%
Target		46% Goal: >70%
		Each 5% increase is clinically beneficial
Low	5%	
Very Low	5%	10% Goal: <4%
Goal: <1%		Each 1% time in range = ~15 minutes

Test Patient DOB: Jan 1, 1970

14 Days: August 8–August 21, 2021

Time CGM Active: 100%

Glucose Metrics

Average Glucose ..... **175 mg/dL**
Goal: <154 mg/dL

Glucose Management Indicator (GMI) **7.5%**
Goal: <7%

Glucose Variability **45.5%**
Defined as percent coefficient of variation
Goal: ≤36%

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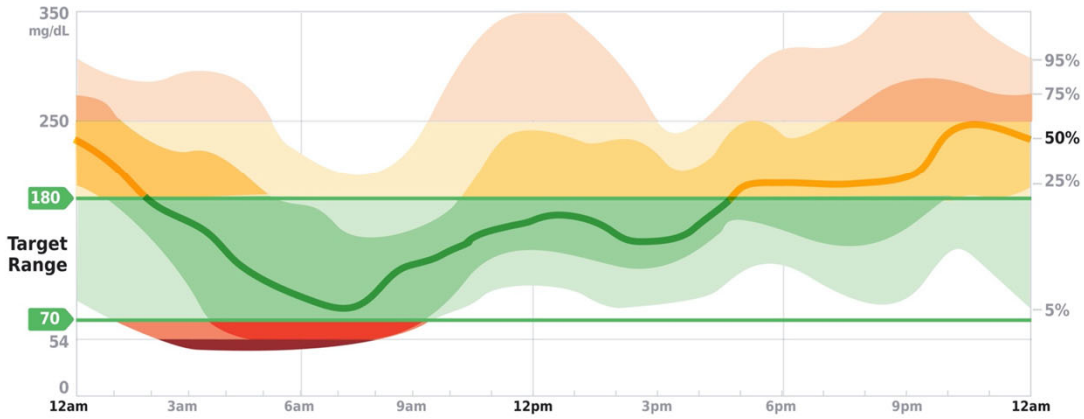
Ambulatory Glucose Profile (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if they occurred in a single day.



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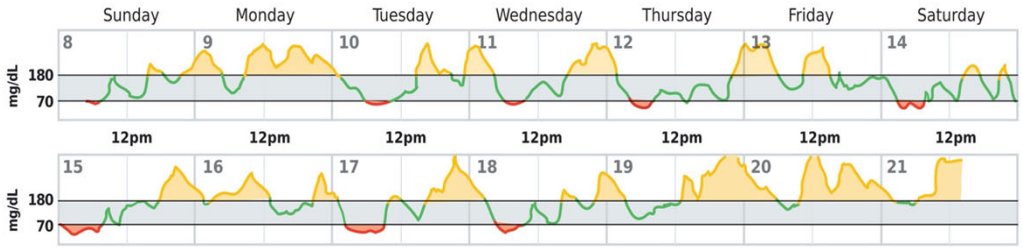
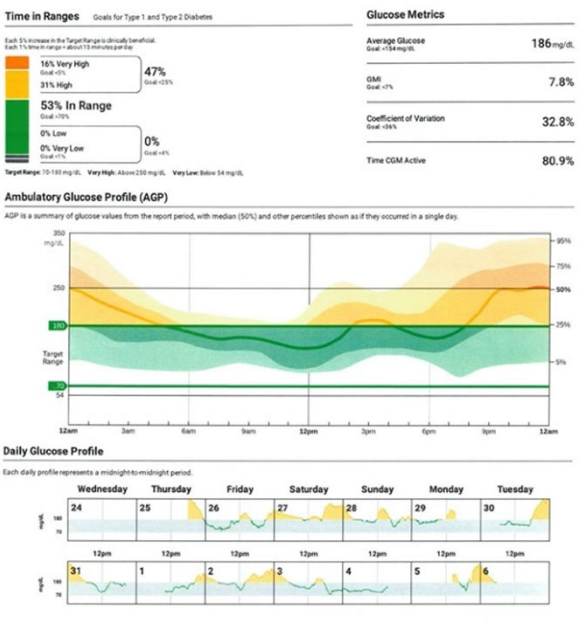
Daily Glucose Profiles

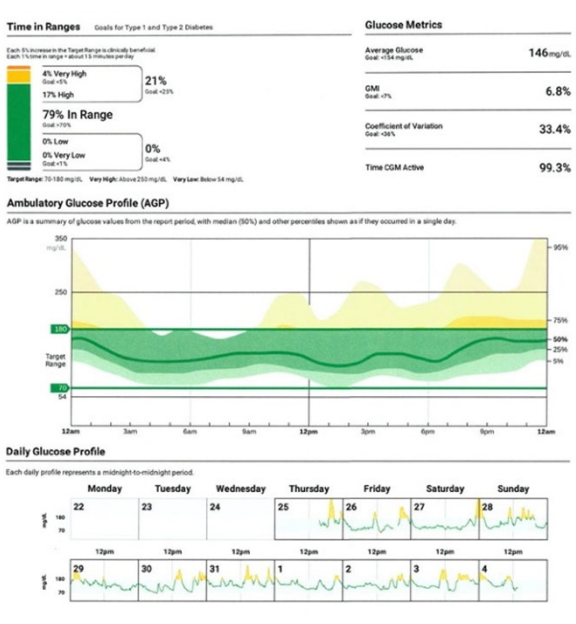
Each daily profile represents a midnight-to-midnight period.



