Updates in Diabetes

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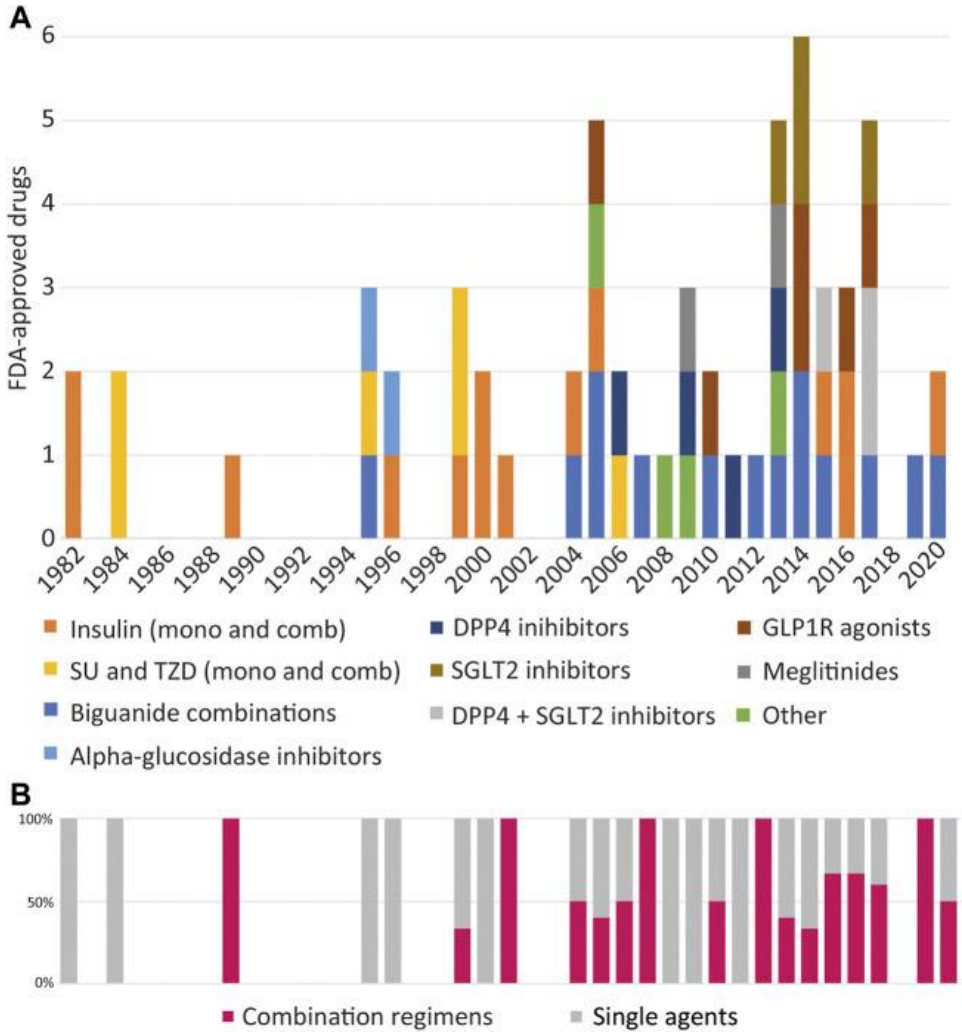
Learning Objectives

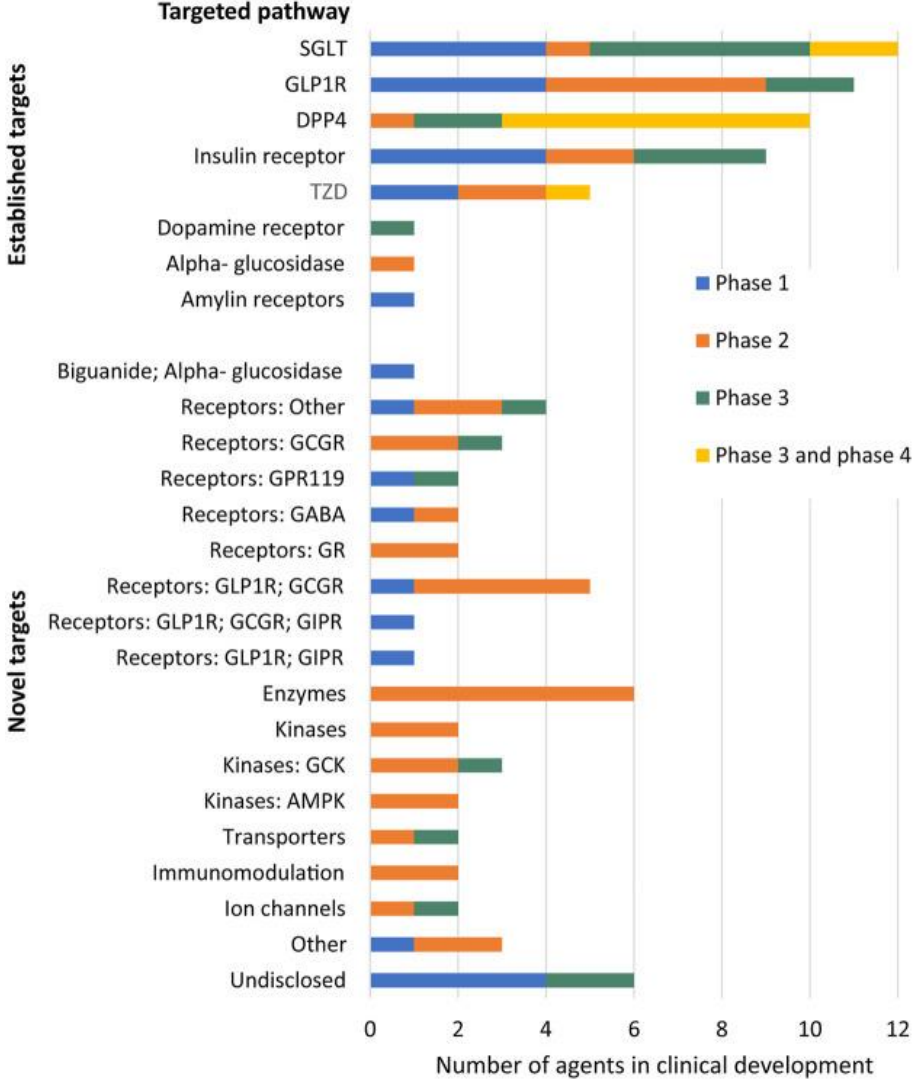
1. Utilize current treatment guidelines to choose the best treatment options for a patient with type 2 diabetes
2. Describe when and how to initiate treatment of diabetes
3. Discuss the side effects and additional benefits of medications used for the treatment of type 2 diabetes

FDA-Approved Drug Classes by Year



Dahlén AD, Dashi G, Maslov I, Attwood MM, Jonsson J, Trukhan V, Schiöth HB. Trends in Antidiabetic Drug Discovery: FDA Approved Drugs, New Drugs in Clinical Trials and Global Sales. Front Pharmacol. 2022 Jan 19;12:807548. doi: 10.3389/fphar.2021.807548. PMID: 35126141; PMCID: PMC8807560.

