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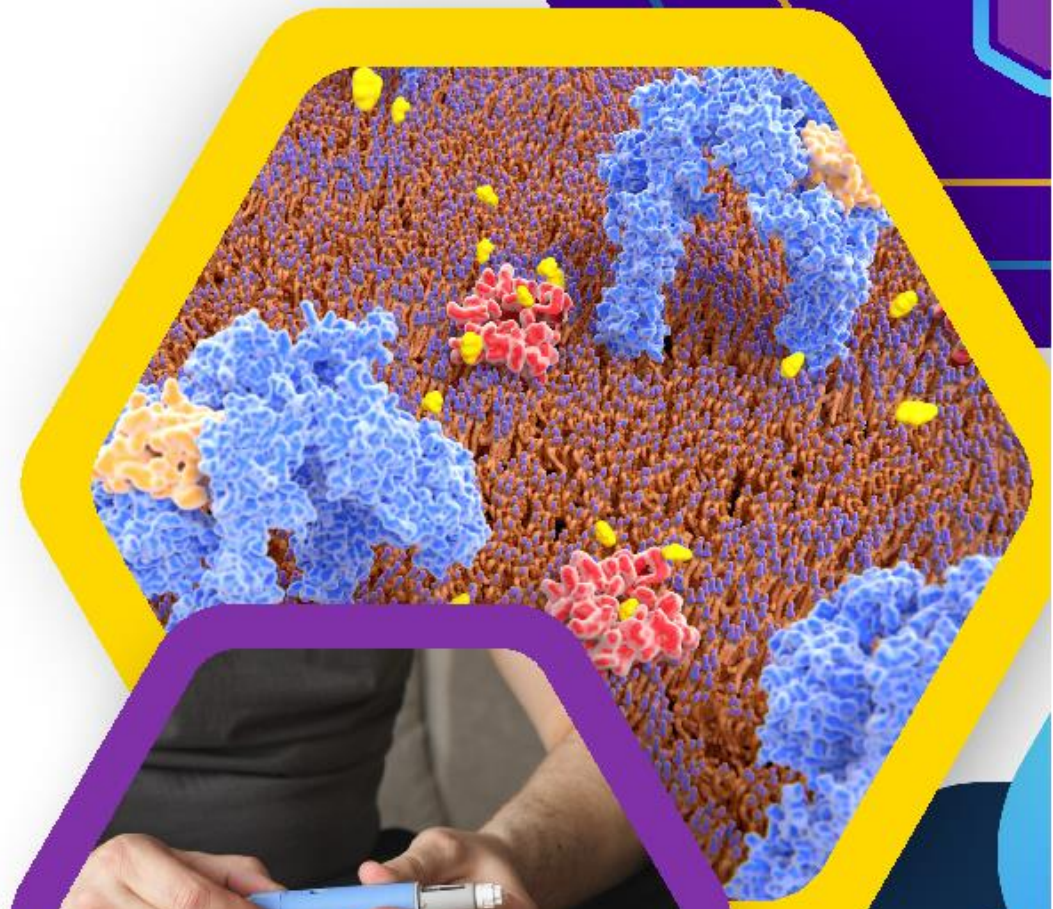
GLP-1 RA's Role in the Management of Diabetes:

TOOLS FOR THE PRIMARY CARE PROFESSIONAL



IN COLLABORATION WITH

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Learning Objectives

1. Apply motivational interview techniques to effectively engage patients in their diabetes management, develop and implement personalized educational strategies tailored to individual patient needs, and utilize various methods to monitor and improve medication adherence among patients with T2D.
2. Employ the latest diabetes management guidelines, algorithms, and therapies to increase awareness of the lower risk of hypoglycemia with the use of GLP1-RAs to lower A1C and understand the mechanism of action, dosing optimization, and administration, glycemic and extra-glycemic effects, safety and tolerability information, and place in therapy.
3. Develop and implement efficient clinic workflows and communication skills to enhance diabetes care and patient management.
4. Identify and overcome barriers contributing to therapeutic inertia and medication reluctance through patient-centered communication and decision-making processes.

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The Promise of Managing T2D Patients With GLP-1 RAs

- GLP-1 RAs can simplify the complexity of medication regimens with weekly dosing.
- Clinical studies have shown GLP-1 RAs can reduce A1C by 2-2.3% and weight by 15-21% from baseline.[1]
- Guidelines recommend use for those with diabetes and atherosclerotic cardiovascular disease (ASCVD).
  - Recent trials suggest improved results in patient with diabetes related to CKD. GLP-1 RAs/GIP reduced apnea events in patients with OSA.
- There is a lower risk of hypoglycemia and weight gain associated with GLP-1 RAs compared to insulin.
- GLP-1 RAs can help control type 2 diabetes (T2D) and has a lower risk of hypoglycemia and of weight gain vs. insulin.

1. US FDA. Drugs@FDA. Accessed March 9, 2023; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

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Greater Uptake in Primary Care Settings Is Needed

- Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are highly efficacious in achieving glycemic control and could aid PCPs in lowering not only A1C but also body weight in patients who are looking to lose weight.[1]
- Despite their potential, the use of GLP-1 RAs in the primary care setting is limited, with one study reporting that from 2015 to 2019, the percentage of T2D patients treated with a GLP-1 RA increased from 3.2% to only 10.7%.[2, 3]
- The use of GLP-1 RAs among patients with T2D and with established ASCVD or cardiovascular disease is reported to be relatively low, ranging from 4.0% to 10.1%, in several studies.[3, 4, 5]
- These data points and the ADA standards of care highlight the need for increased utilization of GLP-1 RAs in managing patients with T2DM who have ASCVD or are at high risk.

1. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. 2022 Oct;28(10):923-1049.
2. Yao H, Zhang A, Li D, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. BMJ. 2024 Jan 29;384:e076410.
3. Eberly LA, Yang L, Essien UR, Eneanya ND, Julien HM, Luo J, Nathan AS, Khatana SAM, Dayoub EJ, Fanaroff AC, Giri J, Groeneveld PW, Adusumalli S. Racial, Ethnic, and Socioeconomic Inequities in Glucagon-Like Peptide-1 Receptor Agonist Use Among Patients With Diabetes in the US. JAMA Health Forum. 2021 Dec 17;2(12):e214182.
4. King A, Miller EM. Glucagon-Like Peptide 1 Receptor Agonists Have the Potential to Revolutionize the Attainment of Target A1C Levels in Type 2 Diabetes-So Why Is Their Uptake So Low? Clin Diabetes. 2023 Spring;41(2):226-238. doi: 10.2337/cd22-0027. Epub 2023 Nov 3.
5. Al Rifai M, Vaughan EM, Abushamat LA, et al. Correlates of Glucagon-Like Peptide-1 Receptor Agonist Use Among Patients With Atherosclerotic Cardiovascular Disease and Type 2 Diabetes Mellitus (from the Department of Veterans Affairs). Am J Cardiol. 2022 Jun 1;172:7-10.

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Meet Jill (Patient Case 1)

Jill is a 48-year-old female that lives with T2D, hypertension, dyslipidemia, and obesity. She takes metformin 1000 mg twice daily, sitagliptin 100 mg daily, dapagliflozin 10 mg daily, atorvastatin 40 mg daily, and lisinopril 20 mg daily. Her most recent A1C=7.5%. She will be starting a GLP-1 receptor agonist today at the lowest dose.

- **Discussion:** What adjustments should be made to her other medications?
  A. Decrease lisinopril to 10 mg daily.
  B. Stop the dapagliflozin.
  C. Stop the sitagliptin.
  D. Decrease metformin to 500 mg twice daily.