AGP Report - Targets

- Time in Range (TIR) > 70% (range 70-180)
- Hypoglycemia < 4%
- Hyperglycemia < 26%
- GMI – Glucose Management Index
  - Calculated a1c





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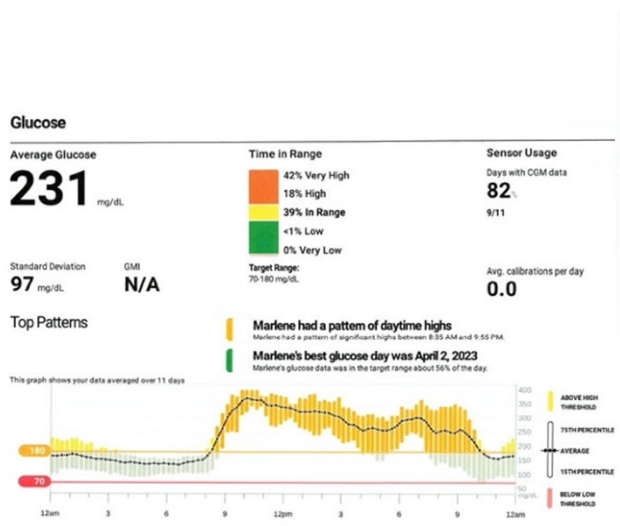

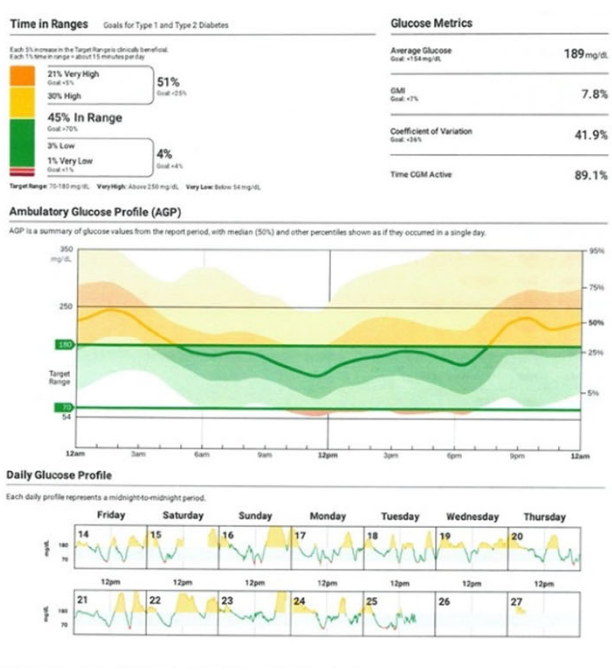

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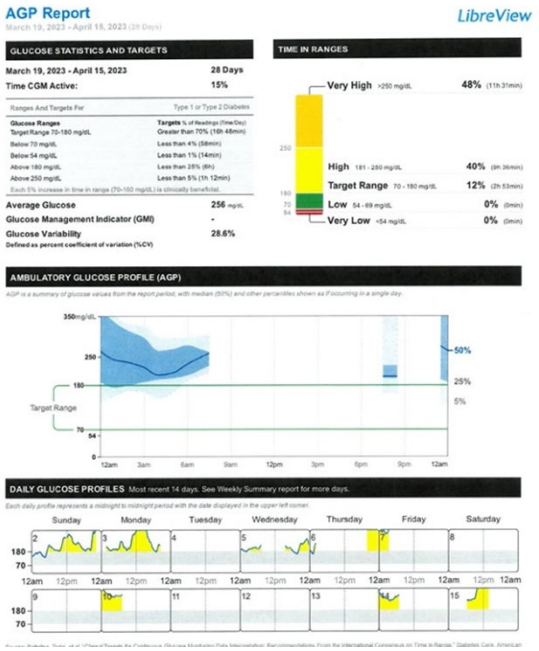

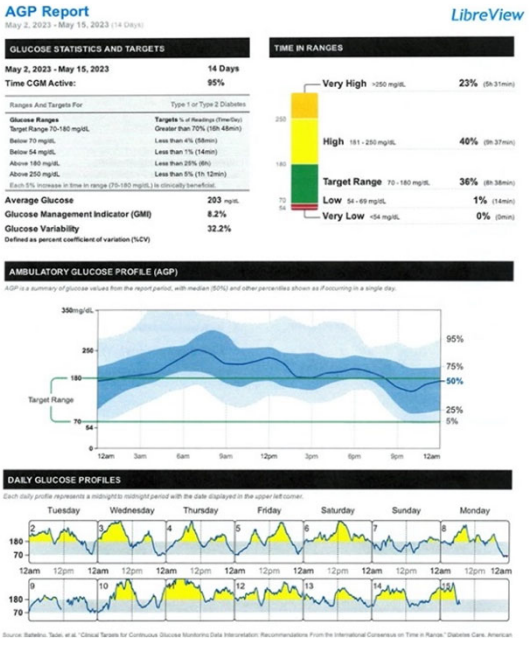

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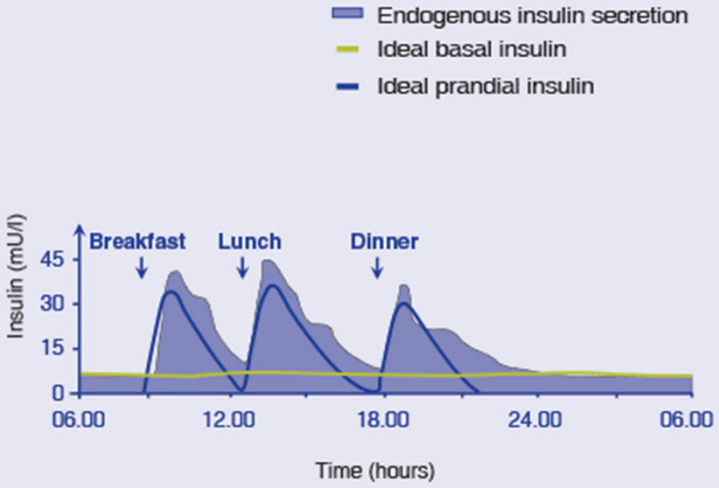
Normal Insulin Secretion