Molecular Targets for 99 Anti-Diabetic Agents in Current Clinical Trials



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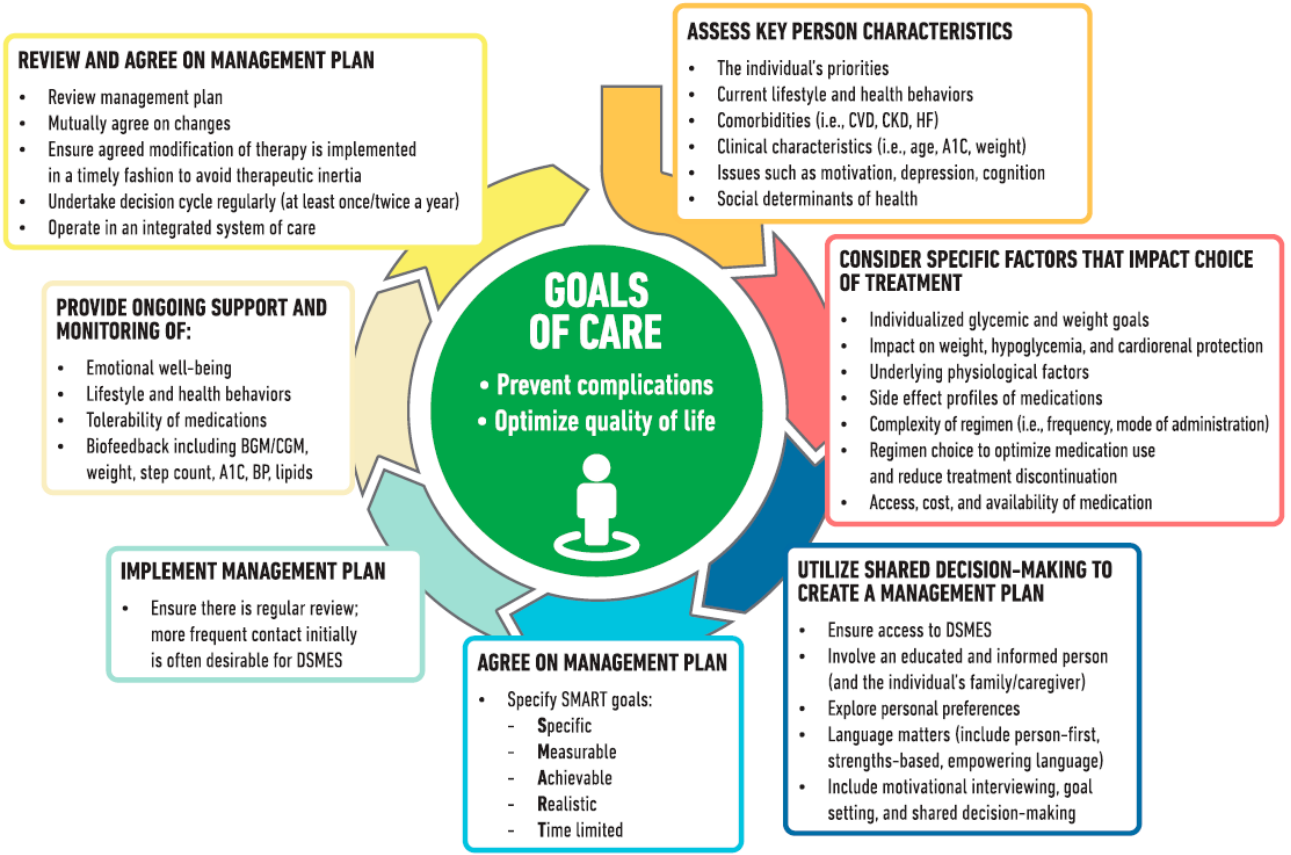
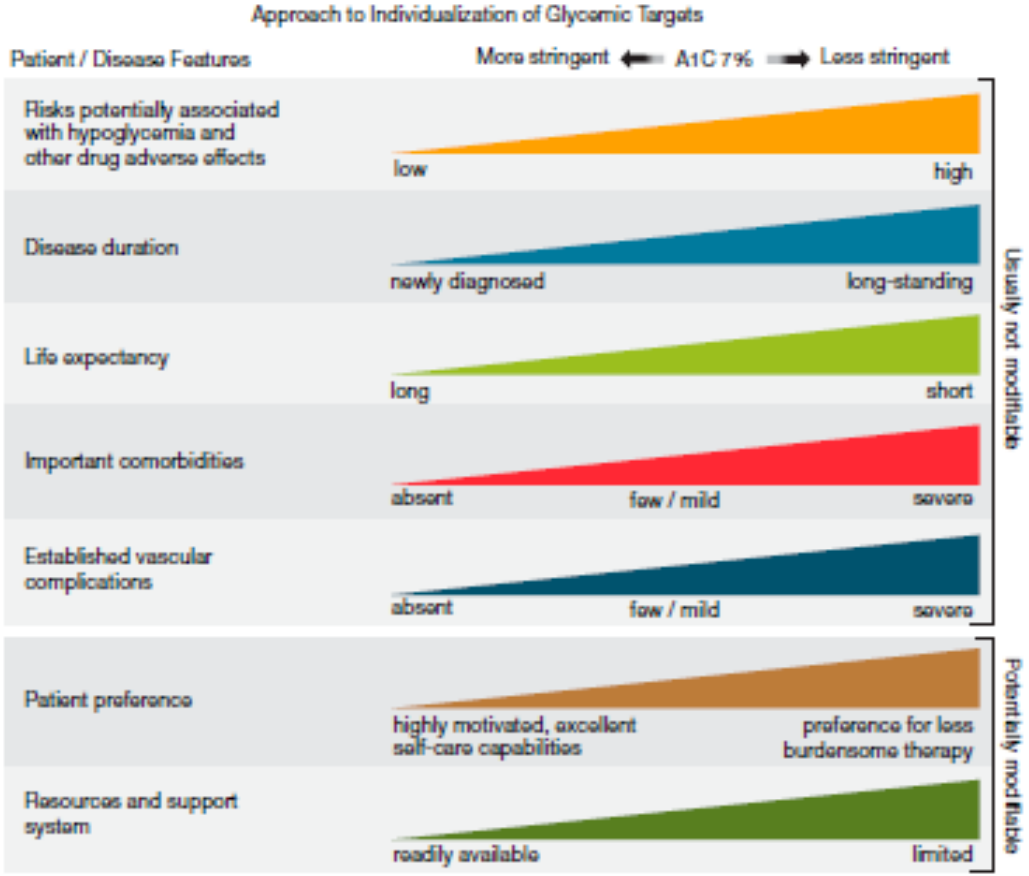
DECISION CYCLE FOR PERSON-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



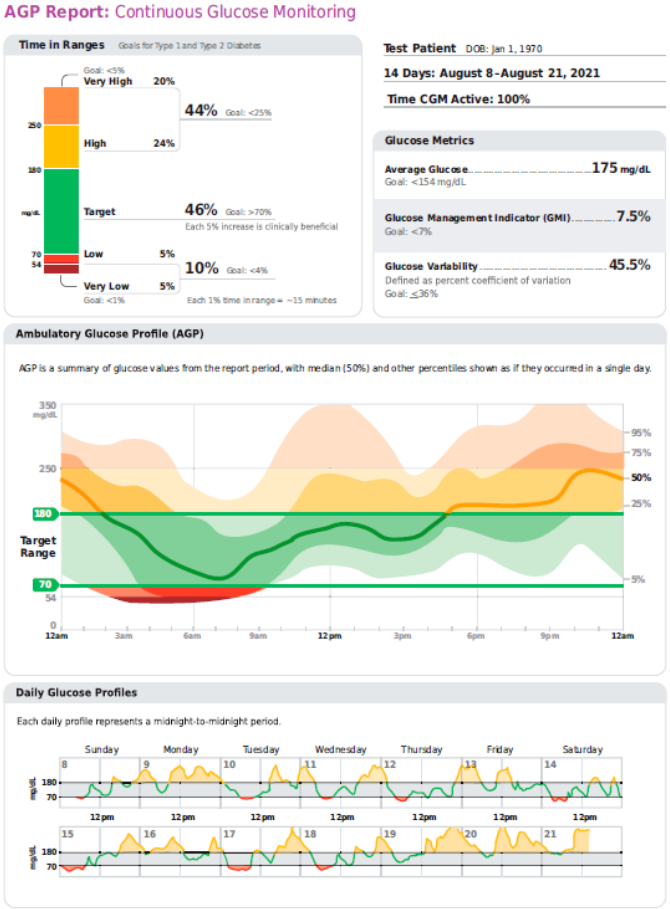
Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Care in Diabetes - 2023. *Diabetes Care* 2023;46(Suppl. 1):S49-S67

- Glycemic targets



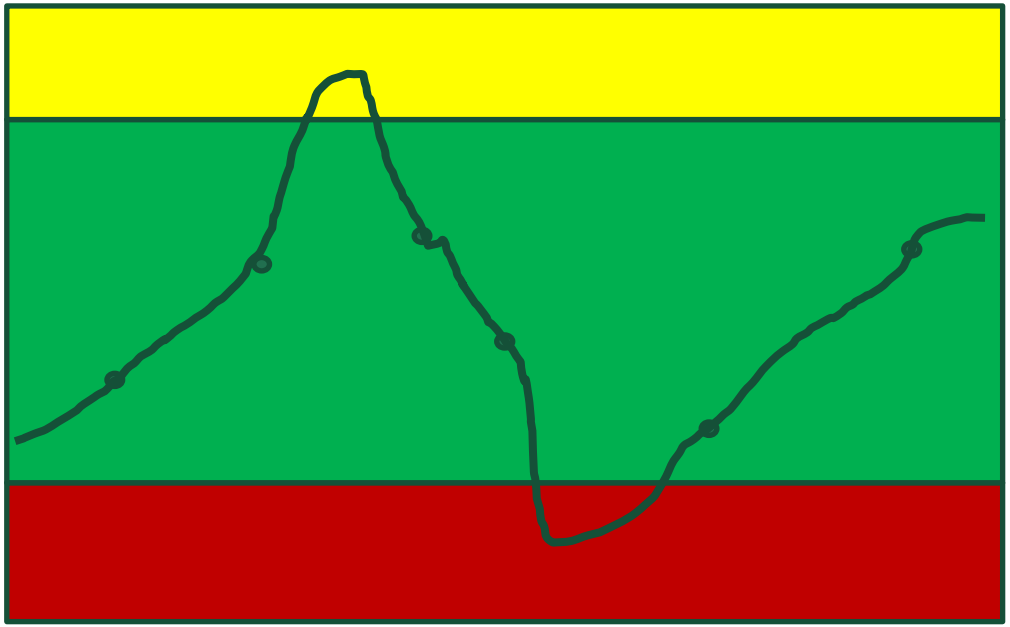
Glycemic Targets:
Standards of Care in Diabetes - 2023. *Diabetes Care* 2023;46(Suppl. 1):S97-S110