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Jill's Four-Week Virtual Visit

- Jill has a BMI of 32 kg/m^2.
- In addition to T2D, Jill wants to lose weight.
- After three weeks on the GLP-1 RA, Jill calls into the clinic and reports nausea and related GI issues.
- These issues occur frequently when eating out and after eating spicy and/or fatty foods.
- **Discussion:** What advice would you give Jill at this visit?

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Jill's Three-Month Office Visit

- After the previous telehealth visit and counseling (eating small meals, avoiding spicy/fatty foods), Jill was kept on 0.75 mg dulaglutide.
- With lifestyle changes, nausea and related GI issues are now well-controlled.
- A1C is checked and shows Jill has reached goal of 6.9%.
- LDL and blood pressure are now in target range.
- **Discussion:** Jill desires additional weight loss. Do you titrate up to 1.5 mg to achieve weight loss or stay at the current 0.75 mg dose?

Jill's Nine-Month Office Visit

- A1C is even better at 6.1% and below goal.
- BMI has been reduced to 26 kg/m^2.
- LDL and blood pressure remain in target range.
- With these improved results, Jill asks if she can go off some medications.
- **Discussion:** What medications could be tapered off (metformin 1000 mg twice daily, dapagliflozin 10 mg daily, atorvastatin 40 mg daily, and lisinopril 20 mg daily)?
- **Discussion:** If considering changes to metformin, is it best to stop the medication, reduce the dose, or stretch out the frequency?

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Outpatient Glucose Targets for Nonpregnant Adults

- An A1C level of 6.5% is recommended for most nonpregnant adults, if it can be achieved safely. To achieve this target A1C level, FPG may need to be <110 mg/dL, and the 2-h postprandial glucose may need to be <140 mg/dL .
- Glucose targets should be individualized with consideration for life expectancy, disease duration, presence or absence of micro- and macrovascular complications, cardiovascular disease risk factors, comorbid conditions, and risk for hypoglycemia, as well as a person's cognitive and psychological status.
- Adopt less stringent glycemic goals (A1C 7% to 8%) in people with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced renal disease, extensive comorbid conditions, or long-standing DM in which the A1C goal has been difficult to attain despite intensive efforts, so long as the person remains free of hyperglycemia-associated symptoms.

Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. 2022 Oct;28(10):939.

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Potential Side Effects

Common side effects (which tend to go away over time):

- Loss of appetite
- Nausea and vomiting
- Constipation
- Diarrhea

Other side effects can include:

- Dizziness
- Mild tachycardia
- Infections
- Headaches
- Indigestion
- Temporary mild itchiness and/or redness at the injection site

- GI adverse events are typically mild and transient, with greatest incidence during dose escalation.
- Side effects may be reduced with slower dose titration.

Important safety information to be aware of include:

- Pancreatitis - limitation
- Medullary thyroid cancer – black box warning
- Medullary endocrine neoplasia – black box warning
- Temporary worsening of diabetes-related retinopathy - important safety information

GLP-1 agonists are generally safe. But there are a few risks to consider, including:

- Allergic reactions
- Use during pregnancy
- Low blood sugar (hypoglycemia) , especially when used with sulfonylureas or insulin

Drucker DJ. Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity. Diabetes Care. 2024 Jun 6:dci240003.

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Meet Carlos (Patient Case 2)

- Carlos is a 47-year-old male patient with a 10-year history of diabetes.
- His other medical problems are obesity and hyperlipidemia.
- He has a BMI of 34.
- Labs show an A1C of 7.8%.
- He is attending his sister's wedding in nine months and wants to aggressively lose weight.
- You review his formulary and prescribe tirzepatide at 2.5 mg weekly for four weeks.
- **Discussion:** Carlos asks what is the difference between tirzepatide and semaglutide. What do you tell him?

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Dual GIP/GLP-1 Receptor Agonists: New Advances for Treating T2D[1]

- GIP and GLP-1, two gastrointestinal incretin hormones, exert complementary actions.
- Dual GIP/GLP-1 receptor agonists (RAs) are more potent than pure GLP-1 RAs.
- Tirzepatide, a unimolecular GIP/GLP-1RA, is indicated in type-2 diabetes.
- Tirzepatide induces dose-dependent reduction in HbA1c and body weight.
- Tolerance of tirzepatide is comparable to that of GLP-1RAs.
- Tirzepatide is being studied in cardiovascular disease, obesity and liver disease (MAFLD)

1. Scheen AJ. Dual GIP/GLP-1 receptor agonists: New advances for treating type-2 diabetes. InAnnales d'Endocrinologie 2023 Apr 1 (Vol. 84, No. 2, pp. 316-321). Elsevier Masson.

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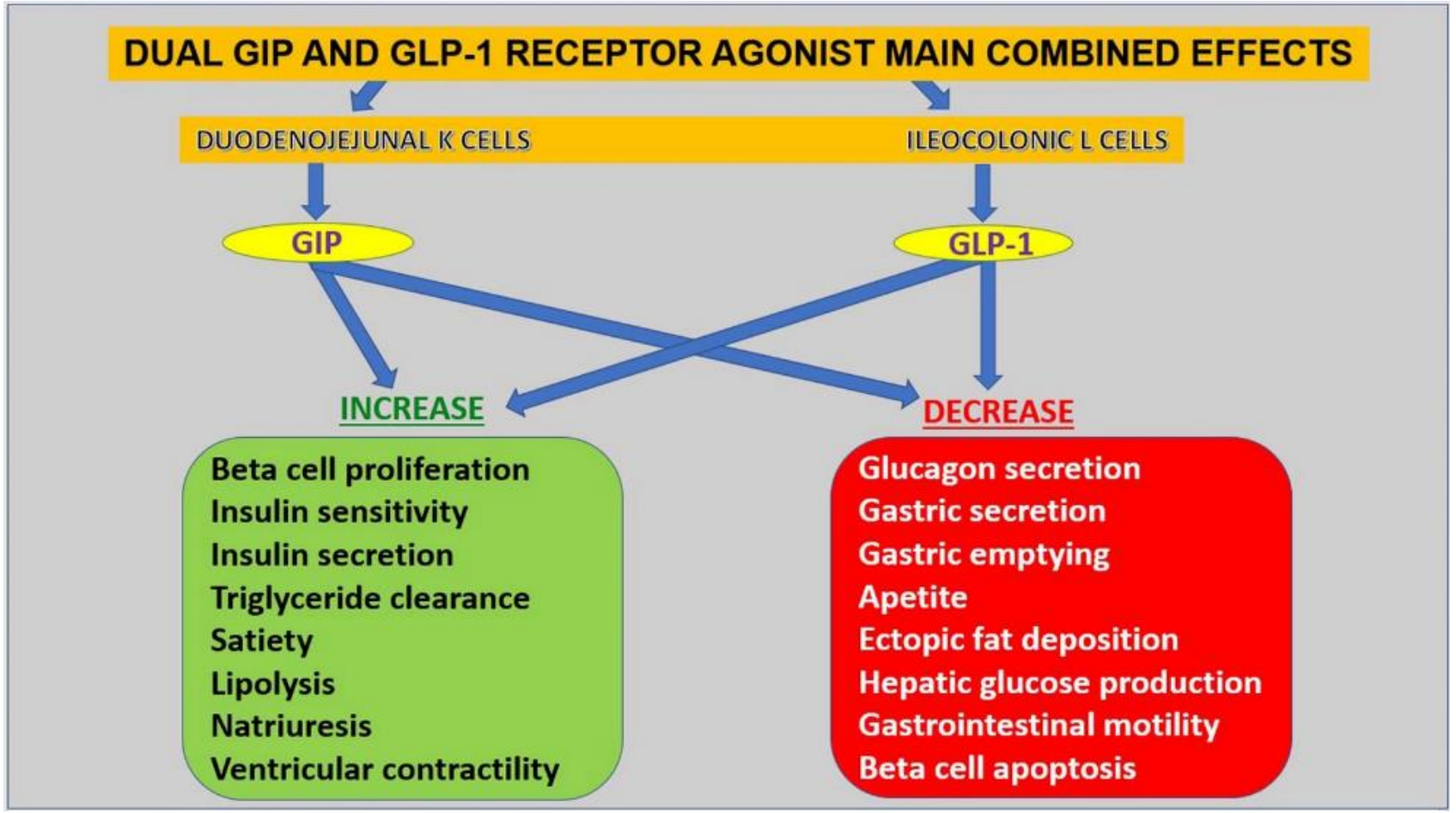
The Dual Glucose-Dependent Insulinotropic (GIP) and GLP-1 RA Tirzepatide