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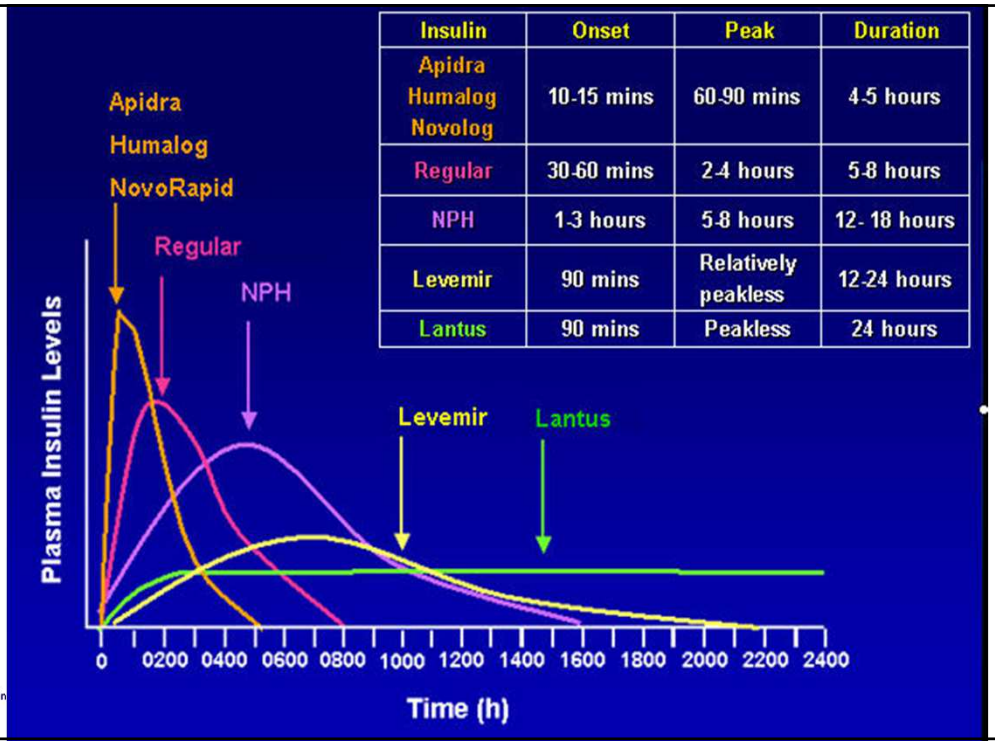

Insulin	Onset	Peak	Duration
Apidra Humalog Novolog	10-15 mins	60-90 mins	4-5 hours
Regular	30-60 mins	2-4 hours	5-8 hours
NPH	1-3 hours	5-8 hours	12- 18 hours
Levemir	90 mins	Relatively peakless	12-24 hours
Lantus	90 mins	Peakless	24 hours

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Total Daily Dose - TDD

- For any diabetic on multiple daily injections
- Basal Insulin – baseline metabolic activity

  ~ 50% total daily insulin dose
- Bolus Insulin – Mealtime coverage and correction insulin
- Type 2 TDD – 1-2 units/kg/day
- Type 1 TDD – 0.5 – 1 units/kg/day

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TDD – Total Daily Dose of Insulin

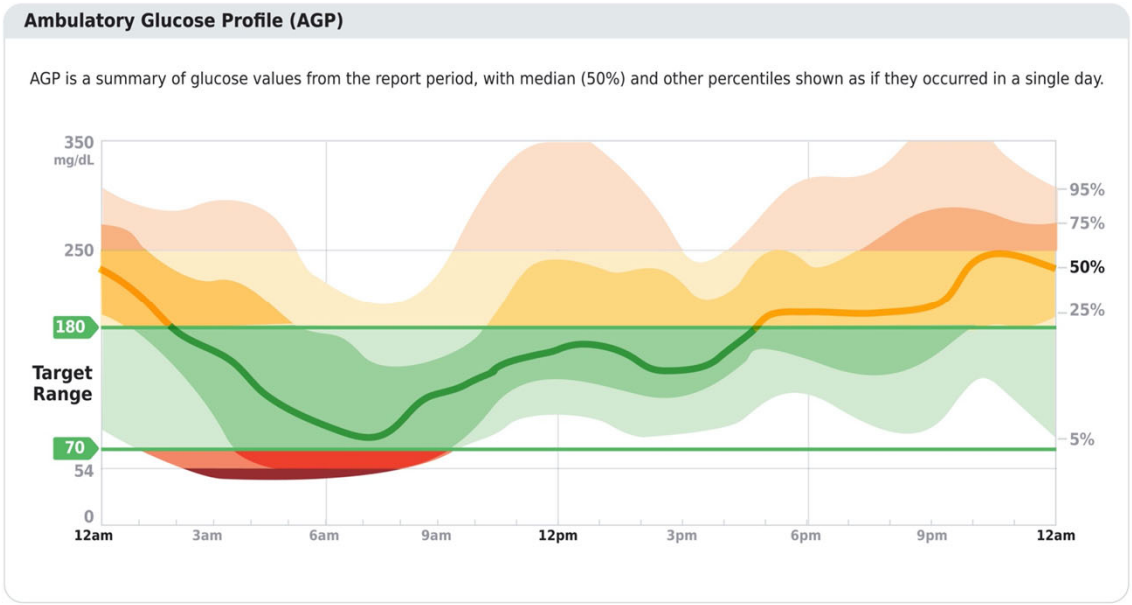
Basal Insulin – Treat to Target Algorithm

Start with 10 IU/day bedtime basal insulin and adjust weekly	
Mean of self-monitored FPG values from preceding 2 days	**Increase of insulin dosage (IU/day)**
≥180 mg/dl (10 mmol/l)	8
140–180 mg/dl (7.8–10.0 mmol/l)	6
120–140 mg/dl (6.7–7.8 mmol/l)	4
100–120 mg/dl (5.6–6.7 mmol/l)	2

The treat-to-target FPG was ≤100 mg/dl. Exceptions to this algorithm were *1*) no increase in dosage if plasma-referenced glucose <72 mg/dl was documented at any time in the preceding week, and *2*) in addition to no increase, small insulin dose decreases (2–4 IU/day per adjustment) were allowed if severe hypoglycemia (requiring assistance) or plasma-referenced glucose <56 mg/dl were documented in the preceding week.

