Type 2 Diabetes Management: A Cased-based Approach for Primary Care

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1

Disclosure

Consultant: Bayer; Boehringer Ingelheim; Corcept Therapeutics; Diasome; Eli Lilly; Sanofi

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Speaker's Bureau: AstraZeneca; Corcept Therapeutics; Novo Nordisk

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2

Case Study 1 - Jim

- 62-year-old man presents for management of T2D, diagnosed 6 years ago
  - Patient takes metformin 1000 mg twice daily
  - Most recent A1C measurement was 9.1%
- CAD diagnosed 3 years ago, for which he has undergone CABGX3
  - He denies any current symptoms of chest pain or shortness of breath
- He recently underwent transthoracic echocardiography, and his LVEF was 50%
- He has a 45 pack-year history of cigarette smoking, but he quit 3 years ago
- He has HTN, treated with atenolol, 50 mg once daily, and lisinopril/hydrochlorothiazide, 20 mg/12.5 mg once daily, and hyperlipidemia controlled with atorvastatin, 80 mg daily
- BP 138/84 mmHg, HR 66 beats/min
- Weight is 176 lbs, BMI = 31 kg/m^2

Case Study 1 – Additional Labs

- Total cholesterol = 112 mg/dL
- LDL cholesterol = 45 mg/dL
- HDL cholesterol = 35 mg/dL
- Triglycerides = 122 mg/dL
- eGFR= 35 mL/min per 1.73 m^2
- UACR= 150 mg albumin/gram creatinine

Which of the Following Is the Next Best Step in Management of T2D?

A. Start once daily insulin glargine
B. Add once-weekly subcutaneous semaglutide (GLP-1RA)
C. Add empagliflozin (SGLT-2i)
D. Add glipizide XL

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Subcutaneous Semaglutide

- Of the options listed, the best next step is to add once-weekly subcutaneous semaglutide, Answer B
- Semaglutide is approved to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in adults with T2D and established CVD
- Recently demonstrated renal outcome benefits in T2D and CKD (FLOW) and now has indication to reduce the risk of worsening kidney disease, kidney failure, and death due to cardiovascular disease in adults with T2D and CKD
- Oral semaglutide
  - CV safety of oral semaglutide established in PIONEER-6
  - SOUL study demonstrated oral version also affords CV risk reduction

Marso SP et al. N Engl J Med. 2016;375(19):1834-1844.
Husain M et al. N Engl J Med. 2019; 381 (9):841-851.
McGuire DK et al. N Engl J Med. 2025; 392(20):2001-2012.

6

GLP-1RA and Renal Benefit?

Trial	Year Published	Treatment (s)	Primary or Secondary	Kidney Outcome	Results
LEADER [39]	2016	Liraglutide vs. placebo	Secondary	Diabetic Nephropathy	HR 0.78 (95% CI 0.67–0.92)
SUSTAIN-6 [40]	2016	Semaglutide vs. placebo	Secondary	Macroalbuminuria, doubling of serum creatinine, Creatinine clearance $\leq$ 45 mL/min or KRT	HR 0.64 (95% CI 0.46–0.88)
AWARD-7 [41]	2018	Dulaglutide vs. insulin glargine	Secondary	eGFR and UACR	A decline in eGFR of the insulin arm but not in the higher-dose dulaglutide arm
REWIND [42]	2019	Dulaglutide vs. placebo	Secondary	300 mg/g > UACR in lower baseline concentration, sustained 30% > eGFR decline, KRT	HR 0.85 (95% CI 0.77–0.93)
Kristensen et. al. meta-analysis [43]	2019	GLP-1's	—	New-onset macroalbuminuria, decline in eGFR, progression of kidney disease or death of kidney cause	HR 0.83 (95% CI 0.78–0.89)
AMPLITUDE-O [44]	2021	Efpeglenatide vs. placebo	Secondary	Incident microalbuminuria > 300mg/g, increase in UACR of at least 30% from baseline, sustained eGFR decrease > 40% for > 30 days, KRT for 90 days or more, eGFR < 15 for 30 days or more	HR 0.68 (95% CI 0.57–0.79)

Sawaf H et al. J Clin Med. 2022;11(2):378.

7

Effects of Semaglutide on CKD in Patients with T2D: the Flow Trial

- Randomly assigned patients with T2D and CKD to receive subcutaneous semaglutide at a dose of 1.0 mg weekly or placebo. CKD defined by the following:

- eGFR of 50 to 75 ml per minute per 1.73 m2 and a UACR of >300 and <5000 mg/g

  or

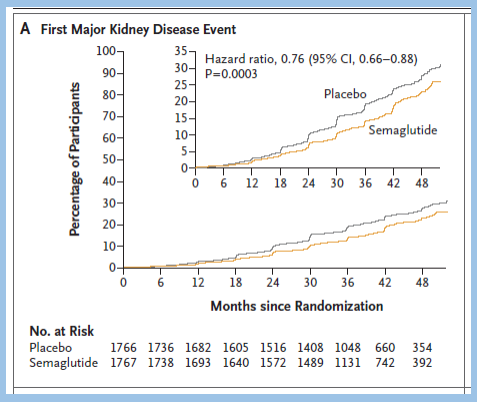
- eGFR of 25 to <50 ml per minute per 1.73 m2 and a UACR >100 and <5000 mg/g

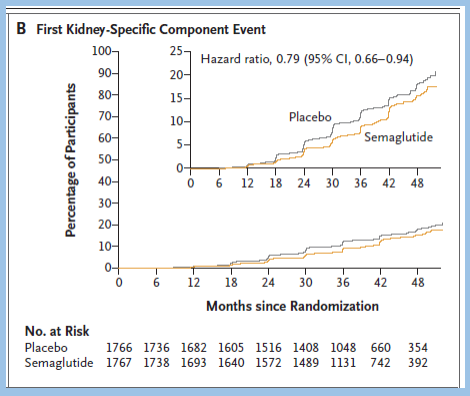
- The primary outcome was major kidney disease events
  - A composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes

Perkovic V et al. N Engl J Med. 2024;391(2):109-121.