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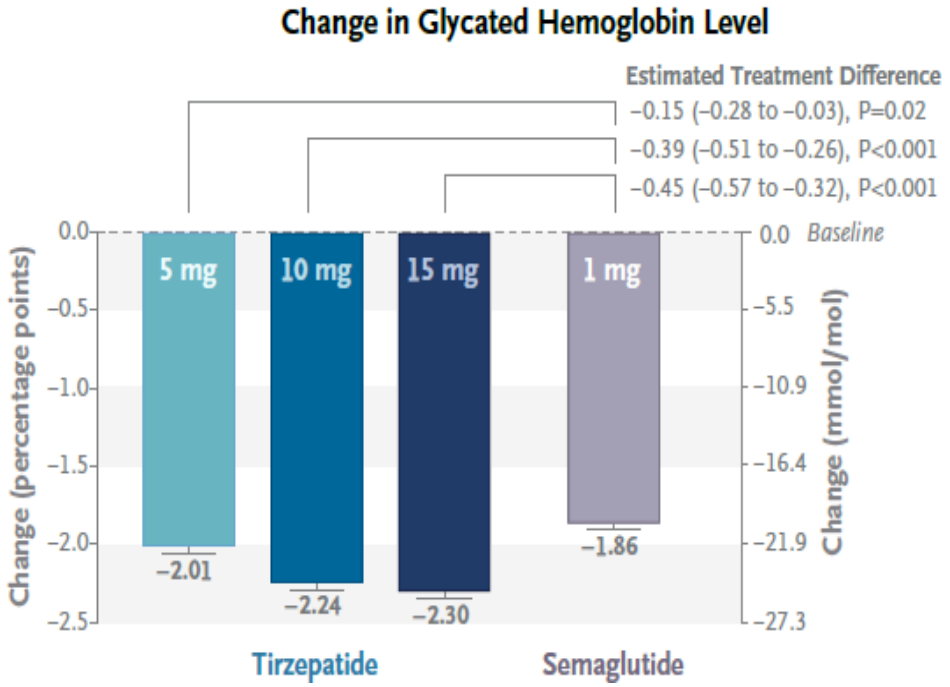
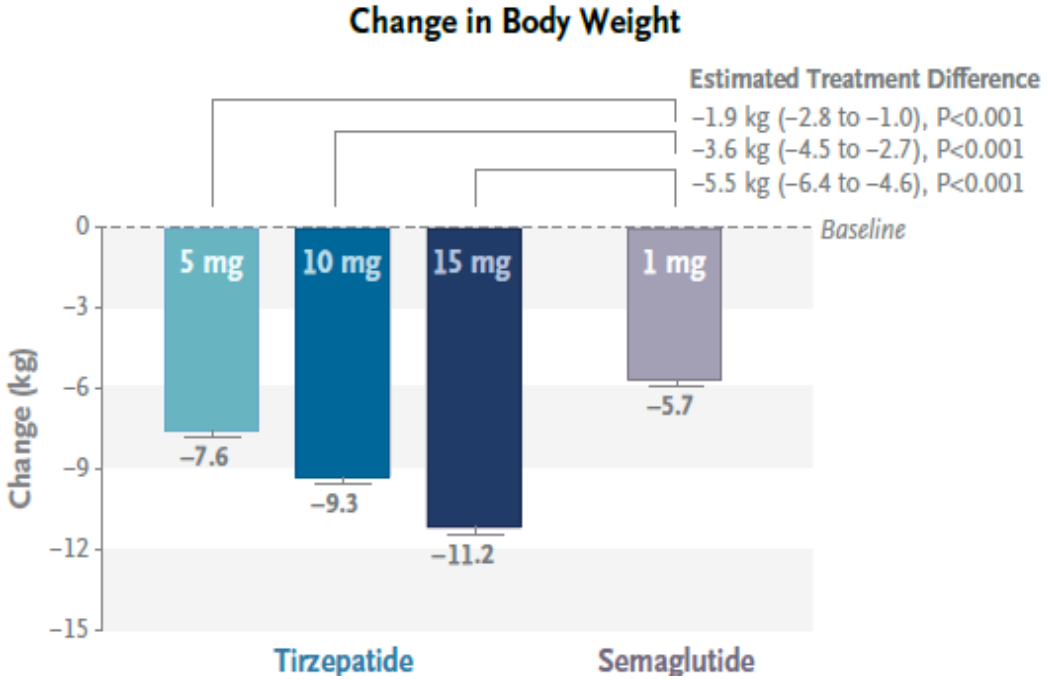
Tirzepatide vs. Semaglutide 1 mg Once Weekly in Patients with Type 2 Diabetes





Conclusion: Tirzepatide was noninferior and also superior to semaglutide in reducing glycated hemoglobin levels in adults with type 2 diabetes (higher doses of semaglutide were not studied.)

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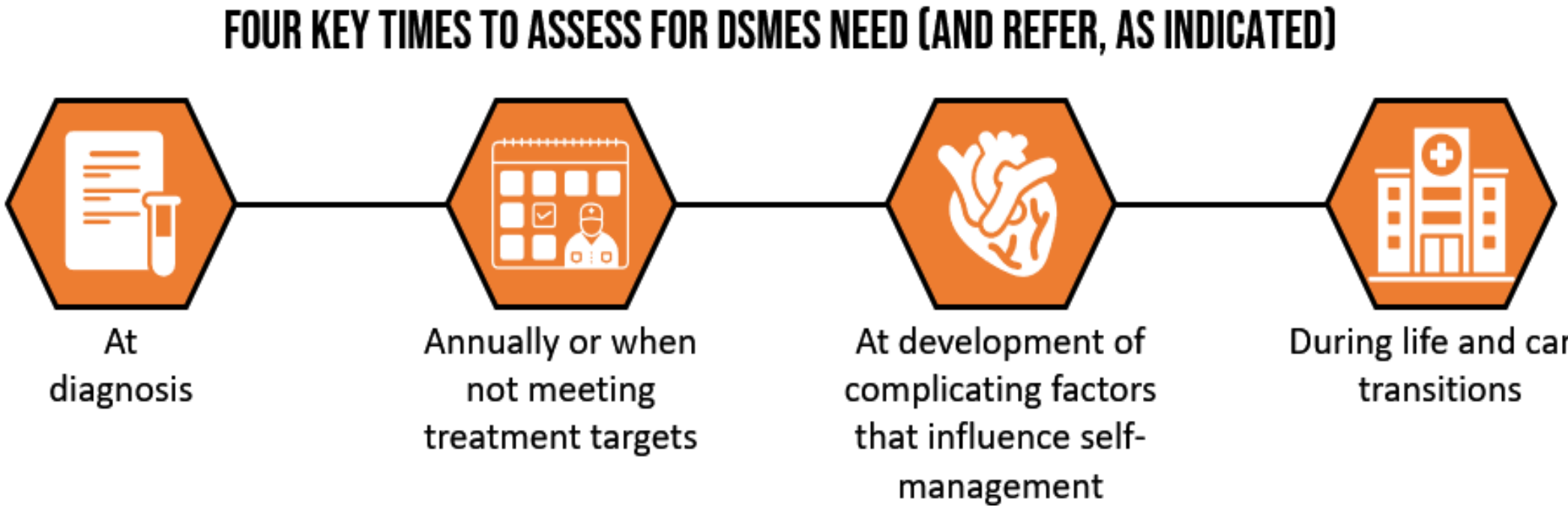
When to Refer to DSMES



American Diabetes Association; ElSayed NA et al. Diabetes Care. 2023;46 (Supple 1):S68-S96

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Carlos’ Three-Month Office Visit

- After four weeks at a virtual visit, tirzepatide dosage was increased to 5 mg weekly.
- At this three-month visit, testing shows A1C at 6.5%.
- Carlos has lost 10 lbs but feels “progress is kind of slow.”
- He has a busy schedule, eats out frequently, and complains he is finding this challenging.
- **Discussion:** What's the best next step to help support his weight loss and healthier eating habits?