Riddle, M. Diabetes Care | November 2003; 26 (11): 3080–3086.

BeAM



Insulin Simplified

- BeAM Factor – diff between Bed and AM glucose
  - Goal < 55
  - Fasting sugars normal
- Start thinking about mealtime insulin when
  - Beam > 55 mg/dl
  - Getting over about 50-60 units of basal insulin

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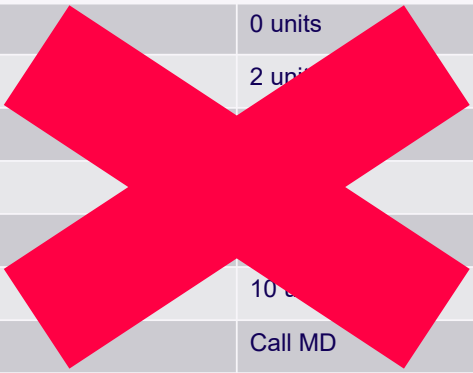
Insulin Sliding Scale

BG Level	Lispro Insulin Dose
70 – 120	0 units
121 – 160	2 uni
161 - 200	
201 – 240	
241 – 280	
281 – 320	10 u
➢ 321	Call MD



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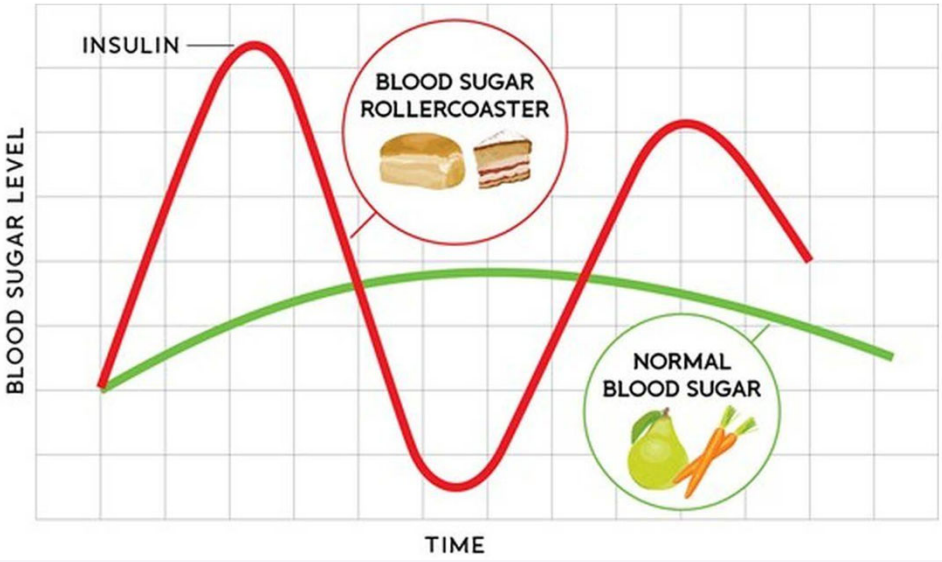
Sliding Scale Roller Coaster



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Mealtime Insulin Simplified

- Fixed Dose +/- correction dose
  - Start 4-6 units of rapid acting insulin with largest meal
- PLUS (pt willing): 1 unit for every 30 mg/dl above 150

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Updated Insulin Sliding Scale

BG Level	Lispro Insulin Dose
70 – 149	4 units
150 - 179	5 units
180 - 209	6 units
210 – 239	7 units
240 – 269	8 units
270 – 299	9 units
➢ 300	10 units

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Insulin and Procedures/Surgery

- Patient Message Portal: “Doctor, I am having a colonoscopy tomorrow, what should I do with my insulin dose tonight? I’m taking 46 units of glargine currently.” After review of your recent progress note, you note their BeAM is 30 and not having fasting hypoglycemia.
  a) Keep the dose the same
  b) Follow the colonoscopy instruction sheet and cut the dose in ½.
  c) Reduce the dose to 40 units
  d) Contact the GI doc

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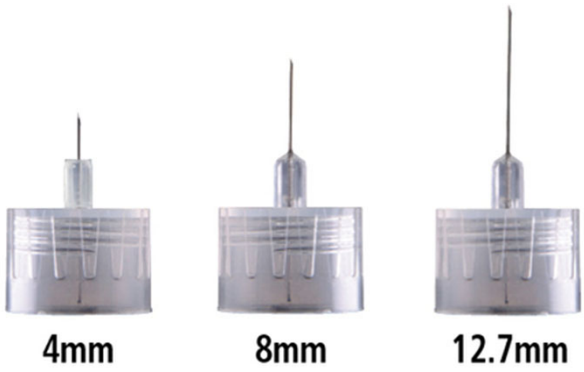
Insulin Injections

- Skin thickness 3mm regardless of age or weight



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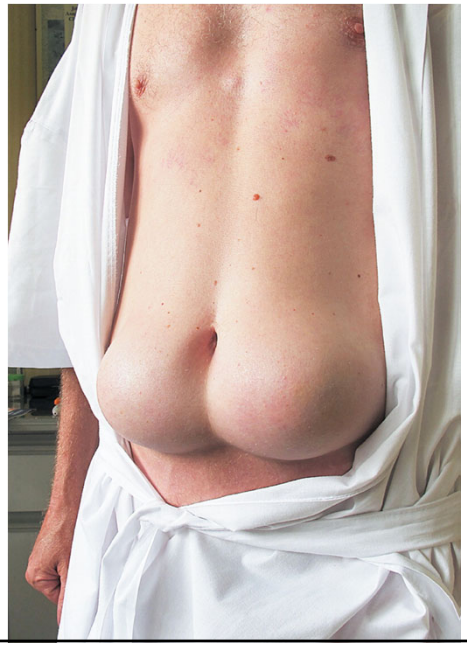
Rotate Injection Sites – Or Else