- Glycemic targets



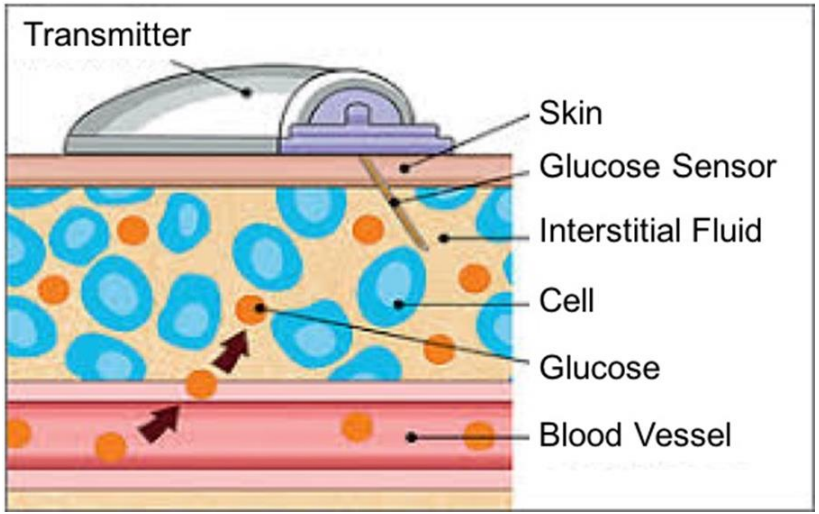
Glycemic Targets:
Standards of Care in Diabetes - 2023. *Diabetes Care* 2023;46(Suppl. 1):S97-S110

What is Continuous Glucose Monitoring (CGM)?



Hyperglycemia
Euglycemia
Hypoglycemia

How CGM Works

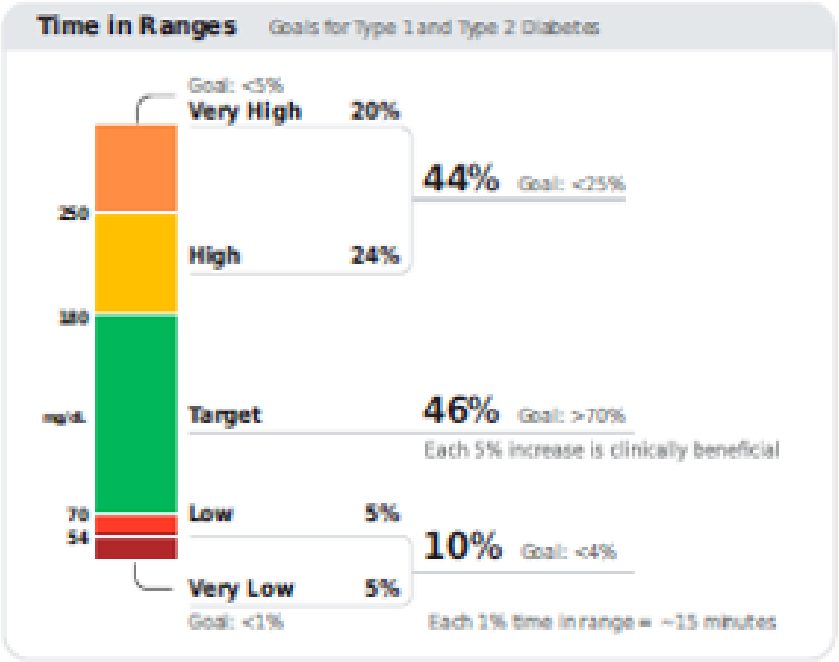


- Glucose is measured in interstitial fluid every 1-5 minutes
- Readings transmitted to reader or smart phone automatically or when scanned
- Current glucose as well as “trends” can be viewed

Soni A, et al. *Archives of Disease in Childhood – Education and Practice*. 2022; 107:188-193

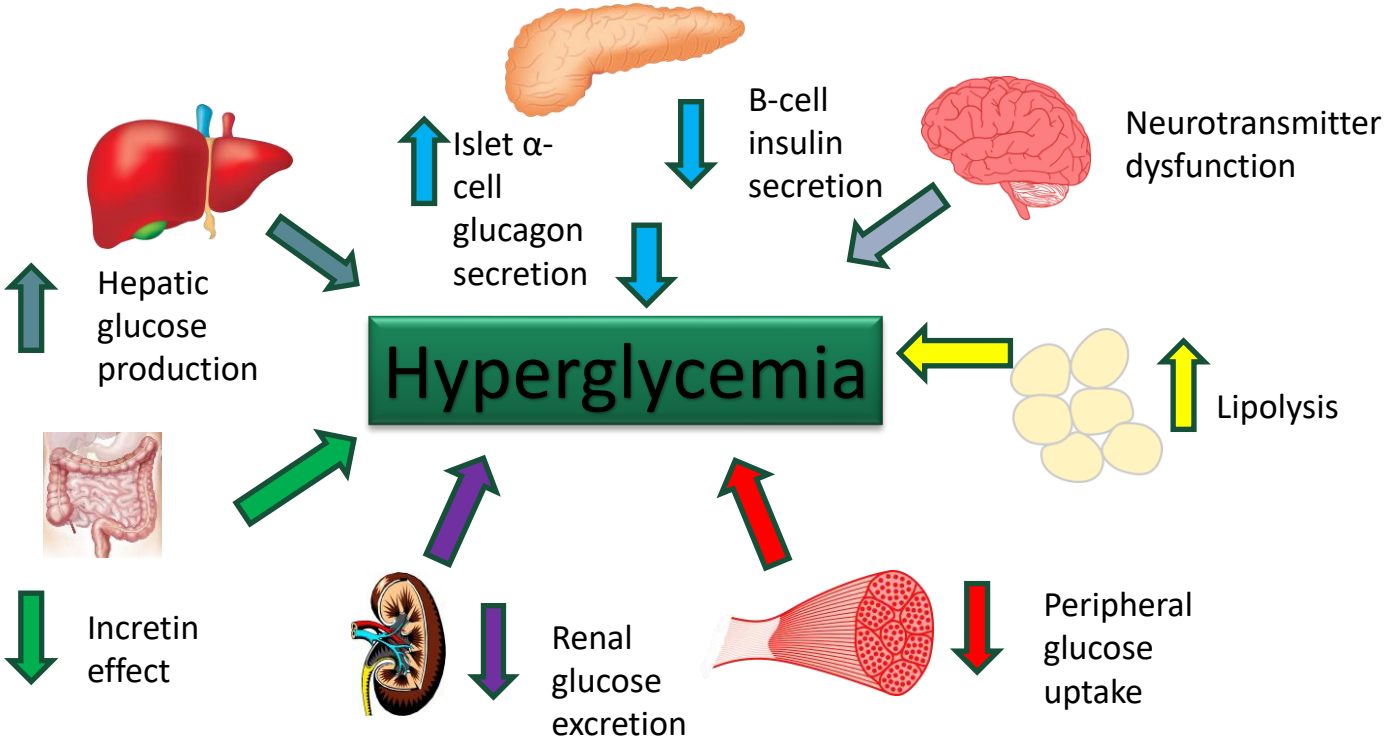
Time in Range (TIR)

- TIR of 70% corresponds to an A1c of about 7%
- Every 10% increase in TIR improves A1c by 0.5%
- Goal of TBR <4%
  - 1% is about 15 minutes