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Carlos' Nine-Month Office Visit

- At his six-month checkup, Carlos was found to have lost another 12 lbs, and A1C was measured at 5.9%.
- A slimmer Carlos is happy that he has achieved his weight loss goals, and he looks forward to attending his sister's wedding with confidence.
- His A1C is now 5.8%, which is great, but there's a problem.
- **Discussion:** Because of his excellent A1C level, Carlos's insurance company denies coverage of tirzepatide! What steps do you take next?

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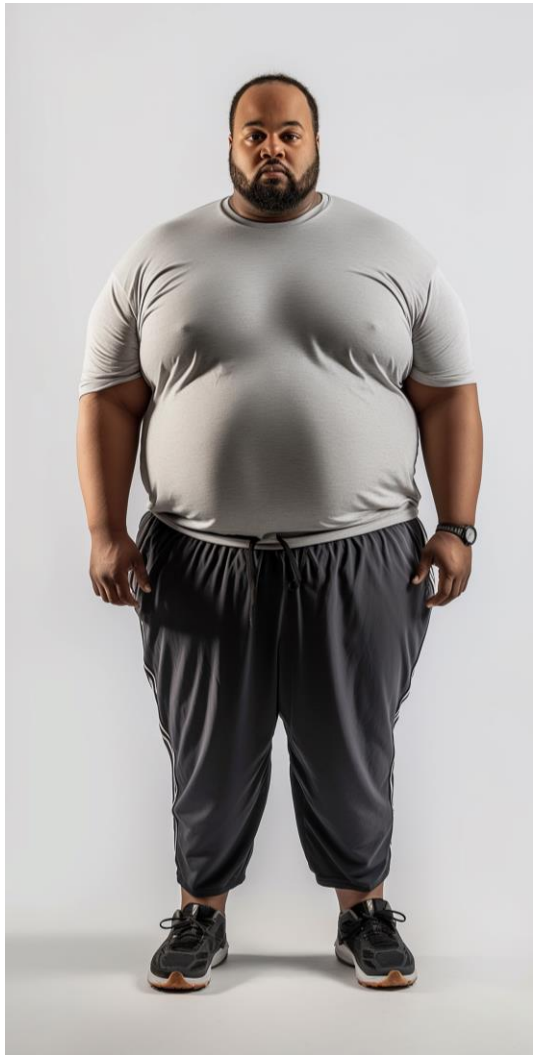
Meet Brian (Patient Case 3)

- Brian is a 45-year-old male with PMHx significant for HTN, obesity, and dyslipidemia.
- He was referred to endocrinology for management of uncontrolled diabetes.
- A1C noted as 9.5% with blood pressure of 135/86 mmHg, heart rate is 85 bpm, body mass index is 34.5 kg/m^2.
- Medications: losartan 100 mg daily, HCTZ 25 mg daily, metoprolol 100 mg daily, insulin glargine 50 u once daily, and insulin lispro 15 u before each meal.
- As A1C is high and he is on insulin. 0.25 mg of semaglutide was added and continuous glucose monitoring (CGM) was started after his first visit.



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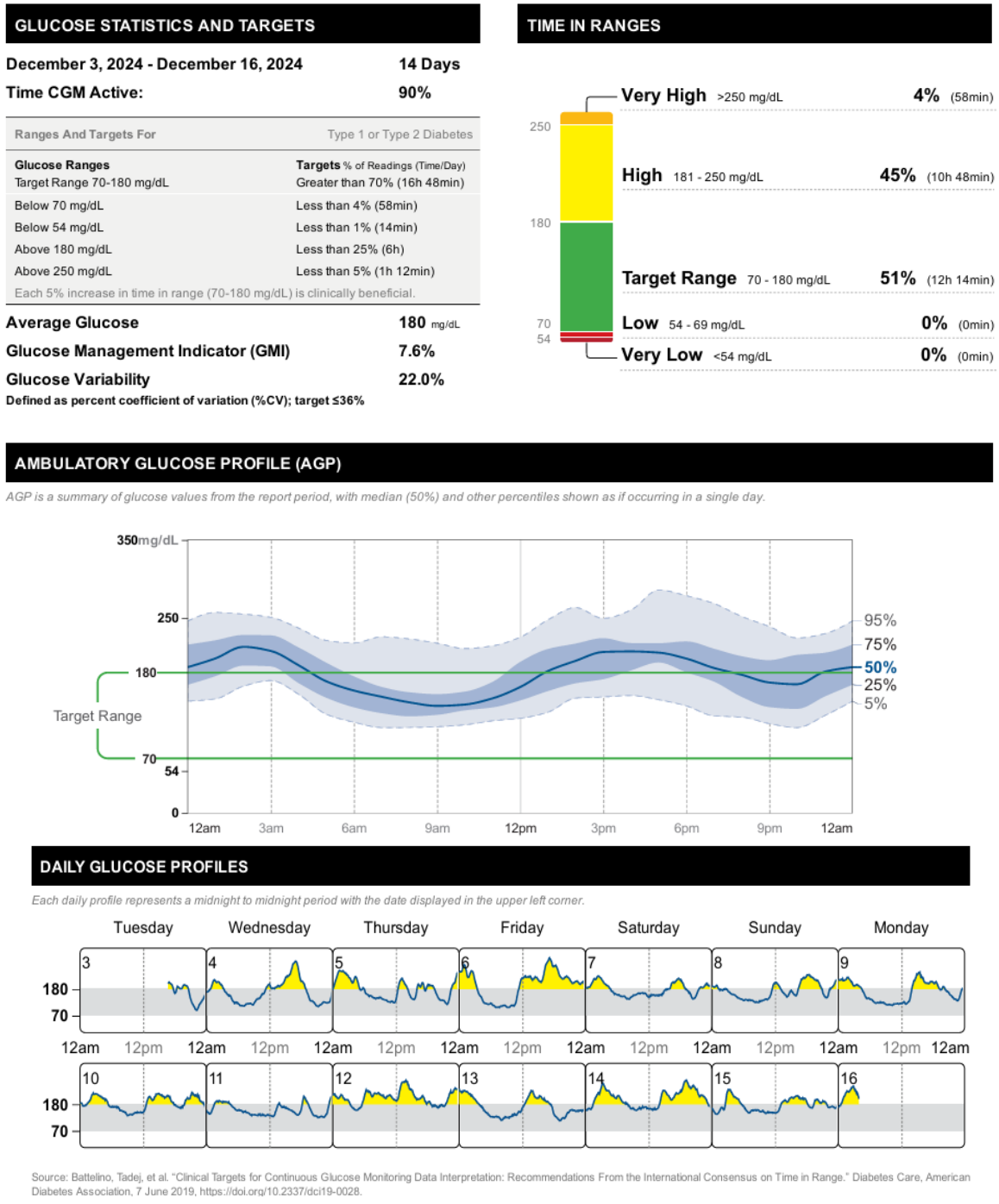
Brian's Two-Week Virtual Visit

- Brian has adjusted to CGM and is managing it well.
- His CGM data shows: 51% in target range, 0% <70mg/dL, 53% above 180mg/dL
- **Discussion:** How do you coach Brian about self-management and pattern management?