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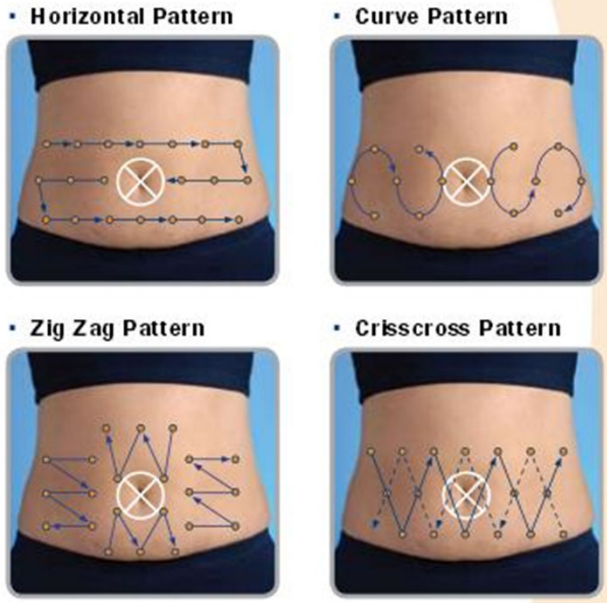
Rotate Injection Sites



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2023 ADA Treatment Guidelines for Type 2 Diabetes

Learning Objectives

- Identify glucose targets for patients with type 2 diabetes
- Identify preventative care measures for type 2 diabetes
- Discuss medication classes available
- Review and compare 2023 to 2021 treatment guidelines and applying them to your practice

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ADA Standards of Care

- Glycemic Targets, Individualized.
  - –A1c < 7%,
  - –TIR > 70%
  - –Preprandial Sugars: 70 – 130
  - –Postprandial Glucose (1-2 hrs): < 180
- Blood Pressure Target
  - – Less than 130/80
  - – Use ACEi or ARB, but not both
- Lipid Target
  - – Secondary Preventions: LDL < 70, 50% reduction
  - – Primary Prevention age 40-75: mod int statin

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ADA Standards of Care

- Aspirin
  - Secondary Prevention
  - Primary Prevention – assess risk
- Neuropathy
  - Yearly monofilament exam and PAD assessment
  - Check b12 if on metformin
  - Education on prevention diabetic foot ulcer
- Nephropathy
  - Yearly Albumin to Creatinine Ratio (ACR) and GFR,
    - < 30 mg/g - confirm twice
  - Primary Prevention – ACE/ARB NOT recommended

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ADA Standards of Care

- Retinopathy
  - Yearly DM Eye Exam
  - Goal A1c < 7%
- Testing BG
  - SMBG – on insulin, risk lows, lifestyle feedback
  - CGM – on insulin
- Lifestyle Interventions
  - CDCES/CDE - Diabetes Educator
  - RD - Dietician

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Non-Insulin Medications for Type 2 Diabetes

- Metformin – decrease gluconeogenesis in liver
  - Helps with weight loss
  - Contraindications: renal or heart failure
  - A1c Reduction ~ 1.5%
- Thiazolidinediones (glitazones) - Insulin sensitizer
  - i.e. Pioglitazone
  - Drawbacks: Expensive, fluid retention, weight gain
  - A1c Reduction ~ 0.5 – 1.5%
- Sulfonylureas - Stimulates insulin secretion
  - i.e. glipizide, glimepiride, avoid glyburide
  - Drawback: hypoglycemia, beta cell burnout
  - A1c Reduction ~1.5%

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Non-Insulin Medications for Type 2 Diabetes

- SGLT2 Inhibitors (gliflozins)
  - Empagliflozin (Jardiance), Canagliflozin (Invokana), Dapagliflozin (Farxiga), Ertugliflozin (Steglatro)
  - Glucose excretion from kidneys, causing glucosuria
- Incretin Mimetics – GLPs, DPP-IV inhibitors
  - i.e. Semaglutide (Ozempic, Rybelsus), Dulaglutide (Trulicity), Liraglutide (Victoza), Exenatide (Bydureon, Byetta),
  - Sitagliptin (Januvia), Saxagliptin (Onglyza)
  - A1c Reduction 0.5 – 1.5%
- Dual Incretin Mimetics – GLP/GIP
  - Terzepitide (Mounjaro)
  - Up to 22% weight loss possible

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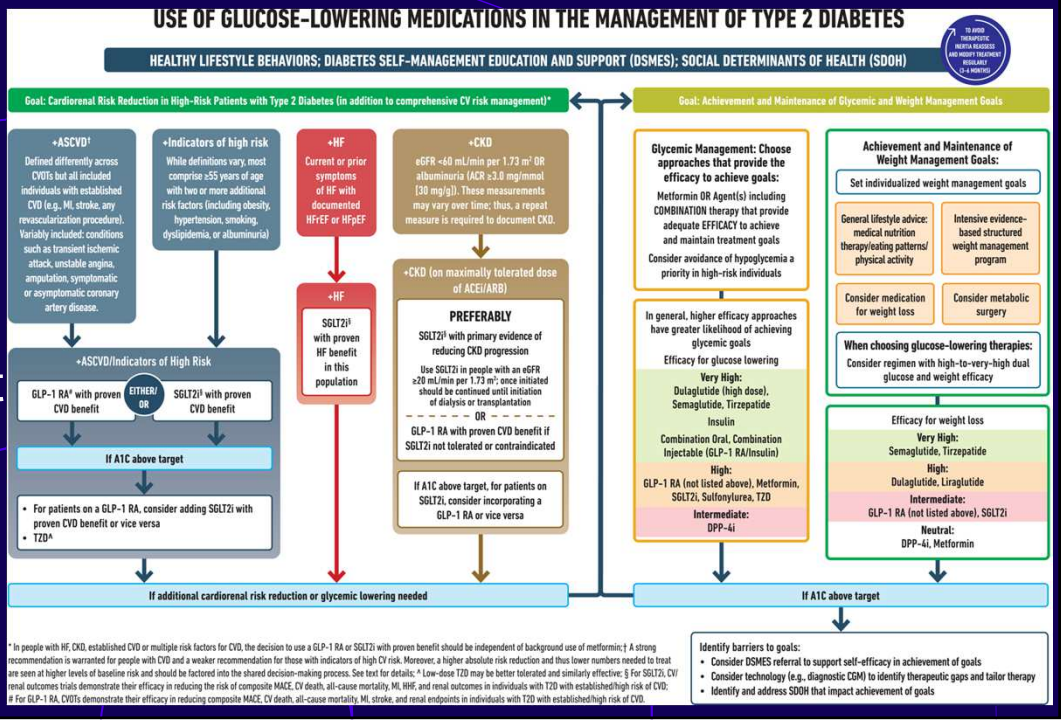
2023 ADA Treatment Guideline