8

The Flow Trial





Perkovic V et al. N Engl J Med. 2024;391(2):109-121.

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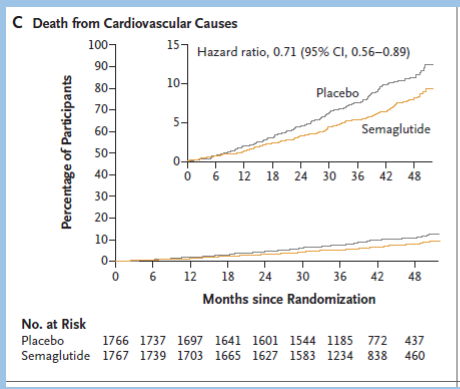
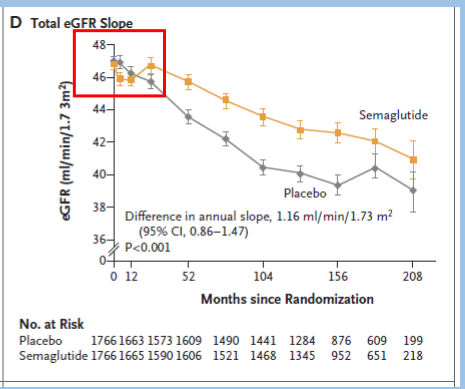
The Flow Trial





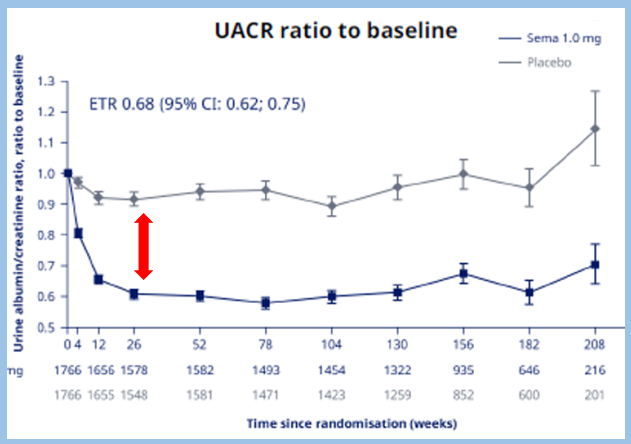
CONCLUSIONS

Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease

Perkovic V et al. N Engl J Med. 2024;391(2):109-121.

10

Flow Trial: UACR



Perkovic V et al. N Engl J Med. 2024;391(2):109-121.

11

Why Not Add SGLT-2i?

- CV, CKD, and CHF risk reduction; SGLT-2i medications are great, no doubt!
- SGLT-2i is a great option to provide outcome benefits in this patient……..but GLP-1RA would allow us to achieve that and more:
  - Consider A1C lowering effect of GLP-1RA vs. SGLT-2i
    - With lower eGFRs, the efficacy of SGLT-2i on glycemic control is reduced
  - Weight reduction greater with GLP-1RA vs. SGLT-2i
  - GLP-RA (sc semaglutide) would provide the CKD and CVD risk reduction and be far more likely to get the A1C < 7% and provide greater chance of achieving a clinically significant weight loss

12

SGLT-2i Vs GLP-1 RA

	SGLT2i	GLP-1 RA or dual GIP/GLP-1 RA	Combination
Effect on A1C	↓	↓↓ / ↓↓↓*	↓↓↓
Effect on weight	↓	↓↓ / ↓↓↓*	↓↓↓
Effect on BP	↓	↓	↓↓
Effect on lipids	↔ / ↓†	↓ / ↓↓*	↓↓
Risk of ASCVD	↔ / ↓‡***	***↓↓	↓↓
Risk of stroke	↔	↓↓	↓↓
Risk of HF	↓↓↓	↓ / ↔ / ↑§	↓↓↓
Risk of CKD	↓↓↓	**↓↓ / ↔‖	↓↓↓
Genital infections	↑	↔	↑
GI adverse effects	↔	↑	↑

Effects of SGLT2i, GLP-1-based therapies and combination therapy in patients with T2D
↓ moderate decrease
↓↓ high decrease
↓↓↓ very high decrease
↔ neutral effects
↑ moderate increase

*Effects are more marked with dual GIP/GLP-1 RA; †SLGT2i modestly decrease triglycerides and increase HDL cholesterol but simultaneously increase LDL cholesterol; ‡Protection from ASCVD with SGLT2i may be restricted to those in secondary prevention; §GLP-1 RA may decrease the risk of new-onset HF, be neutral on HF events in those with HFpEF, but increase the risk of adverse events in HFrEF;

** Results from the FLOW trial provide evidence that GLP-1 RAs (specifically sc semaglutide) reduce the risk of CKD progression; ‖GLP-1 RA predominantly reduce albuminuria with a mostly neutral effect on eGFR; among those with previous CKD, GLP-1 RA may also slow the decline in eGFR; dual GIP/GLP-1 RA may have a greater effect on eGFR decline than GLP-1 RA.