Source: Battelino, Tadej, et al. "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range." Diabetes Care, American Diabetes Association, 7 June 2019, https://doi.org/10.2337/dci19-0028.

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Why Consider Using Continuous Glucose Monitoring?

- In 1993 the DCCT established the “A1C” as the gold standard for estimating diabetes complication risk.
- Despite the introduction of new therapeutic interventions, only 50% of patients are able to achieve their targeted glycemic goals.
- Patients are frustrated by glycemic variability, caused in part by lack of insulin secretion and excess excretion of glucagon.
- The rate-limiting step to diabetes management is hypoglycemia.
- Identifying interventions that can add value to A1C and maintain “in-target” glucose values would improve patient adherence and reduce the occurrence of “dysglycemia.”

Hirsch IB, Verderese CA. Professional flash continuous glucose monitoring with ambulatory glucose profile reporting to supplement A1C: rationale and practical implementation. Endocr Pract. 2017 Nov;23(11):1333-1344.

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When and How Should Glucose Monitoring Be Used

- A1C should be measured at least semiannually in all people with DM and at least quarterly in people not at their glycemic target.
- All people who use insulin should perform glucose monitoring.
    - CGM is recommended for those on insulin.
- More frequent monitoring may be needed by people who are taking multiple daily injections (MDI) injections, people not at A1C targets, or those with a history of hypoglycemia.
- People who do not require insulin or insulin secretagogue therapy may benefit from CGM, especially to provide feedback about the effects of their lifestyle choices and to assess response to pharmacologic therapy.
- If not on hypoglycemic medication, monitoring frequency may be reduced, especially after initiation and titration of GLP-1 RAs.

Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. 2022 Oct;28(10):941-942.

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Value of CGM In Patients With T2DM

- Discover previously unknown hyper and hypoglycemic events.
- Measure glycemic control directly rather than via the surrogate metric of A1C.
- Observe metrics such as glycemic variability, time spent within, below or above targeted glucose range throughout the day.
- Determine the duration and severity of unrecognized hypoglycemia, especially nocturnal.
- Provide actionable information derived from the CGM report.
- Initiate safe and effective management of patients undergoing hemodialysis.
- Analyze glucose effects of targeted pharmacologic interventions (both fasting and post-meal glucose values).
- Determine the individualized duration of action of glucose-lowering therapies.
- Evaluate the effect of exercise on glycemic control.
- Provide behavioral interventions based on real-time glycemic values.

Vigersky R, Shrivastav M. Role of continuous glucose monitoring for type 2 in diabetes management and research. J Diabetes Complications. 2017 Jan;31(1):280-287.

Brian’s Next Office Visits

At One Month

- Some medications can be reduced.
- Lispro is reduced to 10 u with each meal; insulin glargine is reduced to 35 u once daily.

At Three Months

- Semaglutide is increased to 0.5 mg.
- Insulin lispro is further reduced to 5 u before meals.
- A1C is measured at 8.5%.

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Brian's Six-Month Office Visit

- Semaglutide is titrated up to 2 mg weekly.
- A1C is down to 7.4%, and he has lost 25 lbs.
- There has been a reduction in albuminuria and an improvement in Brian's GFR.
- Losartan 100 mg daily and metoprolol 100 mg are continued.
- As blood pressure is down to 100/60, HCTZ is discontinued.
- Insulin lispro before meals is discontinued, and insulin glargine is reduced to 20 u once daily.
- **Discussion:** Brian is at high-risk for cardiovascular issues. What should you watch for moving forward and should you add a sodium-glucose cotransporter-2 (SGLT2) inhibitor?

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Meet Marsha (Patient Case 4)

- Marsha is a 66-year-old female.
- Medical history: breast cancer (in remission), depression, hypertension, hyperlipidemia, peripheral neuropathy, stage 3 chronic kidney disease, osteoarthritis, and coronary artery disease (s/p stent 5 years ago).
- Medications: duloxetine 60 mg daily, losartan 50 mg daily, atorvastatin 80 mg daily, aspirin 81 mg daily, metformin 1000 mg twice a day, and empagliflozin 2 mg daily.
- A1C is up over the last three months, from 6.8% to 8%.
- She says, "I'm just tired of dealing with diabetes."
- She has been eating out a lot and has not been very active, as the arthritis in her knee has been bothering her.
- She has gained 8 lbs. since her last visit.
- **Discussion:** What is an appropriate response in helping your patient reach he glycemic targets?

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Identifying Diabetes Distress

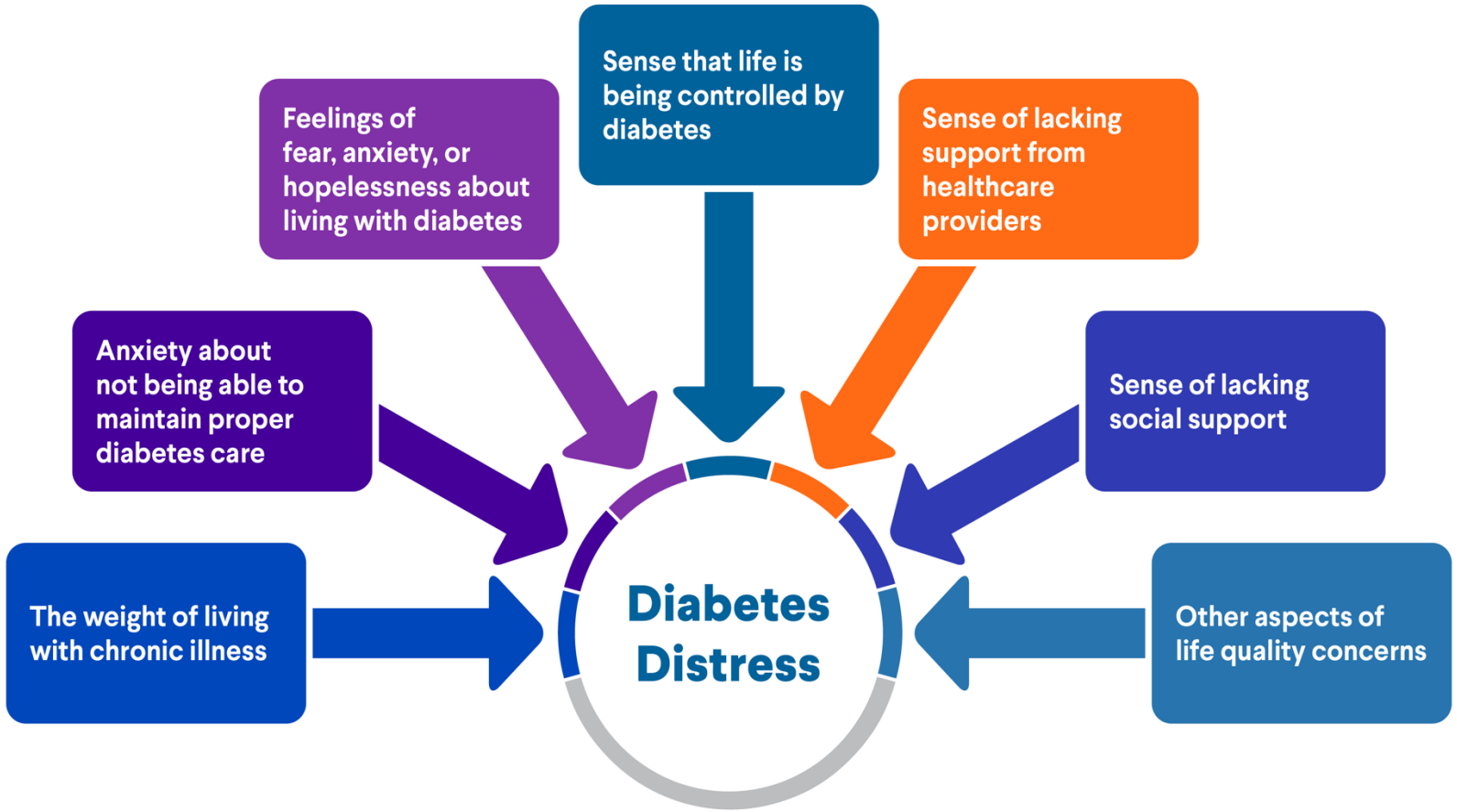

Figure adapted from Tareen RS, Tareen K. Psychosocial aspects of diabetes management: dilemma of diabetes distress. Translational Pediatrics. 2017 Oct;6(4):383-396.