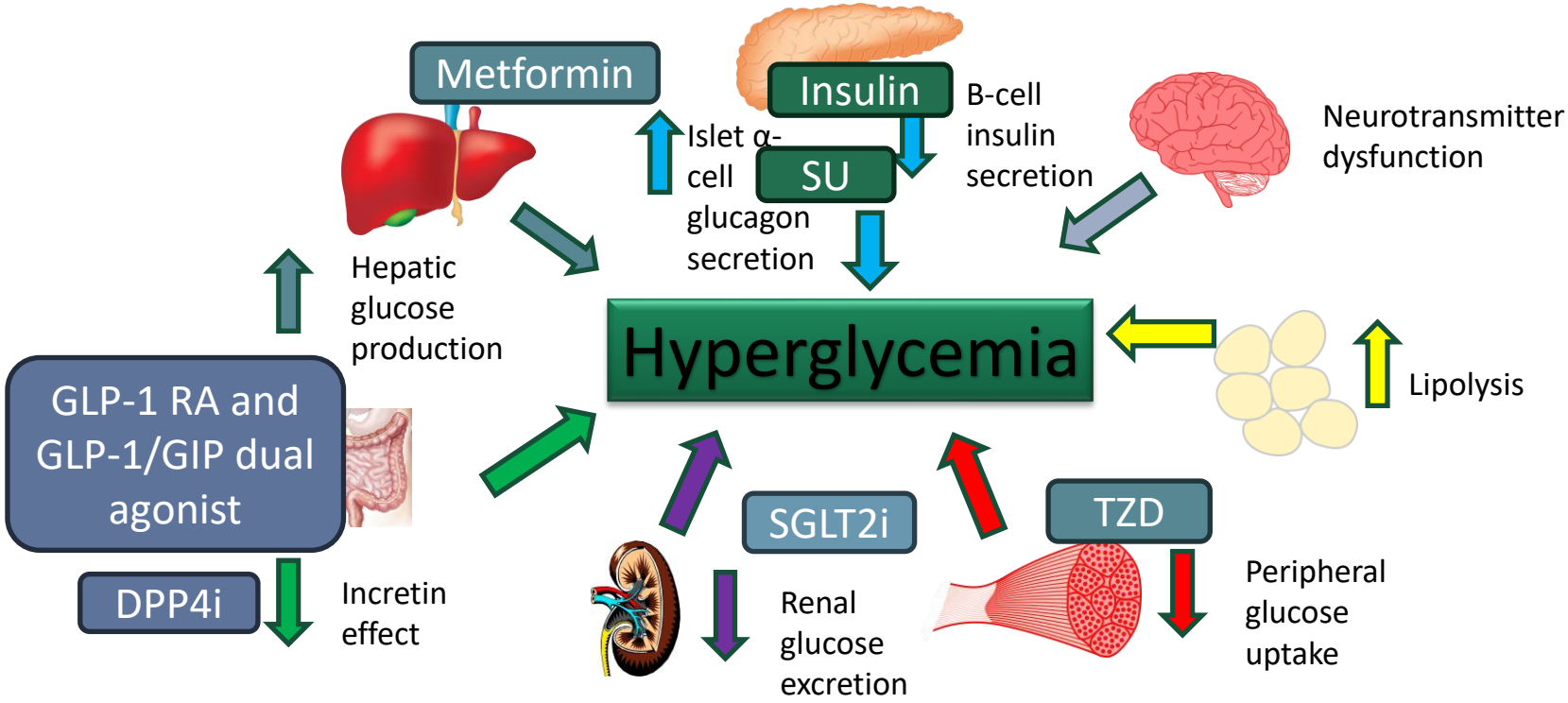


ElSayed NA, et al. *Diabetes Care.* 2023;46(Suppl_1):S111-S127.

Ominous Octet



Ominous Octet



Case 1

- 60-year-old woman presents with an A1c of 8.8% and random blood glucose 260 mg/dL
  - BMI 35.2
  - Currently taking Atorvastatin 40mg and Lisinopril 40mg
  - Owns her own clothing shop and is on her feet most of the day
  - Has felt tired in the afternoon, like she needed to nap
  - History of HTN and elevated LDL, both controlled on medication

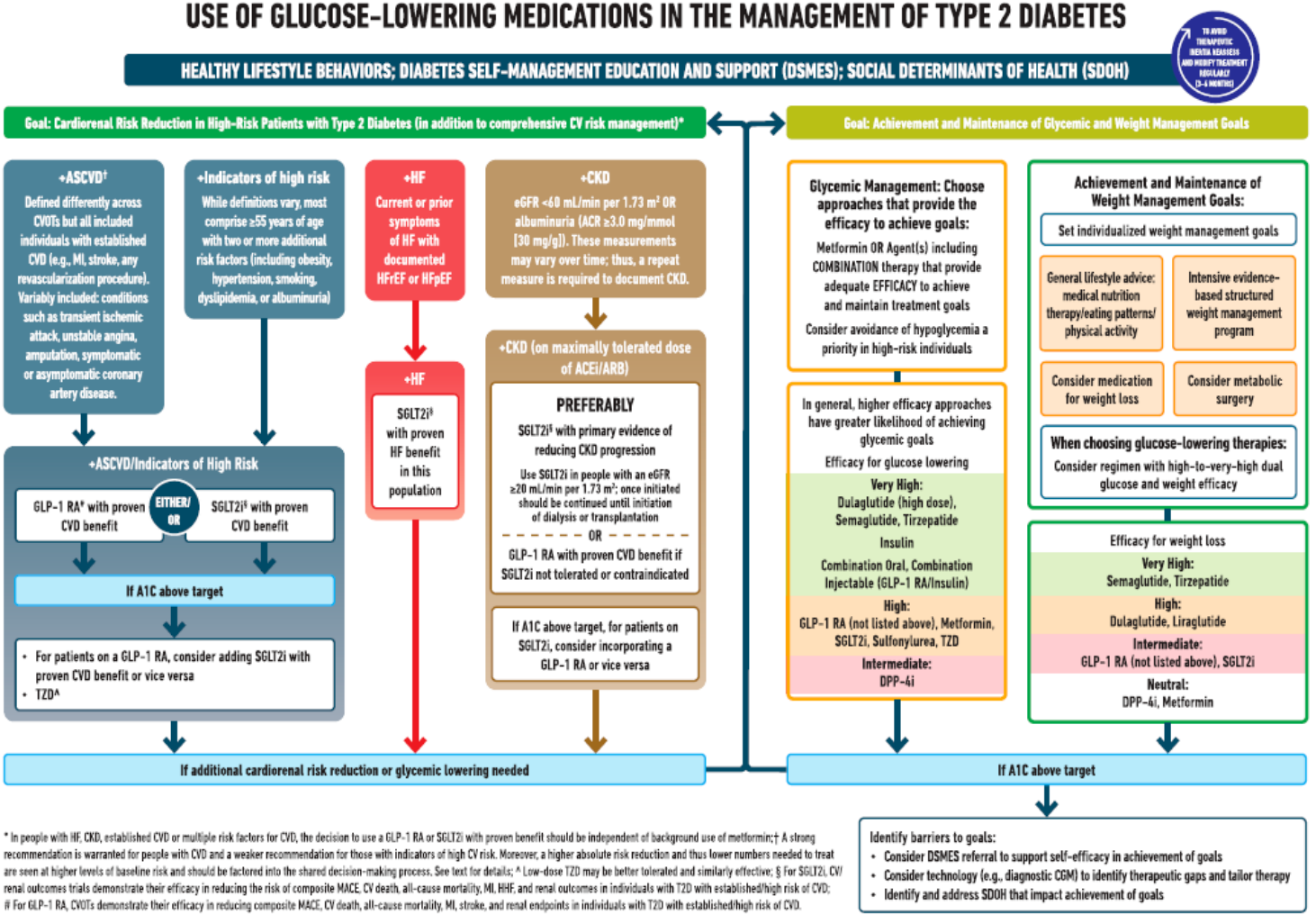
Case 1

- What would you prescribe as her initial therapy?
  - A. Metformin
  - B. A GLP-1 RA
  - C. Metformin plus a SGLT2 inhibitor
  - D. Metformin plus a GLP-1 RA

Case 1

- What would you prescribe as her initial therapy?
  - A. Metformin
  - B. A GLP-1 RA
  - C. Metformin plus a SGLT2 inhibitor
  - **D. Metformin plus a GLP-1 RA**

ADA Standards of Care 2023



Pharmacologic Approaches to Glycemic Management: *Standards of Care in Diabetes - 2023*. *Diabetes Care* 2023;46(Suppl. 1):S140-S157 Used by permission.