*** CVOTs with SGLT-2i and GLP-1RA are numerous and demonstrate consistent and robust results.

BP = blood pressure; GI = gastrointestinal; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Vale C et al. Diabetes Obes Metab. 2025;27:468-481.

13

SGLT-2i Efficacy and eGFR

SGLT-2 inhibitors still offer moderate glycemic control benefits as eGFR drops, but their efficacy diminishes significantly at lower eGFR levels

- **eGFR > 45-60 mL/min**: SGLT-2 inhibitors are most effective in this range, with robust HbA1c lowering and additional benefits for kidney function
- **eGFR 30-45 mL/min**: The HbA1c lowering effect is reduced, but CKD and HF patients can still benefit; careful monitoring is essential
- **eGFR < 30 mL/min**: At this stage, SGLT-2i are largely added for HF and CKD benefits, and can continued all the way down to start of dialysis
  - eGFR > 20 at time of initiation for empagliflozin and > 25 for dapagliflozin
  - Minimal effect on HbA1c lowering effect when eGFR < 30 mL/min

14

Case Study 2 - Jill

- 59-year-old woman returns for T2D management
  - Diagnosed 15 years ago
- Initially treated with oral agents, but she has been receiving insulin therapy for the past 5 years
- A1C has ranged between 7.0% to 9.0% over the past few years
- Most recent A1C 7.3%
- Comorbidities include HTN, HPL and CKD with macroalbuminuria
- Peripheral neuropathy is well controlled with pregabalin

Case Study 2: Current Meds

Metformin 1000 mg twice daily
Insulin aspart 10 units before meals (3 times daily)
Insulin degludec 30 units at bedtime
Lisinopril 40 mg daily
Aspirin 81 mg daily
Clopidogrel 75 mg daily
Metoprolol tartrate 50 mg twice daily
Chlorthalidone 25 mg once daily
Rosuvastatin 10 mg once daily
Pregabalin 50 mg twice daily

Case Study 2

Physical Exam

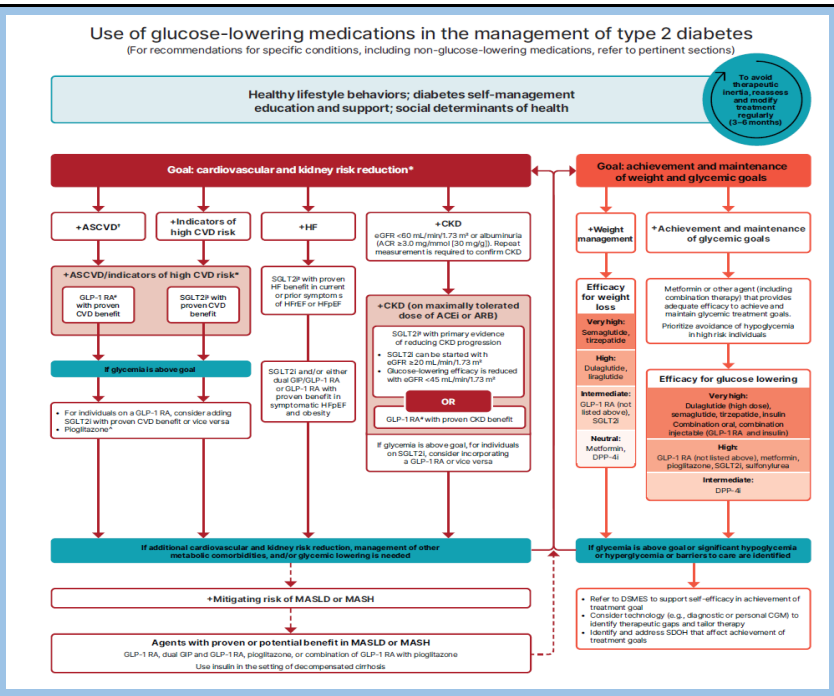
- Weight is 225 lbs, BMI = 34 kg/m²
- BP 134/82 mm Hg, HR 74 bpm
- 1+ pitting edema and 2+ dorsalis pedis pulse in the bilateral lower extremities
- Lungs are CTAX2, and heart RRR with no audible murmur
- Decreased sensation to 10-g monofilament testing on the distal plantar aspect of his feet bilaterally

Laboratory Test Results

- Electrolytes, normal
- Serum Cr 1.5 mg/dL (0.7-1.3)
- eGFR 50 mL/min per 1.73 m²
- HbA1C= 7.3%
- Urine albumin-to-creatinine ratio = 520 mg/g Cr
  - Normal: <30 mg/g Cr

Which of the Following Medications Should Be Started as the Best Next Step in This Patient's Treatment?