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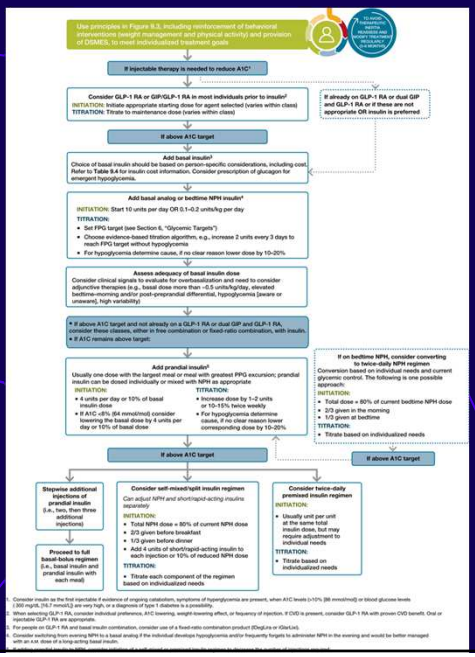
2023 ADA Treatment Intensification



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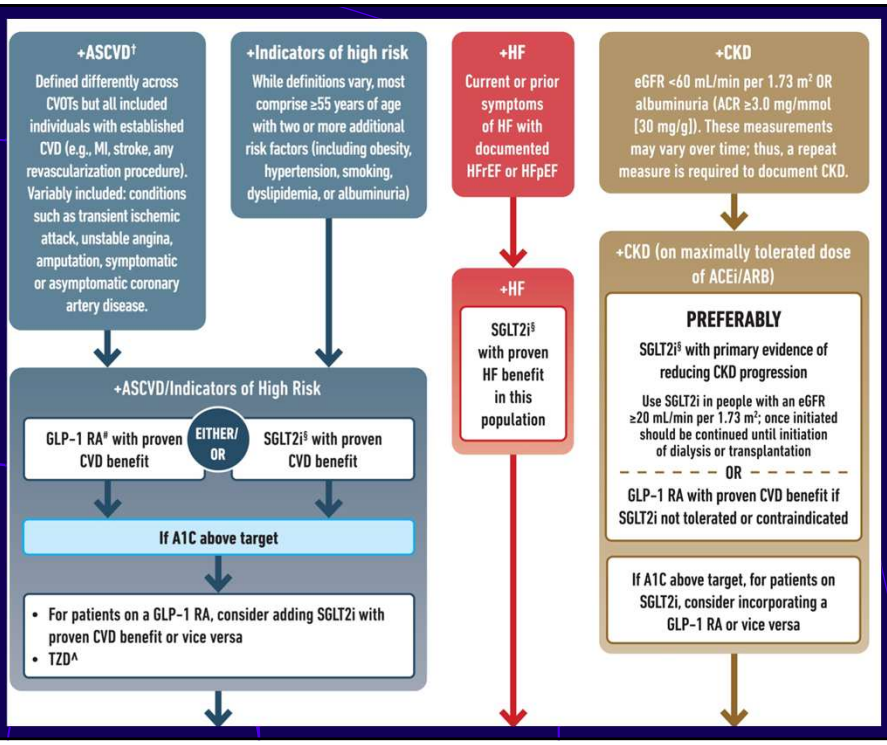
2023 ADA Treatment Guideline



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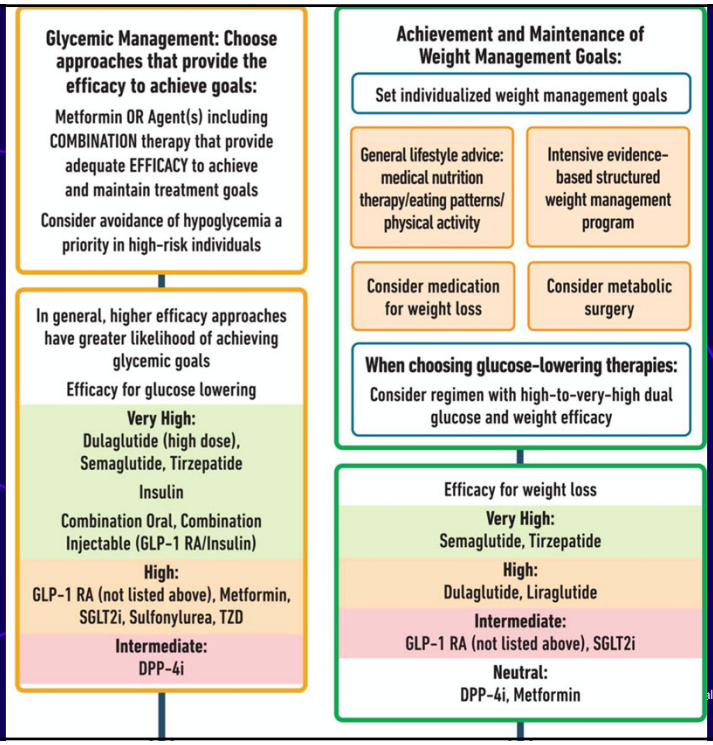
2023 ADA Treatment Guideline