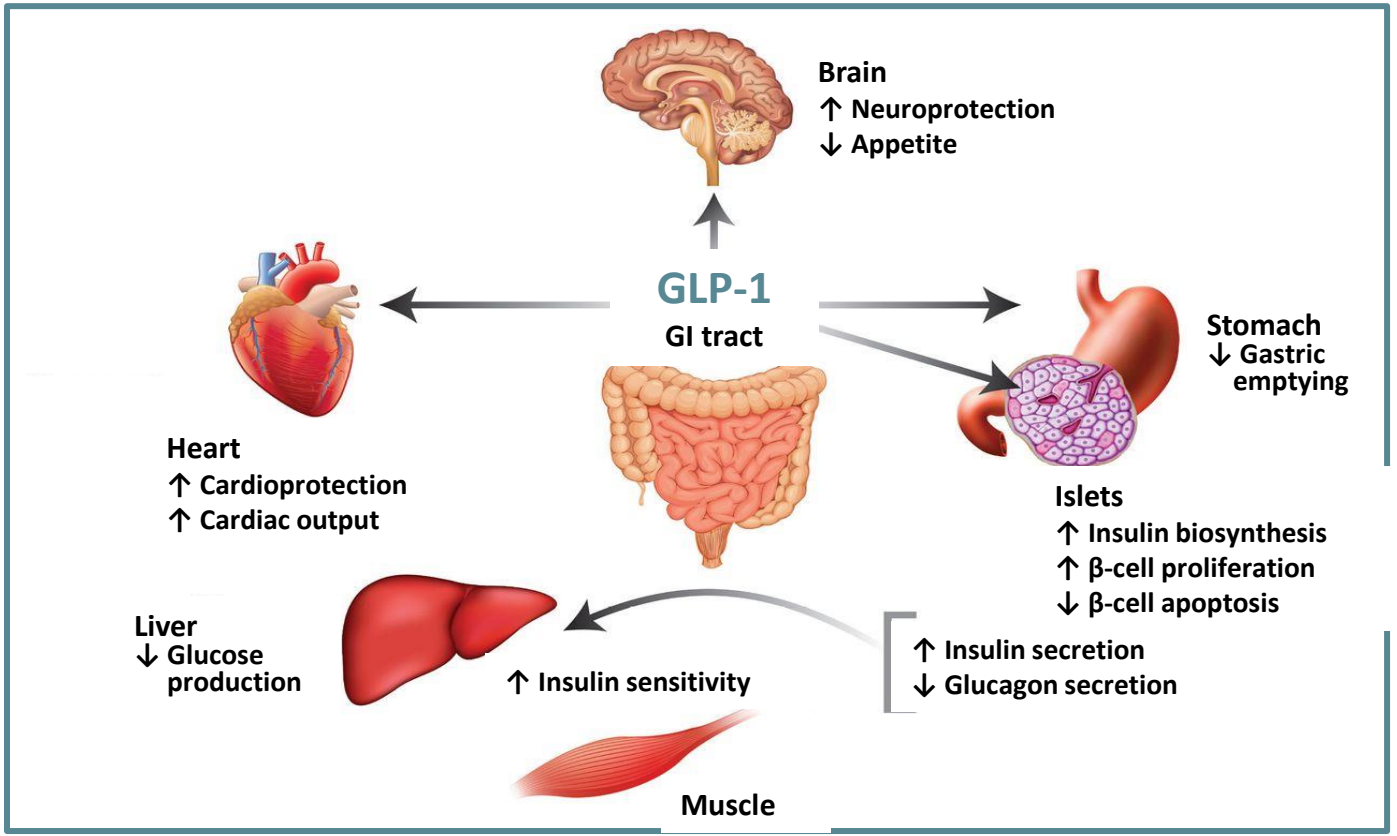
GLP-1 RECEPTOR AGONISTS

Injectable Medications for Diabetes

- GLP-1 Receptor Agonists
  - Exenatide
  - Dulaglutide
  - Liraglutide
  - Semaglutide (subcutaneous and oral)

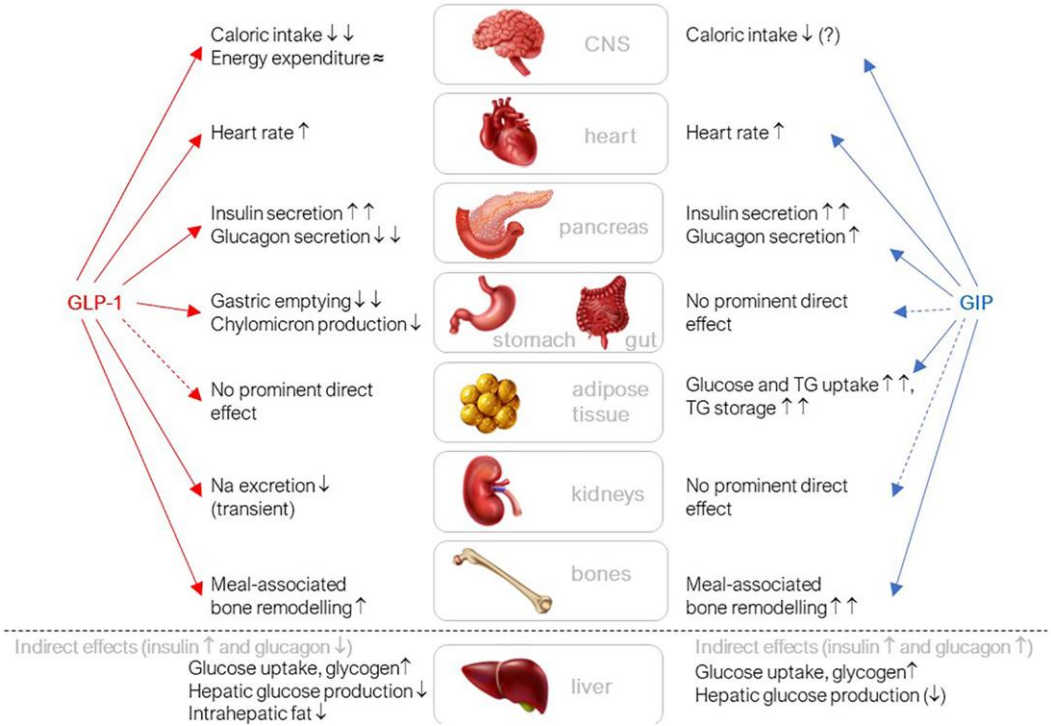
- GLP-1 RA/GIP Dual Agonists
  - Tirzepatide

GLP-1 RA Mechanism of Action



- Hinnen D. *Diabetes Spectr*. 2017;30:202-210. Used under Creative Commons CC-BY-NC-ND

Pathophysiological Effects of GLP-1 RA and GIP



Diabetes Obesity Metabolism, Volume: 23, Issue: S3, Pages: 5-29, First published: 26 July 2021, DOI: (10.1111/dom.14496)

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

9.10 In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. **A**

9.11 If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. **A**

9.12 Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. **A**

Pharmacologic Approaches to Glycemic Management: *Standards of Care in Diabetes - 2023*. *Diabetes Care* 2023;46(Suppl. 1):S140-S157