A. Losartan
B. Aliskiren
C. Amlodipine
D. Dapagliflozin



*In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1RA or SGLT-2i with proven benefit should be made irrespective of background use of metformin or A1C

9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026; *Diabetes Care 2026;49(Suppl. 1):S183–S215*

19

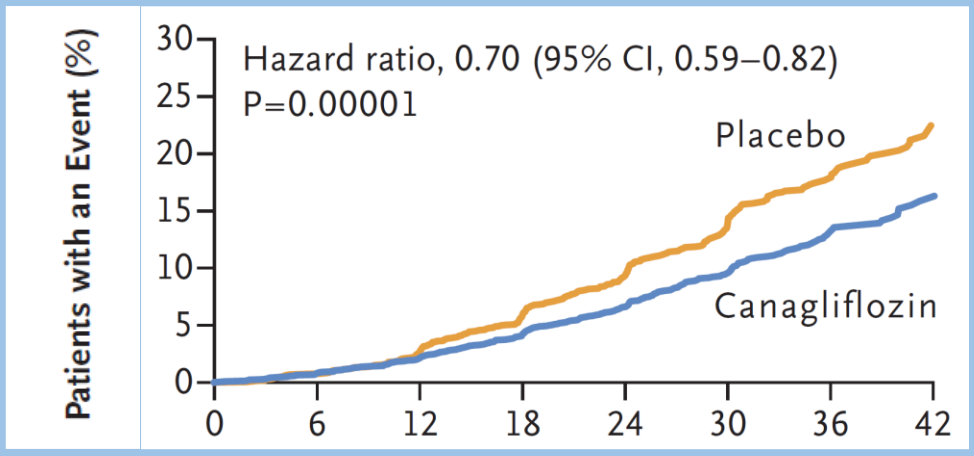
Correct Answer (D) Dapagliflozin (SGLT-2i)

- This patient has T2D, CKD, and macroalbuminuria
- Patient had A1C of 7.3%
  - Even if A1C was < 7% there is still an indication to initiate SGLT-2i for renal risk reduction
  - Nicely compliment regimen of insulin therapy (MDI) to help reduce glycemic variability
  - SGLT-2i will provide a way of the body to dispose of excess glucose independent of insulin action (complementary and synergistic effect)
- BP above target
  - Likely will observe mild BP lowering effect with SGLT-2i

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

20

CREDENCE-Renal Outcomes*
Primary Outcome: ESKD, Doubling of Serum Cr, Renal Death, CV Death



All patients had T2D, eGFR 30-90 mL/min/1.73m^2 and urinary albumin:Cr > 300 to 5000 mg/g, and were treated with renin-angiotensin system blockade (ACE/ARB)

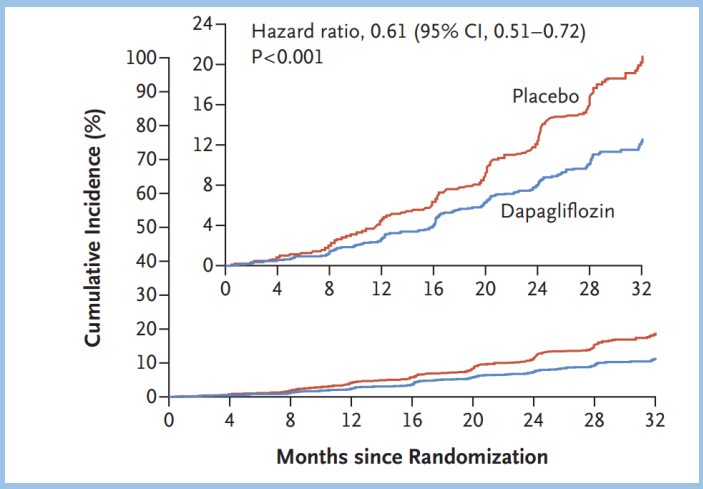
Perkovic V et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

* Included only patients with T2D

21

DAPA-CKD*

Primary Composite Outcome: Sustained ≥50% Egfr Decline, ESKD, Renal or CV Death



All patients had eGFR 25-75 mL/min/1.73m^2 and urinary albumin:Cr ratio > 200 to 5000 mg/g

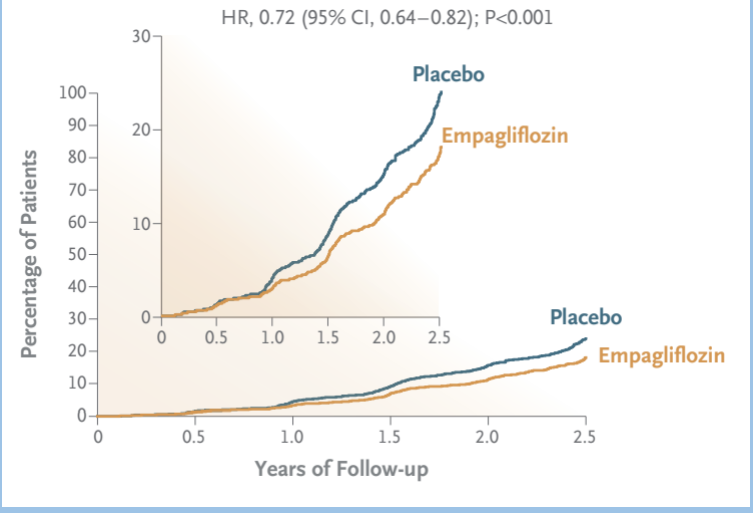
Heerspink HJL et al. N Engl J Med 2020; 383:1436-1446.

*Included patients with and without T2D

22

EMPA-Kidney*

Primary Composite Outcome: ESKD (Sustained Egfr <10 Ml/Min/1.73 M2), Sustained of ≥40% Egfr, Renal or CV Death



All patients had eGFR 20 to <45 mL/min/ 1.73m^{2}eGFR or 45 to <90 mL/min 1.73 m^2 and urinary alb:Cr ratio of at least 200 mg/g

Empa-Kidney Collaborative Group. 2023 Jan 12;388(2):117-127.

*Included patients with and without T2D

23

Other Answer Options

A) In the ONTARGET trial, the combination of ACE/ARB was associated with more adverse events without an increase in benefit. For these reasons, addition of the ARB losartan is incorrect. ACE/ARB combination therapy is not recommended.