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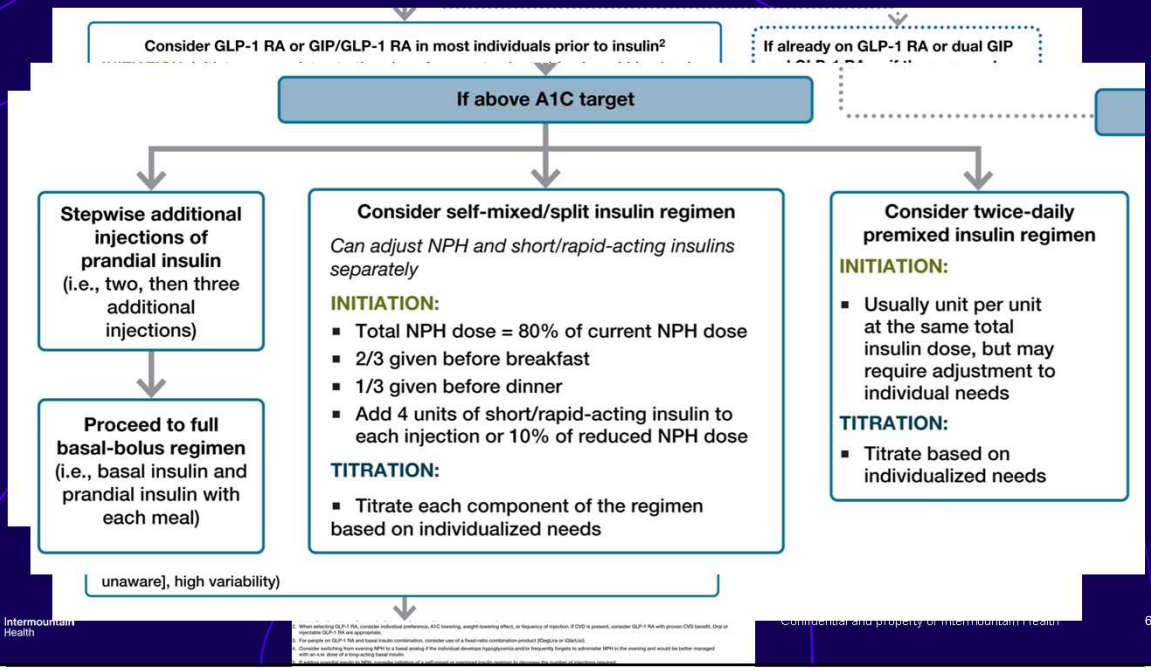
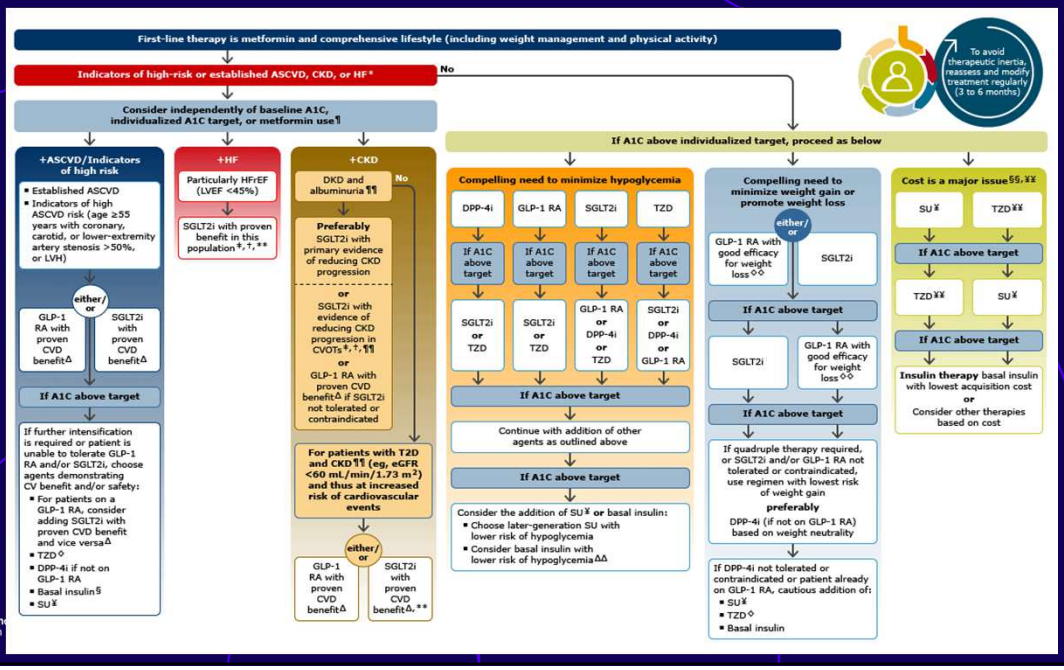
2023 ADA Treatment Intensification

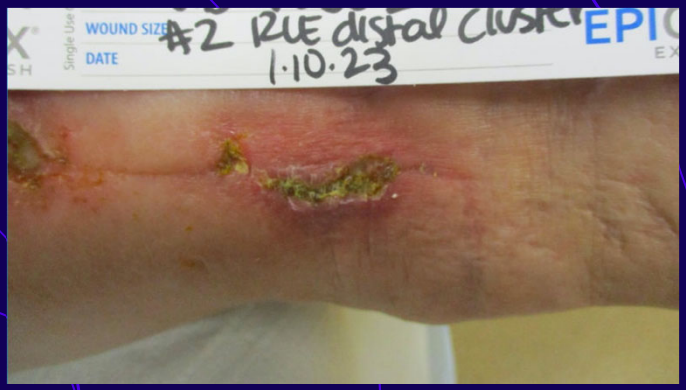


2021 ADA Treatment



Case Discussion – Putting It All Together

- 81 yo female with T2DM, CAD, OSA, HTN and recently hospitalized after ORIF for AKI, resp failure and sepsis from wound infection and cholecystitis.
- A1c 9.2%
- Hx UTIs



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Case Discussion

- Previously on Lantus 36 units and Humalog 18 units for breakfast and lunch and 22 units before dinner
- Post Hospitalization was on Lantus 20 and an unknown lispro sliding scale to the SNF
- 6 weeks later discharged from SNF and came to clinic
- Poor appetite d/t chronic cholecystitis
- Admitted guessing at insulin dose
  - Lantus was increased at SNF to 26

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Case Discussion

- Where do we start?