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Social Determinants of Health (SDOH)

- SDOH are non-medical factors affecting health, like socioeconomic status, and geographic location[1].
- SDOH affect as much as 50% of county-level variation in health outcomes.[1]
- Addressing SDOH can enhance health and lead to better outcomes.[2]

The five social determinants of health. Social Determinants of Health. Public Health Professionals Gateway. CDC. https://www.cdc.gov/public-health-gateway/php/about/social-determinants-of-health.html. Accessed 6 Jan 2025.

1. Whitman A, et al. Addressing social determinants of health: Examples of successful evidence-based strategies and current federal efforts. Off Heal Policy. 2022 Apr 1;1:1-30.
2. https://www.cdc.gov/public-health-gateway/php/about/social-determinants-of-health.html

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Motivational Interviewing and Patient Engagement

- An intervention strategy in the treatment of lifestyle problems and chronic diseases such as diabetes
- Client-oriented, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence
- Built on four guiding principles:
  1. Express empathy.
  2. Develop discrepancies.
  3. Roll with resistance.
  4. Support self-efficacy.

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Concert CM, et al. The effectiveness of motivational interviewing on glycemic control for adults with type 2 diabetes mellitus (DM2): a systematic review. JBI Evidence Synthesis. 2012 Jan 1;10(42):1-7.

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Addressing/Preventing Therapeutic Inertia for People With Diabetes

Empower Patients Build Engagement and Trust	**Optimize Care AND Treatment** Person-Centered and Evidence-Based	**Leverage Tools AND TECHNOLOGY** for Enhanced Decision Support
BE A BARRIER BUSTER	**ACT NOW**	**IMPROVE DECISION-MAKING**
Schedule diabetes-only visits.	Conduct practice-based screening for likely therapeutic inertia.	Follow a diabetes treatment algorithm.
Set and track shared goals and time frames.	Make personalized diabetes care plans.	Create and use a patient registry.
Integrate screening for social/emotional barriers and identify support.	Implement a team-based approach to increase the frequency and quality of engagement.	Integrate decision support into the workflow.
Prescribe thoughtfully.	Utilize A1C and glucose data to drive rapid-cycle treatment intensification.	Utilize technology to enhance communication with people with diabetes.
Refer to diabetes self-management education and support (DSMES).	Stratify follow-up based on A1C/glucose data and changes in therapy.	Disseminate unblinded quality metrics.
Do your patients know you are their champion?	Have you done everything in your control to optimize therapy and support during, after, and in between visits?	Have you enabled everyone in your practice to make high-quality treatment decisions quickly and consistently?

American Diabetes Association Primary Care Advisory Group. 9. Pharmacologic approaches to glycemic treatment. *Standards of Care in Diabetes–2024* abridged for primary care professional. Clin Diabetes 2024;42:206-208

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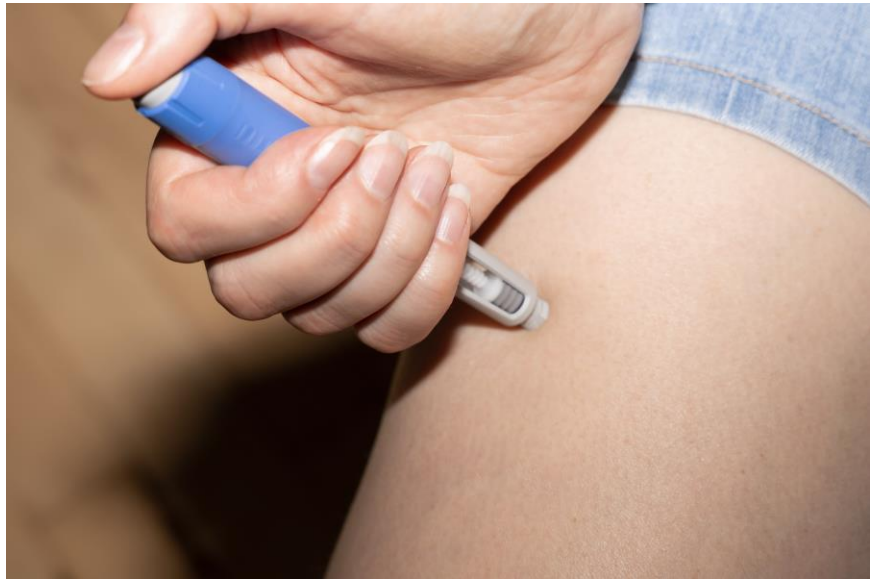
Marsha's One-Month Office Visit

- Duloxetine is increased to 90 mg daily.
- Depression score (PQH-9) has improved. She feels more confident and less apathetic but is having issues paying her rent and worries about eviction.
- Missing one of her medications "a few times a week."
- As she is struggling managing her diabetes, a referral to a social worker is made.
- You schedule an appointment to see her again in two weeks.

Marsha's Next Office Visit

- Marsha is feeling more confident about managing her diabetes now that she is getting some support.
- Adding a GLP-1 RA is also being considered now since she has both a history of CKD and cardiovascular disease.
- You check that she has had all of her screenings — she has.
- Remember, metformin should be discontinued with a GFR less than 30 — so monitor closely.
- **Discussion:** What would be a good GLP-1 RA to prescribe?



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Marsha's Vital Signs/Lab Tests