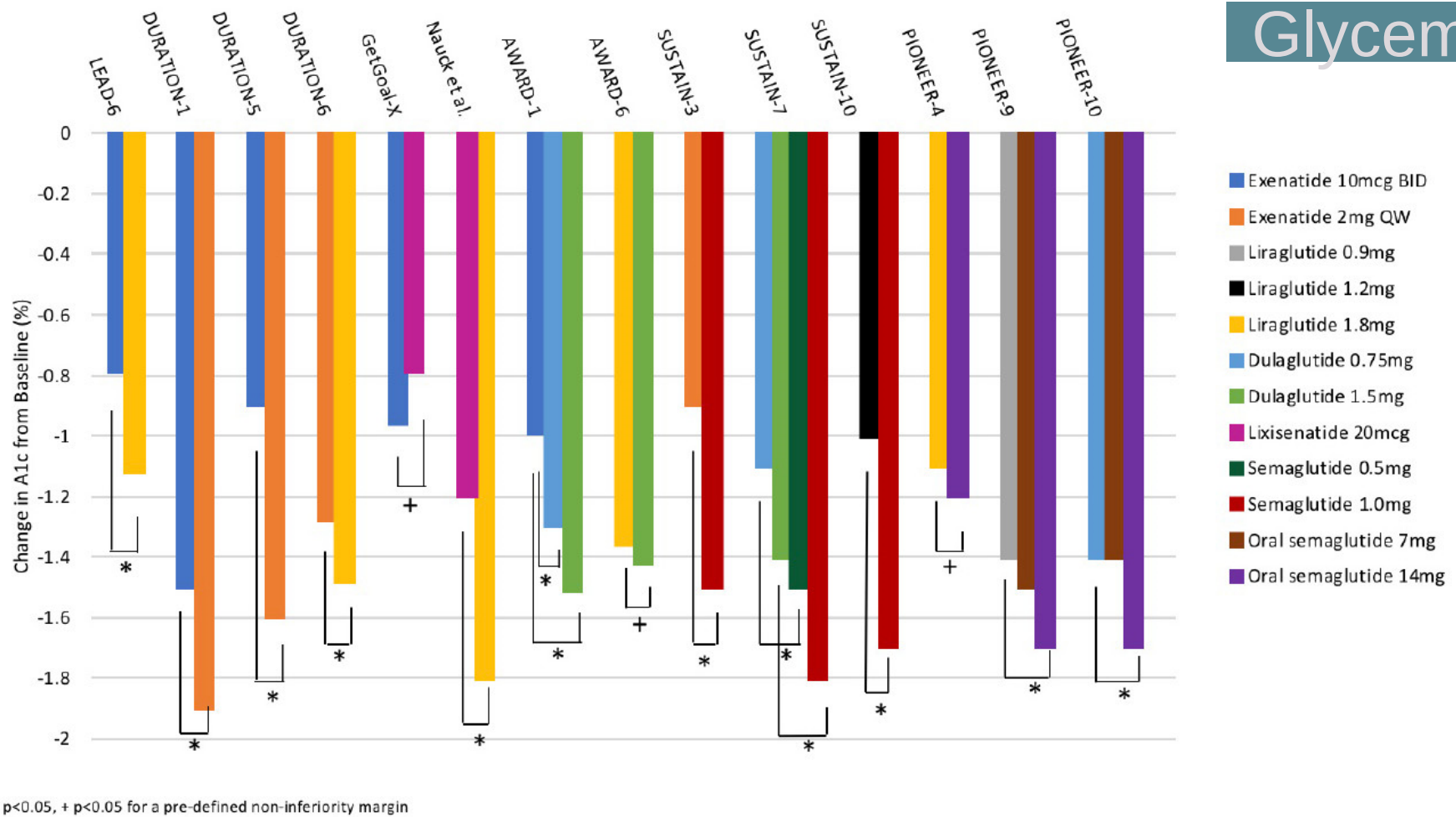
Benefits of GLP-1 RA

Glycemia

Cardiovascular Disease

Overweight and Obesity

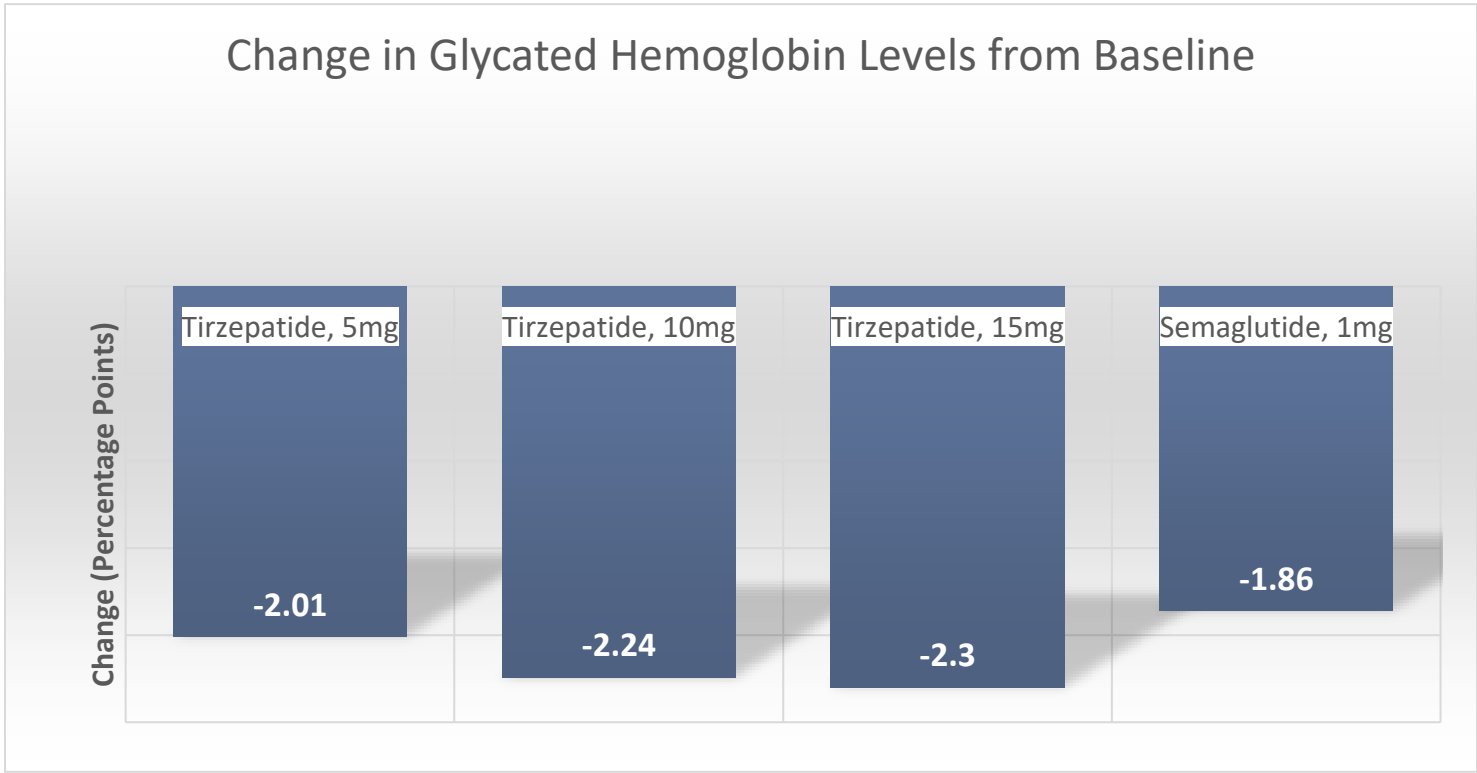
Glycemia



* p<0.05, + p<0.05 for a pre-defined non-inferiority margin

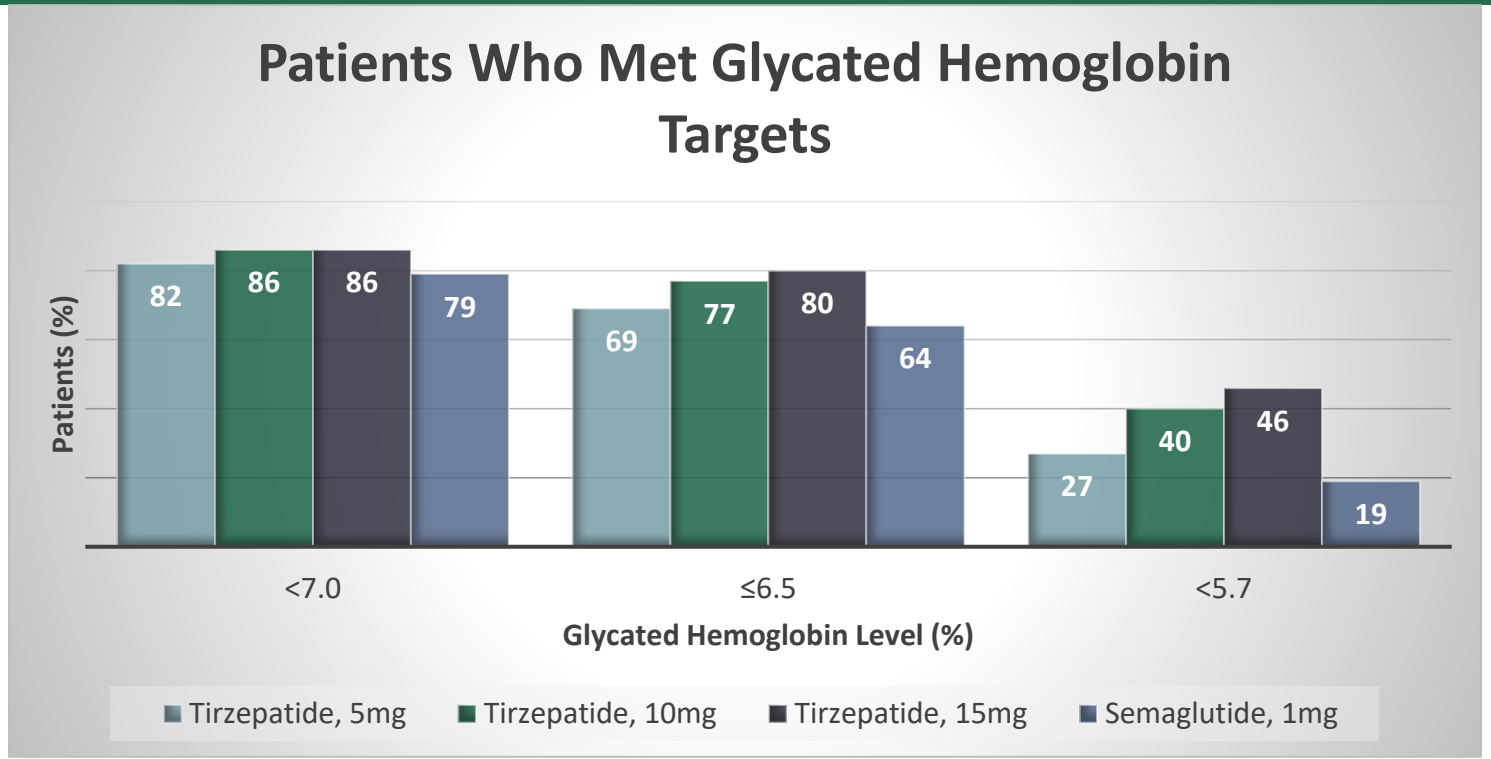
Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. Therapeutic Advances in Endocrinology and Metabolism. 2021;12. doi:10.1177/2042018821997320.