- Data
- States Current BGs since home are all > 300

Case Discussion

- Increased Lantus to 30
- Fixed dose for meals at 14 units with a correction scale of 25
- Also added a skipped meal scale
- Get back on Dexcom CGM

Case Discussion

Sensitivity Factor	Fixed Mealtime Dose
25 mg/dL/unit	14 units

BG (mg/dL)	Insulin (units)
125 - 149	14
150 - 174	15
175 - 199	16
200 - 224	17
225 - 249	18
250 - 274	19
275 - 299	20
300 - 324	21
325 - 349	22
350 - 374	23
375 - 399	24
400 - 424	25
425 - 449	26
450 - 474	27
475 - 499	28
500 - 524	29

skipped meals

BG Target

120 mg/dL

Sensitivity Factor

20 mg/dL/unit

BG (mg/dL)	Insulin (units)
120 - 139	0
140 - 159	1
160 - 179	2
180 - 199	3
200 - 219	4
220 - 239	5
240 - 259	6
260 - 279	7
280 - 299	8
300 - 319	9
320 - 339	10

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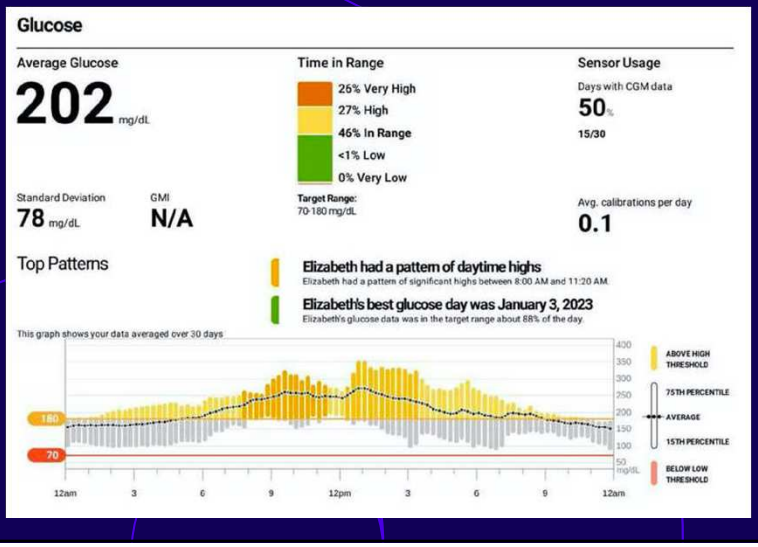
Case Discussion

1 week later



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Case Discussion

Mealtime Injections
HumaLOG KwikPen Insulin 100 unit/mL Inpn
Last edited by Justen W Rudolph, MD on 1/17/2023 at 11:43 AM

The patient will be instructed to take their fixed mealtime dose at the blood glucose target, and will dose in 1 unit increments.

Mealtime	Fixed Mealtime Dose (units)	Sensitivity Factor (mg/dL/unit)	BG Target (mg/dL)
breakfast	16	25	125
lunch	14	25	125
dinner	14	25	125
skipped meals	0	20	120

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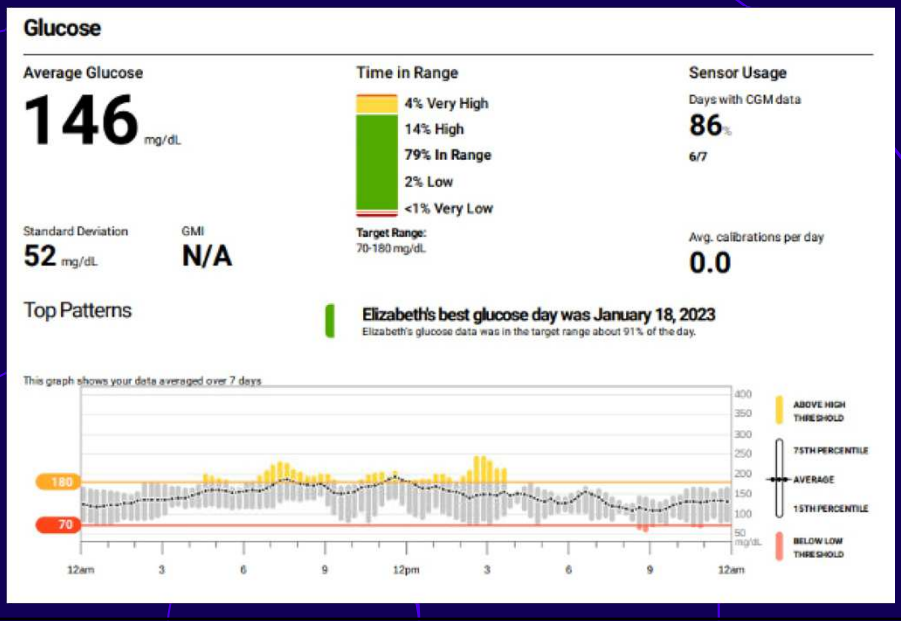
Case Discussion



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Summary – Knowing the Acronyms

- Reviewed GLP-1 and SGLT2 Inh
- CGM and AGP reports
- BeAM factor and adjusting basal insulin and starting mealtime insulin for a TDD
- ADA Treatment Guidelines 2023

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Questions

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Thank You

Chico Primary Care Conference

MT Chapter AAFP

Justen Rudolph, MD