B) Aliskiren, a direct renin inhibitor, should not be added to the regimen of a patient treated with an ACE inhibitor or ARB. The ALTITUDE study (Aliskiren Trial in T2D Using Cardiorenal Endpoints) failed to identify a benefit of aliskiren as an adjunct to therapy with an ACE inhibitor or an ARB and found that vs. placebo, aliskiren was associated with more cases of nonfatal stroke, renal complications, hyperkalemia, and hypotension.

C) Amlodipine may lower BP < 130/80, but will not provide the significant reduction in UACR afforded by RAASi or SGLT-2i, and will not address the residual A1C elevation observed in this patient. If BP remained above target, despite SGLT-2i, this would be a reasonable option.

Parving H et al. N Engl J Med 2012; 367:2204-2213.
Yusuf S et al. ONTARGET Investigators. N Engl J Med. 2008;358(15):1547-1559.

24

Case Study 3 - Larry

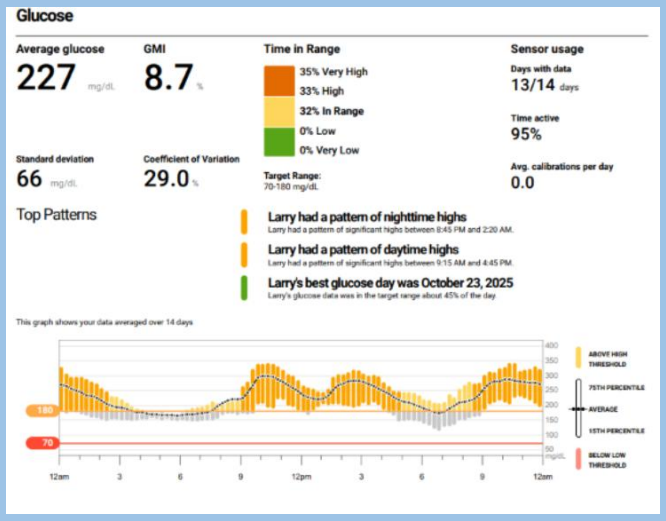
- 62-year-old man who presents for management of T2D, which was diagnosed 6 years ago
- He takes metformin 1000 mg BID and insulin glargine 20 units daily
- His most recent A1C measurement was 8.3%
- Weight is 212 lbs, BMI = 36 kg/m^2
- eGFR = 35 mL/min per 1.73 m^2
- UACR normal

Which of the Following Options Is the Next Best Step in George's Treatment?

A. Add Glipizide XL
B. Add SGLT2i
C. Add GLP-1RA
D. Increase insulin glargine

GLP-1 RA vs. SGLT2i
-eGFR
-HF
-A1C
-BMI

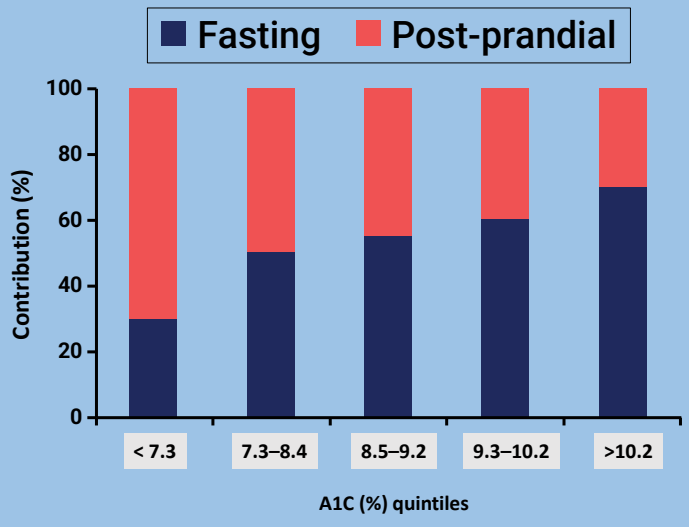
Would This Data Have Changed Your Mind?



1) What is driving the residual A1C elevation?
Fasting blood glucose?
Post Prandial blood glucose?
Both?

27

Contribution of Fasting and Postprandial Glycemia to A1C in T2D

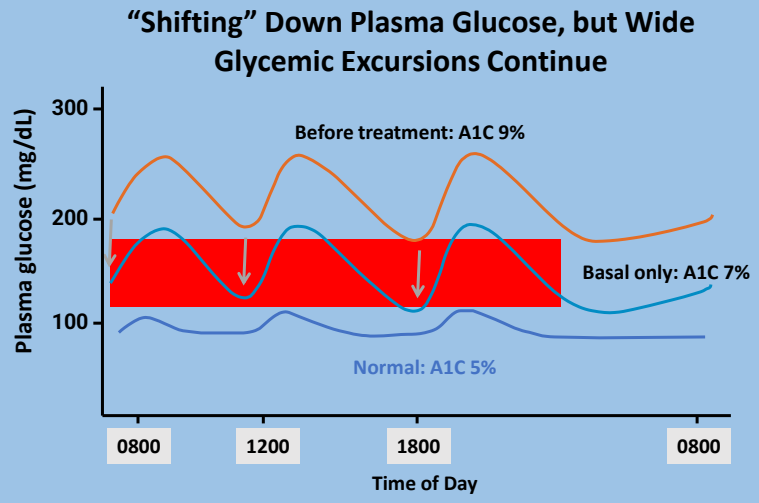


Modified from Monnier L et al. Diabetes Care. 2003;26:881-885.