Tirzepatide vs. Semaglutide
Glycated Hemoglobin



Adapted from JP Frías et al. N Engl J Med 2021;385:503-515

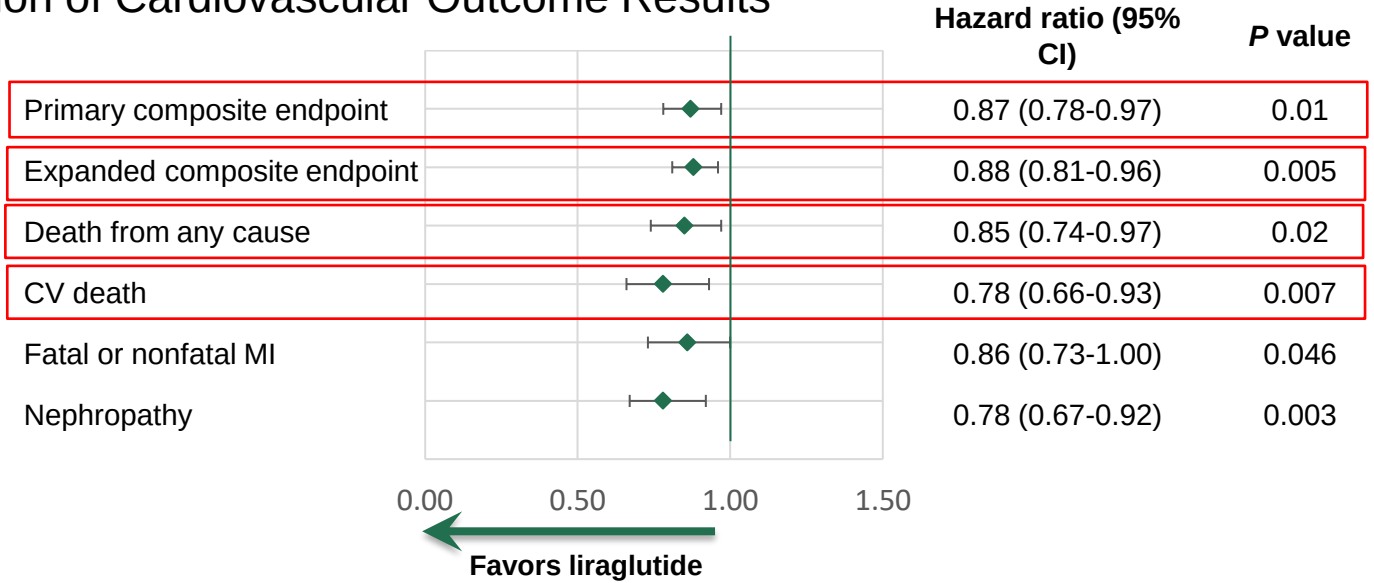
Tirzepatide vs. Semaglutide Glycemic Targets



Adapted from JP Frías et al. N Engl J Med 2021;385:503-515

LEADER: Primary Endpoints

LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

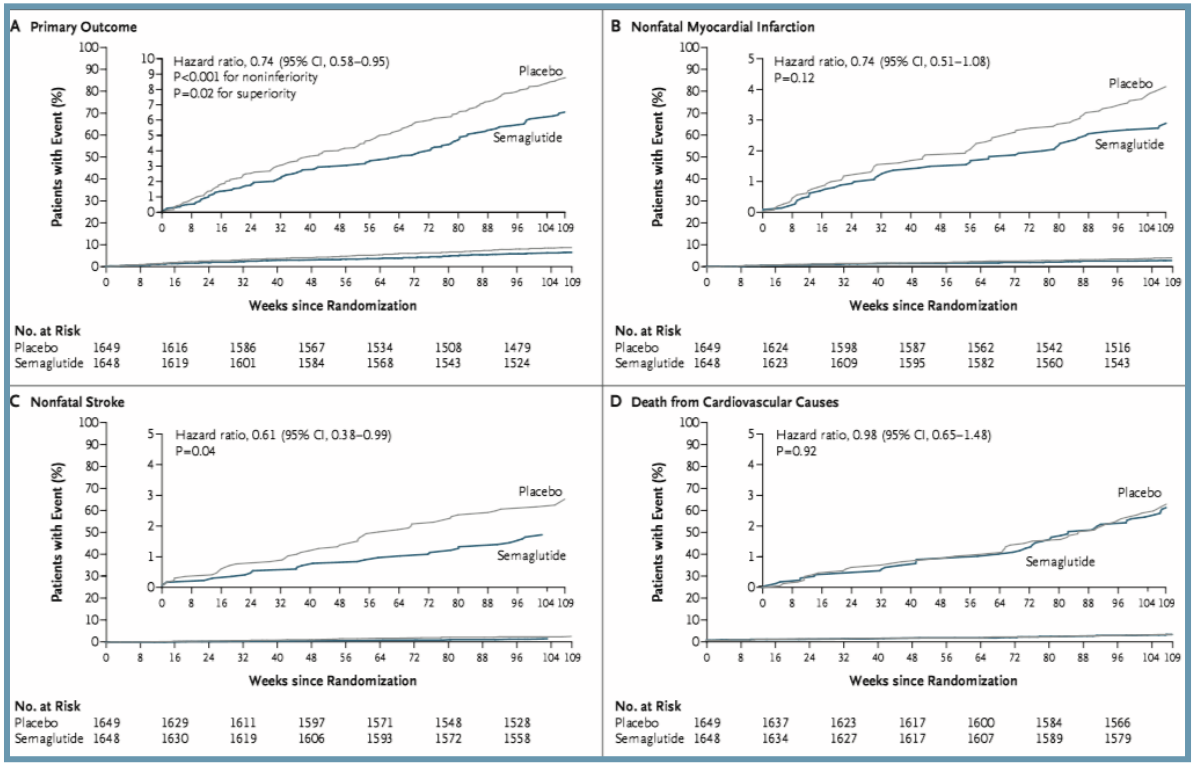


- N=9340 patients with T2DM
- Primary composite endpoint: CV death, nonfatal MI (including silent MI), or nonfatal stroke
- Secondary: composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF

- Median follow-up: 3.5 years
- CV outcomes: noninferior to placebo
- Primary: HR 0.87 (95% CI 0.78 to 0.97); *P*=0.01 for superiority
- Secondary HR: 0.88 (95% CI 0.81 to 0.96); *P*=0.005 for superiority
- Significantly lower rates of all-cause death and CV death with liraglutide

Adapted from Marso SP, et al. *N Engl J Med*. 2016; 375:311-322.

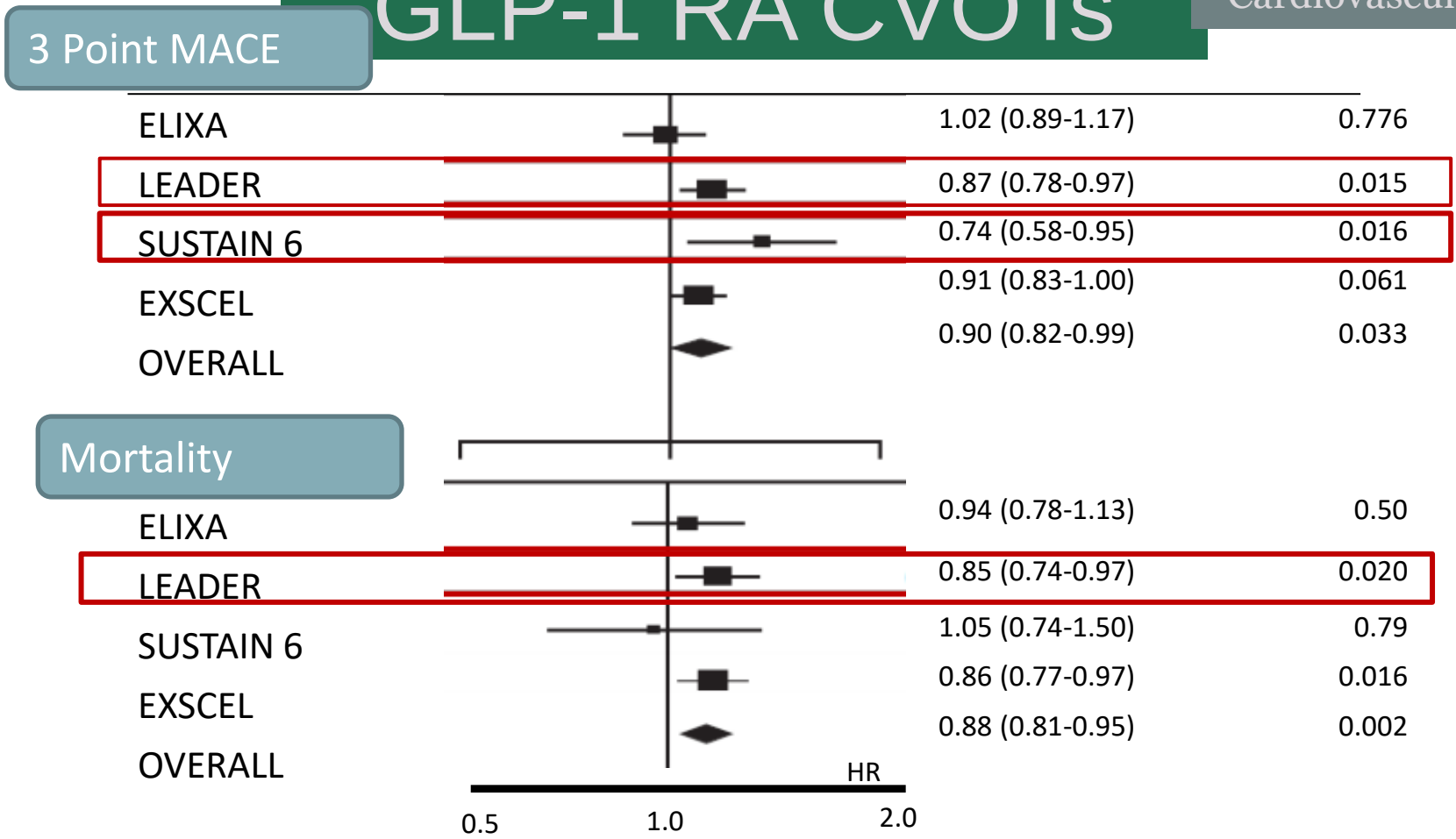
SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes



Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844.