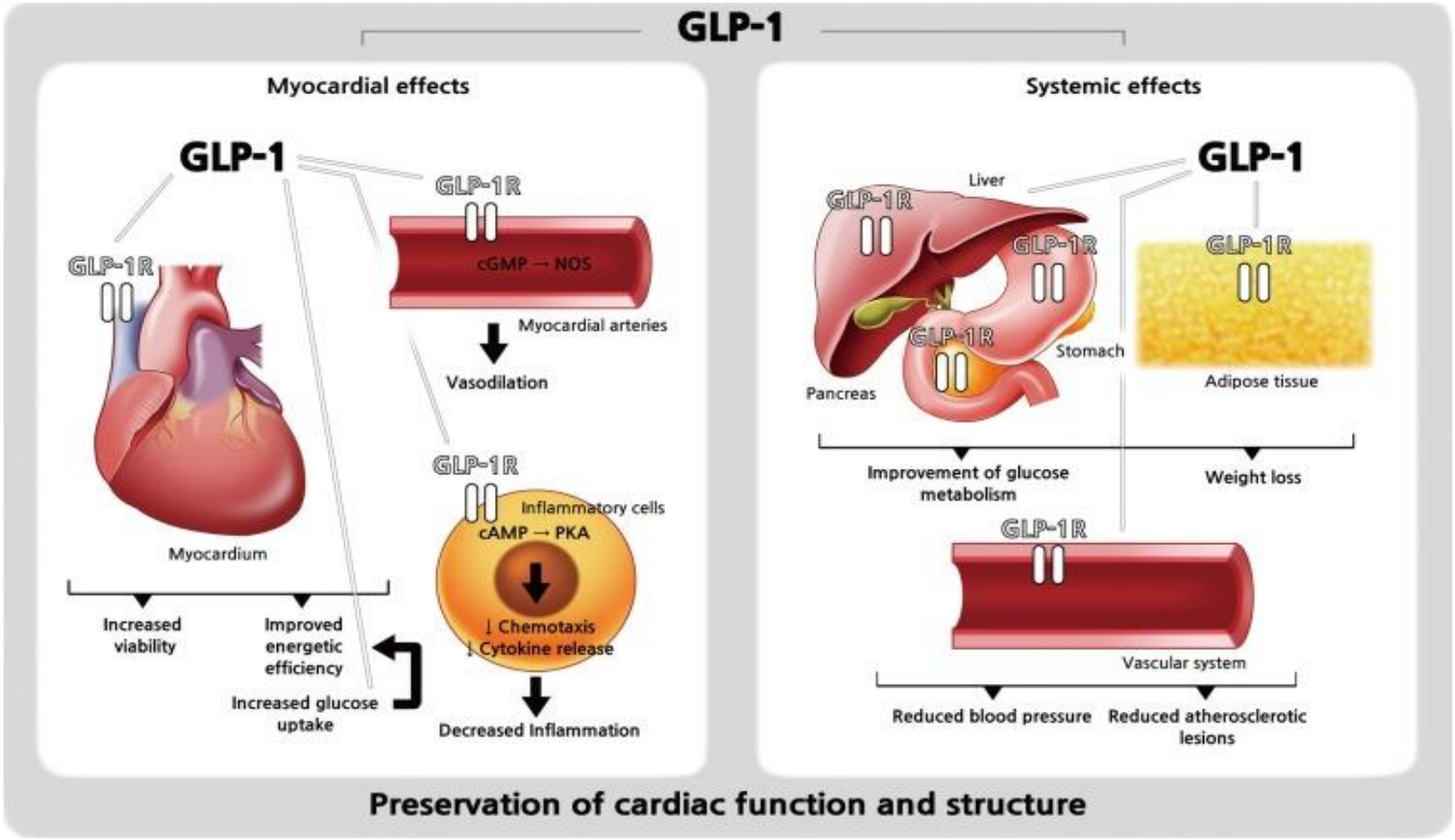
Vital Signs

- BP: 124/78 mm Hg
- Pulse: 74 bpm
- RR: 15 bpm
- Temp: 98.5 F
- Height: 64 inches
- Weight: 205 lbs
- BMI: 35.2 kg/m^2

Laboratory Tests

- FBG: 162mg/dL
- A1C: 8%
- SCr: 1.7 mg/dL
- LDL: 67 mg/dL
- HDL: 47 mg/dL
- TC: 241mg/dL
- UACR: 420mg/g
- EGFR: 48 $mL/min/1.73\ m^2$

Cardiovascular Benefits of GLP-1 RAs



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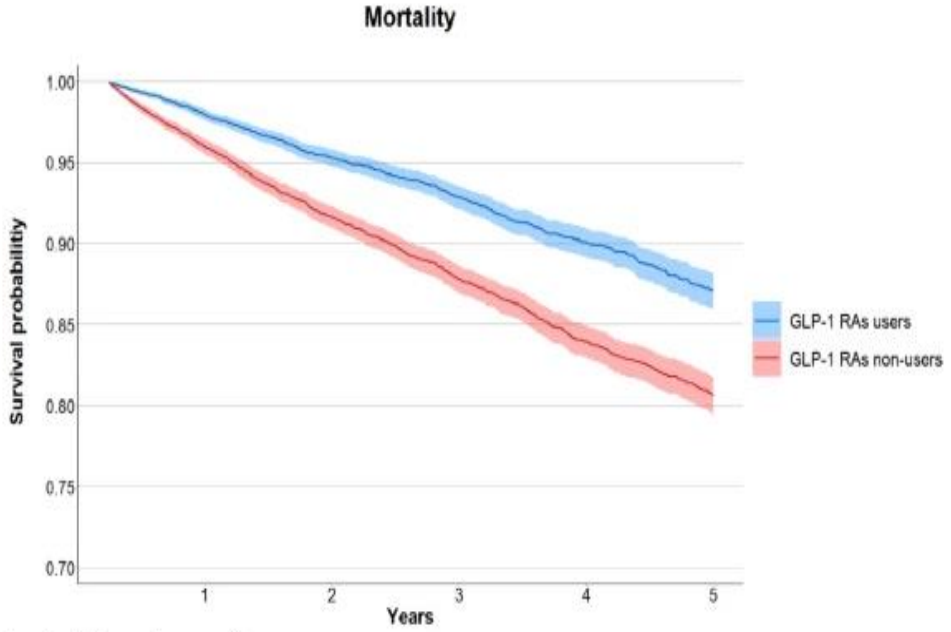
Renal Benefits of GLP-1 RAs

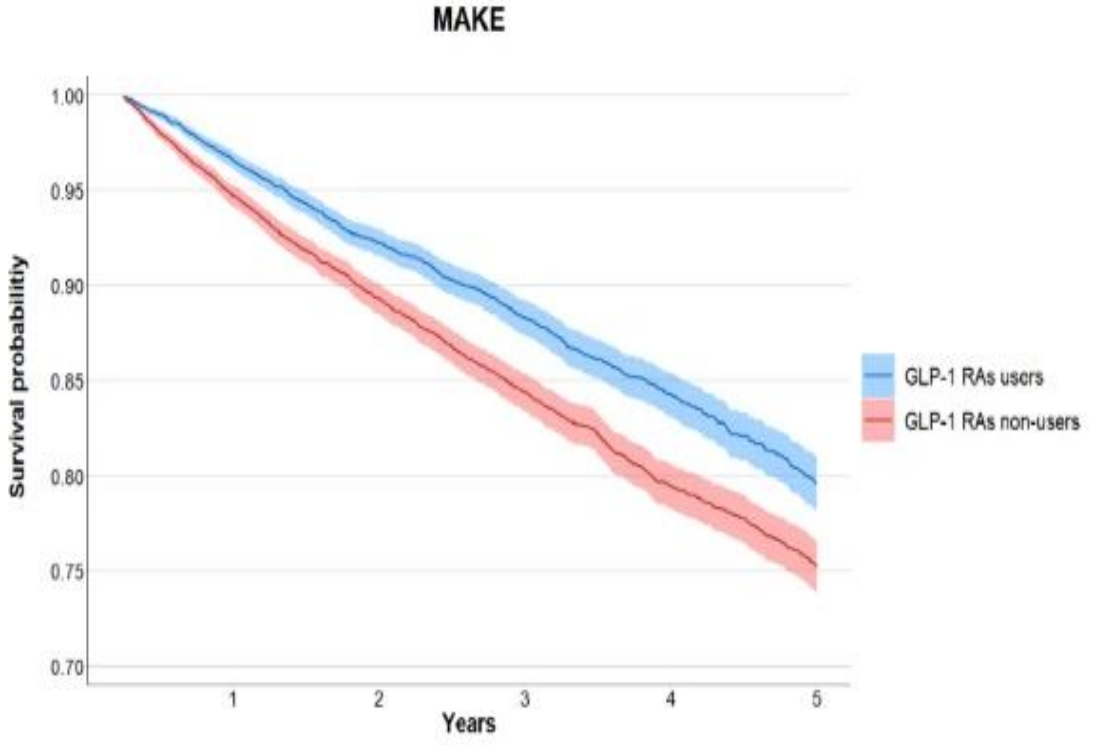
Fig. 2: Kaplan-Meier curves showing the long-term outcomes of interest following the use of GLP-1 RAs in a propensity score-matched counterpart.