28

Glucose Profiles in T2D

Correcting Fasting/Basal Vs Postprandial Hyperglycemia



Scheiner G. Postprandial hyperglycemia: it's all in the timing (https://infodiabet.wordpress.com/2010/07/22/postprandial-hyperglycemia-it%E2%80%99s-all-in-the-timing/.) Accessed 10/10/25.

29

Glycemic Control Is Still Important!

- HbA1c: Average glycemia during the past 3 months
- Continuous glucose monitors provide real-time feedback to patients in terms of their BG control, and often pick up more detailed information regarding overall BG control, via Time-in-Range vs. HbA1c alone
- CGM allows one to identify the areas where improved glycemic control are necessary, or unrecognized hypoglycemia

30

BGM Vs CGM

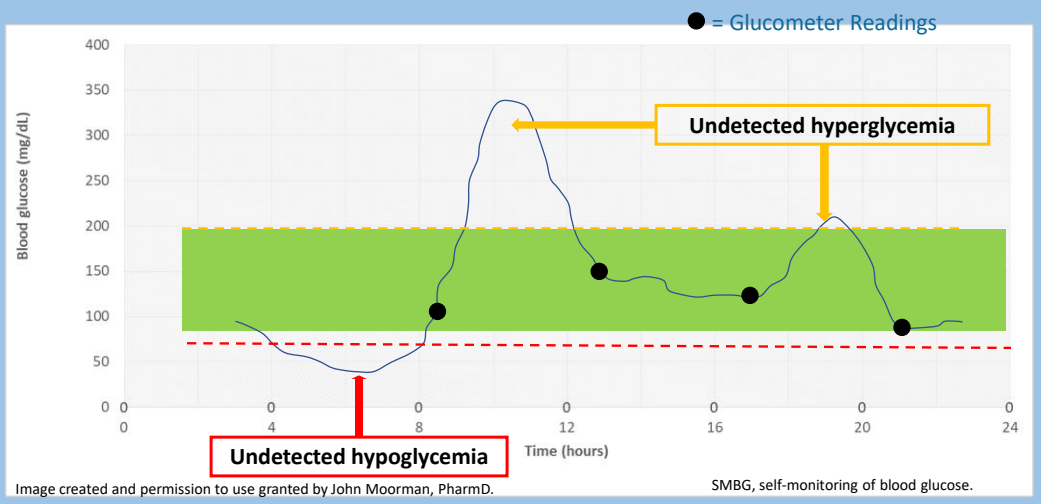
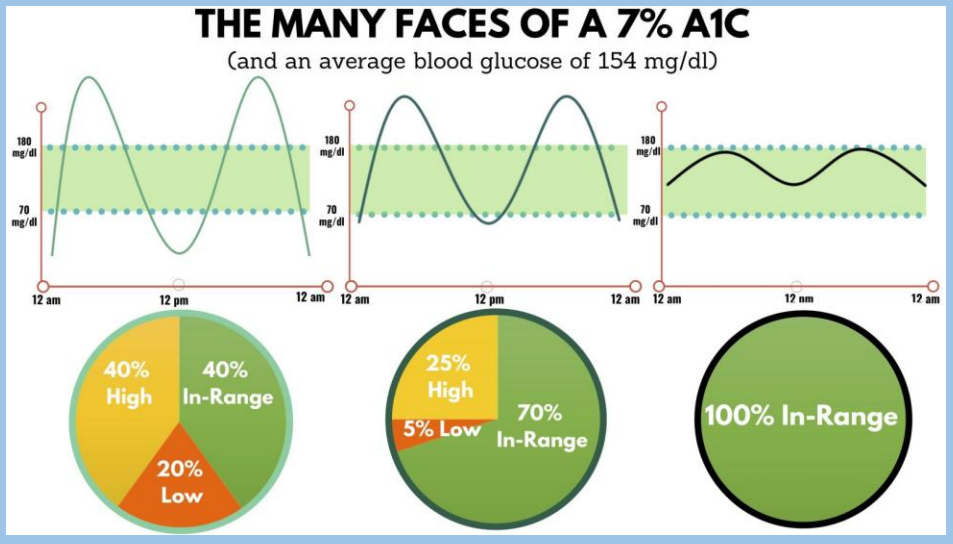


Image created and permission to use granted by John Moorman, PharmD.

SMBG, self-monitoring of blood glucose.

31

A1C Alone Is Often Not Enough



https://diatribe.org/time-range.

32

Personal CGM Options

Freestyle Libre 2+

Freestyle Libre 3+

Eversense 365

Guardian 4

Simplera and Simplera Sync

Dexcom G6

Dexcom G7

33

Personal CGM Comparison

	Dexcom G6	Dexcom G7	Libre 2 Plus	Libre 3 Plus	Simplera, Simplera Sync	Eversense 365
Maximum wear time	10 days	10.5 days	Plus: 15 days		7 days	365 days
Warm-up time	2 hours	<30 minutes	1 hour		2 hours	24 hours
Calibrations	Optional	Optional	None		Optional, required to enter auto mode	After 14 days, weekly
Water depth	8 feet, 24 hours	8 feet, 24 hours	3 feet, 30 minutes		8 feet, 30 minutes	3.28 feet, 30 minutes
Alerts/alarms	High, low, predictive low, rise/fall rate	High, low, predictive low 20 min, rise/fall rate	High, low		High, low, predictive 60 min, rise/fall rate	High, low, predictive 30 min, rise/fall rate
Data platform	Dexcom Clarity		LibreView		CareLink	Eversense Data Management System

For MRI/CT scan the Libre 2 + and 3 +are compatible!