(A)



Mortality : Number at risk (number event)

GLP-1 RAs user	7492(0)	7340(152)	7190(302)	7101(391)	7027(465)	6984(508)
GLP-1 RAs non-users	7492(0)	7192(300)	6938(554)	6753(739)	6619(873)	6524(968)



MAKE : Number at risk (number event)

GLP-1 RAs user	6513(0)	5999(214)	5785(428)	5666(547)	5565(648)	5512(701)
GLP-1 RAs non-users	6478(0)	6156(322)	5886(592)	5542(796)	5542(936)	5444(1034)

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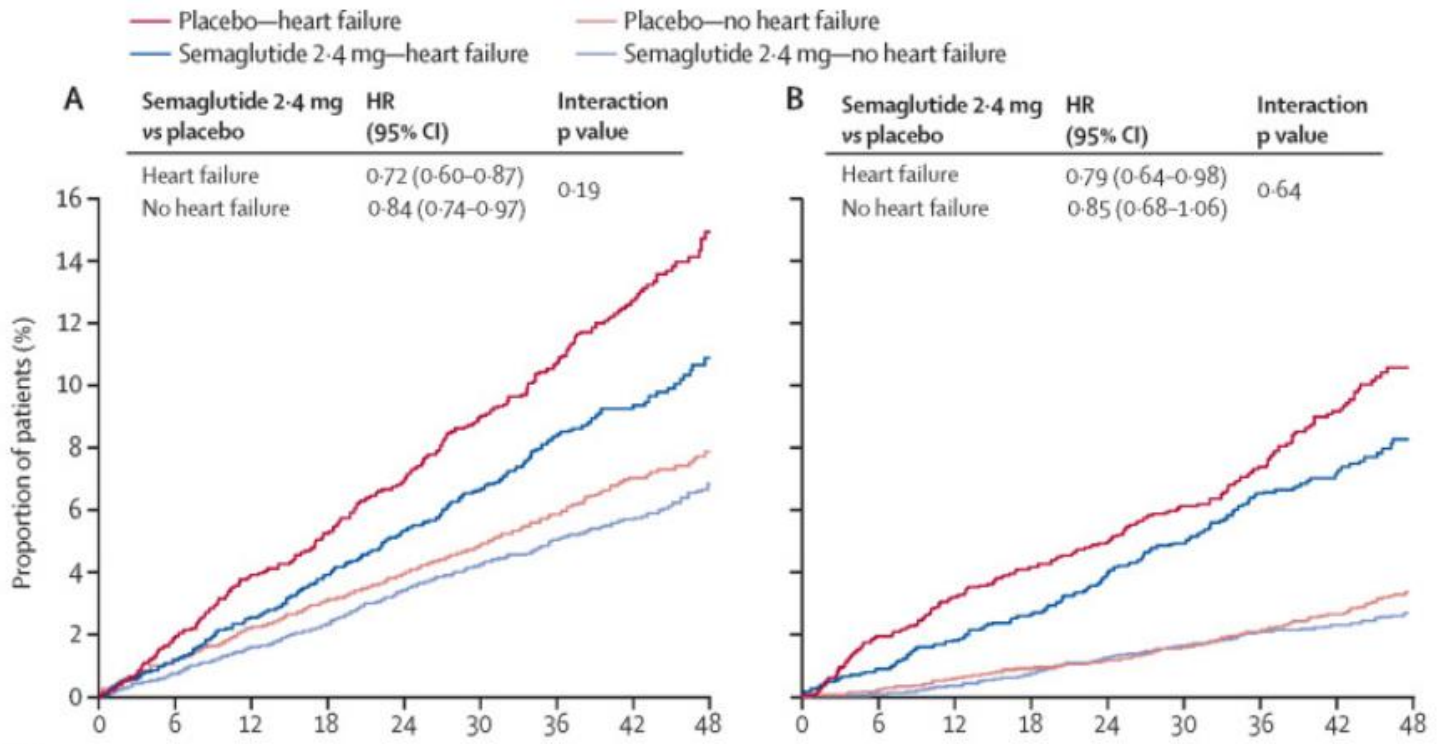
https://www.nature.com/articles/s41467-024-50199-y

Semaglutide and Heart Failure



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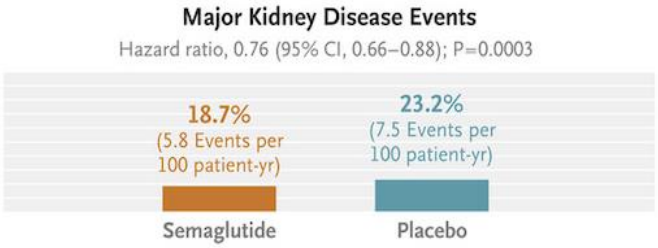
Semaglutide and Kidney Function

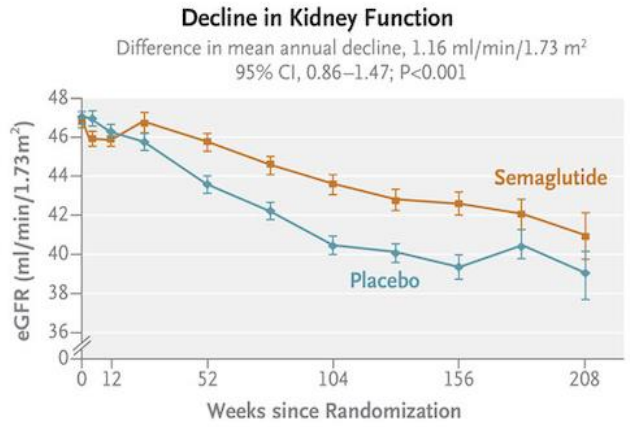
RESULTS

The trial was stopped early at a median follow-up of 3.4 years after an interim analysis showed efficacy. The semaglutide group had fewer primary-outcome events than the placebo group, equivalent to a 24% lower risk with semaglutide.

Kidney function declined more slowly in the semaglutide group than in the placebo group.

Serious adverse events were less common in the semaglutide group than in the placebo group.





HOW WAS THE TRIAL CONDUCTED?

3533 participants with type 2 diabetes and chronic kidney disease were randomly assigned to receive weekly subcutaneous semaglutide (1.0 mg) or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (initiation of dialysis, kidney transplantation, or an estimated glomerular filtration rate [eGFR] of <15 ml per minute per 1.73 m^2), at least a 50% reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes.

***** Semaglutide 1mg received FDA approval for CKD in January 2025.**

Trial Registration: ClinicalTrials.gov number NCT03819153
Trial Funding: Novo Nordisk

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Marsha's Three-Month Office Visit

- A1C is now at goal (6.7%).
- Marsha has lost the weight that she had gained previously.
- Her LDL has decreased by 20 points.
- Her proteinuria has reduced from 325 to 120.
- Her knee is feeling better in part due to weight loss.
- Overall, Marsha is happy with her results and feels much more motivated to manage her condition.

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Key Takeaways About GLP-1 RAs

- GLP-1 RAs are highly efficacious in achieving glycemic control and could aid PCPs in getting patients to their A1C target.
- GLP-1 RAs can improve diabetes control, weight management, and cardiovascular outcomes.
- Despite their potential, the use of GLP-1 RAs in the primary care setting is underutilized.
- Side effects are manageable and typically occur when patients start the medication or when dosage increases.
- Resources like DSMES are available to help support patients on their journey.
- Ongoing communication and monitoring are critical.

Resources

For copies of these slides, additional diabetes education and resources, visit:

- AACE Diabetes Resources
- AANP CE Center
- AANP Clinical Resources

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Thank you!