Eversense implantable, outer transmitter should be removed for MRI/CT

- Dexcom. Accessed May 8, 2025. https://dexcompdf.s3.us-west-2.amazonaws.com/en-us/G7-CGM-Users-Guide.pdf; Dexcom. Accessed May 8, 2025. https://dexcompdf.s3.us-west-2.amazonaws.com/en-us/G6-CGM-Users-Guide-new.pdf; Abbott. Accessed May 8, 2025. https://www.freestyle.abbott/us-en/freestyle-libre-3-resources.html; Abbott. Accessed May 8, 2025. https://www.freestyle.abbott/us-en/freestyle-libre-3-resources.html; Medtronic. Accessed May 8, 2025. https://hcp.medtronic-diabetes.com.au/sites/default/files/guardian_4_sonsor_ifu.pdf; Eversense. Accessed May 8, 2025. https://www.eversensecgm.com/user-guides/

34

Personal CGM Comparison (Cont)

	Dexcom G6	Dexcom G7	Libre 2 Plus	Libre 3 Plus	Simplera & Simplera Sync	Eversense 365
FDA ages &approved sites	Abdomen (≥2 years), upper buttocks (aged 2-17 years)	Upper arm (≥7 years), upper buttocks (aged 2-6 years)	Upper arm ≥2 years		Upper arm ≥7 years	Upper arm ≥18 years
Approved in pregnancy	No	Yes	Yes		No	No
Transmitter	3 months	Disposable	Disposable		Disposable	Charge daily
Frequency of glucose	5 minutes	5 minutes	1 minute		5 minutes	5 minutes
Drug interactions	Hydroxyurea	Hydroxyurea	Vitamin C		Acetaminophen, hydroxyurea	Tetracycline antibiotics, mannitol

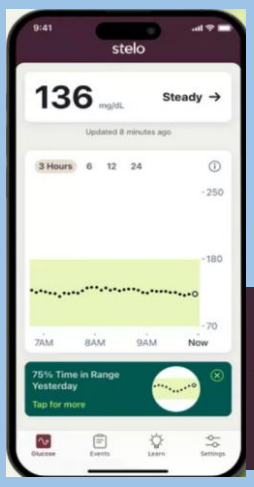
- Dexcom. Accessed May 8, 2025. https://dexcompdf.s3.us-west-2.amazonaws.com/en-us/G7-CGM-Users-Guide.pdf; Dexcom. Accessed May 8, 2025. https://dexcompdf.s3.us-west-2.amazonaws.com/en-us/G6-CGM-Users-Guide-new.pdf; Abbott. Accessed May 8, 2025. https://www.freestyle.abbott/us-en/freestyle-libre-3-resources.html; Abbott. Accessed May 8, 2025. https://www.freestyle.abbott/us-en/freestyle-libre-3-resources.html; Medtronic. Accessed May 8, 2025. https://hcp.medtronic-diabetes.com.au/sites/default/files/guardian_4_sonsor_ifu.pdf; Eversense. Accessed May 8, 2025. https://www.eversensecgm.com/user-guides/

35

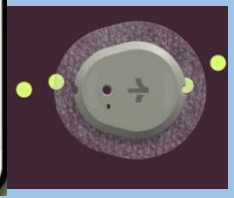
OTC CGMs

Abbott Lingo

Seems more geared to athletes or "health nuts"



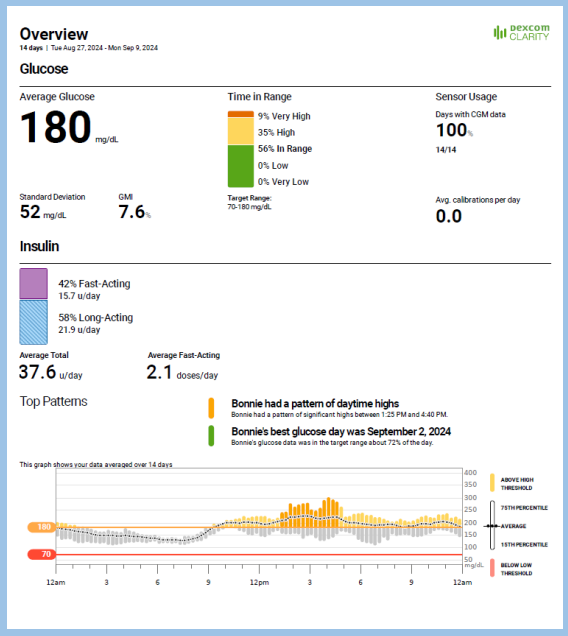
Dexcom Stelo



- Can be purchased without a prescription
- Price is ~$89/month and they are meant for people not taking insulin

36

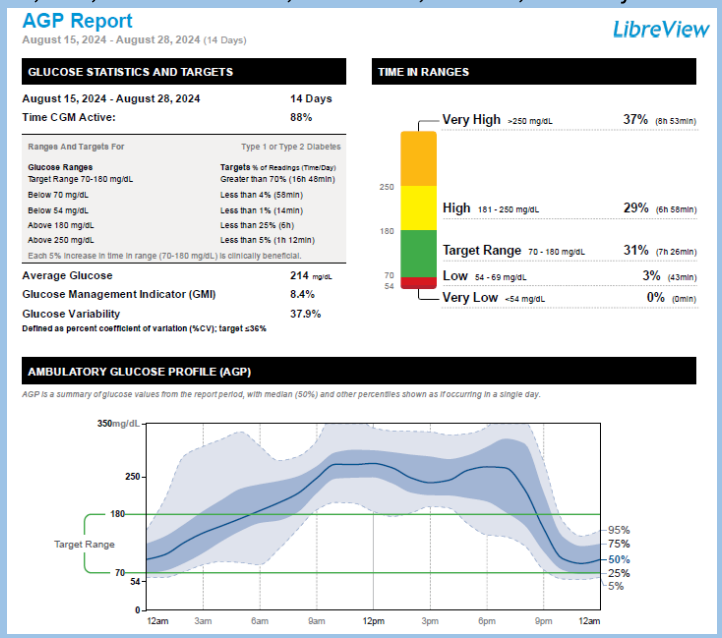
65-Year-Old Woman, T2D, on MDI, A1C 6.5%



Illustrates higher average glucose, time above range despite “well controlled A1C”

37

59-Year-Old Woman, T2D, on Basal Insulin, Metformin, SGLT-2i, Recently Started GLP-1RA, A1C 8.2%



Average glucose in CGM lines up with A1C, but illustrates that A1c cannot capture variability and hypoglycemia

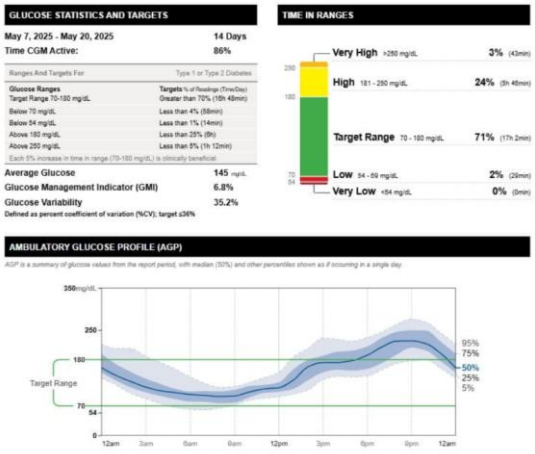
38

44-Year-Old Woman, T2D, metformin, SGLT-2i, A1C 7.6%

39

Case Study 4 - Bill

56-year-old man
A1C 6.9%
-insulin degludec 30 units daily
-insulin lispro 8 units at meals



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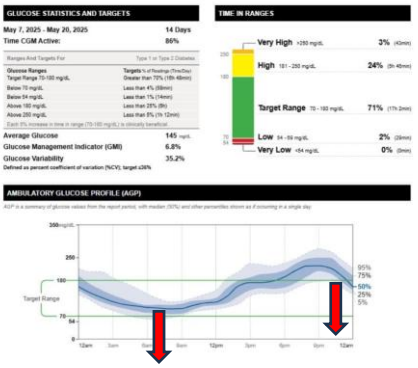
40

How Should the Insulin regimen Be Adjusted?

A. Continue basal insulin, increase prandial insulin
B. Decrease basal insulin, increase prandial insulin
C. Continue basal insulin, continue prandial insulin
D. Decrease basal insulin, continue prandial insulin



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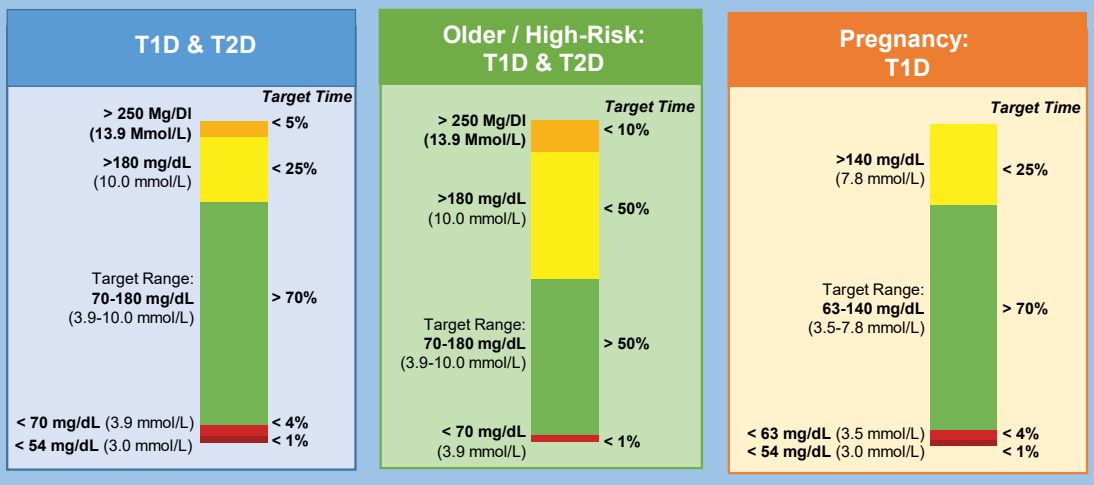
41

Time in Range



1% of the day is ≈15 minutes.

Battelino T et al. Diabetes Care. 2019;42(8):1593-1603.

42

Conclusions

- A1C reduction/goal attainment is **STILL** important
  - How you get there is important too!
- Assess comorbidities to assist with choice of T2D medication
  - A1C goal attainment is no longer “enough”
  - CV, Renal, HF
  - Weight reduction
  - Avoidance of hypoglycemia
- CGM can assist patients and providers to improve glycemic control

43