GLP-1 RA CVOTs

Cardiovascular



Adapted from Bethel et. Al Lancet 2018; 6:105

- Cardiovascular Disease and Risk Management

Table 10.3B—Continued

	ELIXA (208) (n = 6,068)	LEADER (203) (n = 9,340)	SUSTAIN-6 (204)* (n = 3,297)	EXSCEL (209) (n = 14,752)	REWIND (207) (n = 9,901)	PIONEER-6 (205) (n = 3,183)
Key secondary outcome§	Expanded MACE 1.02 (0.90–1.11)	Expanded MACE 0.88 (0.81–0.96)	Expanded MACE 0.74 (0.62–0.89)	Individual components of MACE (see below)	Composite microvascular outcome (eye or renal outcome) 0.87 (0.79–0.95)	Expanded MACE or HF hospitalization 0.82 (0.61–1.10)
Cardiovascular death§	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.91 (0.78–1.06)	0.49 (0.27–0.92)
MI§	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.96 (0.79–1.15)	1.18 (0.73–1.90)
Stroke§	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	0.76 (0.61–0.95)	0.74 (0.35–1.57)
HF hospitalization§	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.93 (0.77–1.12)	0.86 (0.48–1.55)
Unstable angina hospitalization§	1.11 (0.47–2.62)	0.98 (0.76–1.26)	0.82 (0.47–1.44)	1.05 (0.94–1.18)	1.14 (0.84–1.54)	1.56 (0.60–4.01)
All-cause mortality§	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.90 (0.80–1.01)	0.51 (0.31–0.84)
Worsening nephropathy§‖	—	0.78 (0.67–0.92)	0.64 (0.46–0.88)	—	0.85 (0.77–0.93)	—

—, not assessed/reported; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of *Diabetes Care*. *Powered to rule out a hazard ratio of 1.8; superiority hypothesis not prespecified. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EXSCEL, which reported medians. ‡Significant difference in A1C between groups ($P < 0.05$). ^A1C change of 0.66% with 0.5 mg and 1.05% with 1 mg dose of semaglutide. §Outcomes reported as hazard ratio (95% CI). ‖Worsening nephropathy is defined as the new onset of urine albumin-to-creatinine ratio >300 mg/g creatinine or a doubling of the serum creatinine level and an estimated glomerular filtration rate of <45 mL/min/1.73 m^2, the need for continuous renal replacement therapy, or death from renal disease in LEADER and SUSTAIN-6 and as new macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy in REWIND. Worsening nephropathy was a prespecified exploratory adjudicated outcome in LEADER, SUSTAIN-6, and REWIND.

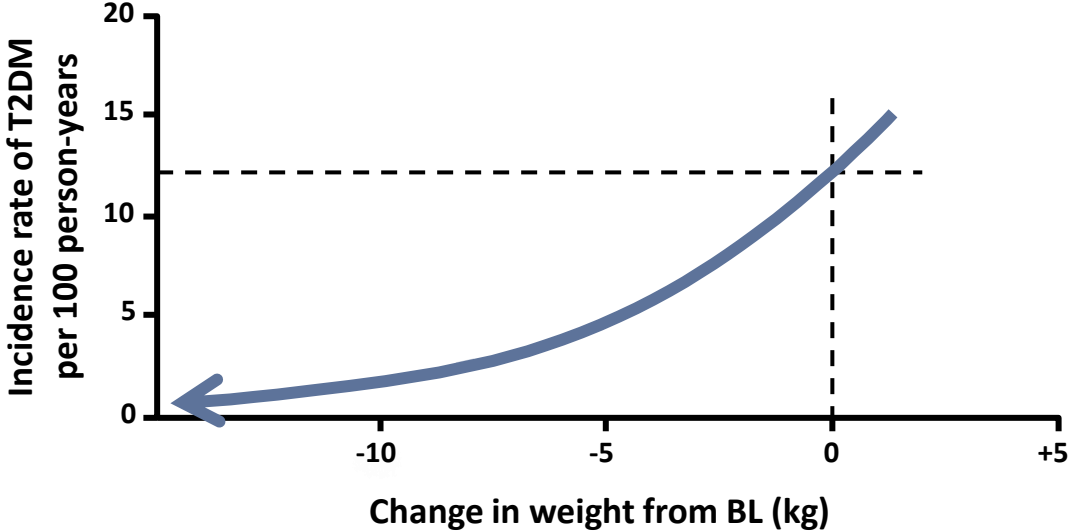
Table 10.3B—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: GLP-1 receptor agonists (2 of 2)

Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes - 2023*. *Diabetes Care* 2023;46(Suppl. 1):S158-S190

Nuha A. ElSayed, Grazia Aleppo, Vanita R. Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Sandeep R. Das, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Mikhail Kosiborod, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane Jeffrie Seley, Robert C. Stanton, Robert A. Gabbay; on behalf of the American Diabetes Association, 10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2023*. *Diabetes Care* 1 January 2023; 46 (Supplement_1): S158–S190. https://doi.org/10.2337/dc23-S010

How Much Weight Loss Is Needed to Provide Benefit?

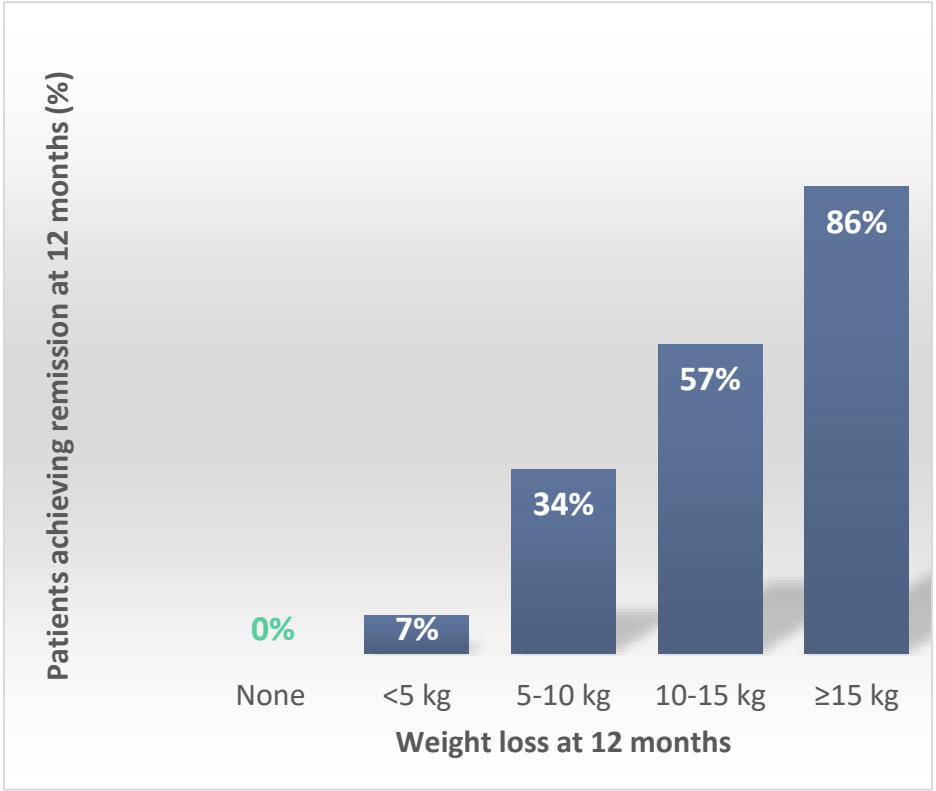
- Modest weight loss (5%-10%) improves glycemia, BP, lipids, need for medications, mobility, and QoL
- In the Diabetes Prevention Program, weight loss averaged 5.5 kg and reduced the risk of conversion from impaired glucose tolerance to T2DM by 58%



Bray GA, Ryan DH. *Diabetes Obes Metab*. 2021;23(suppl 1):50-62.

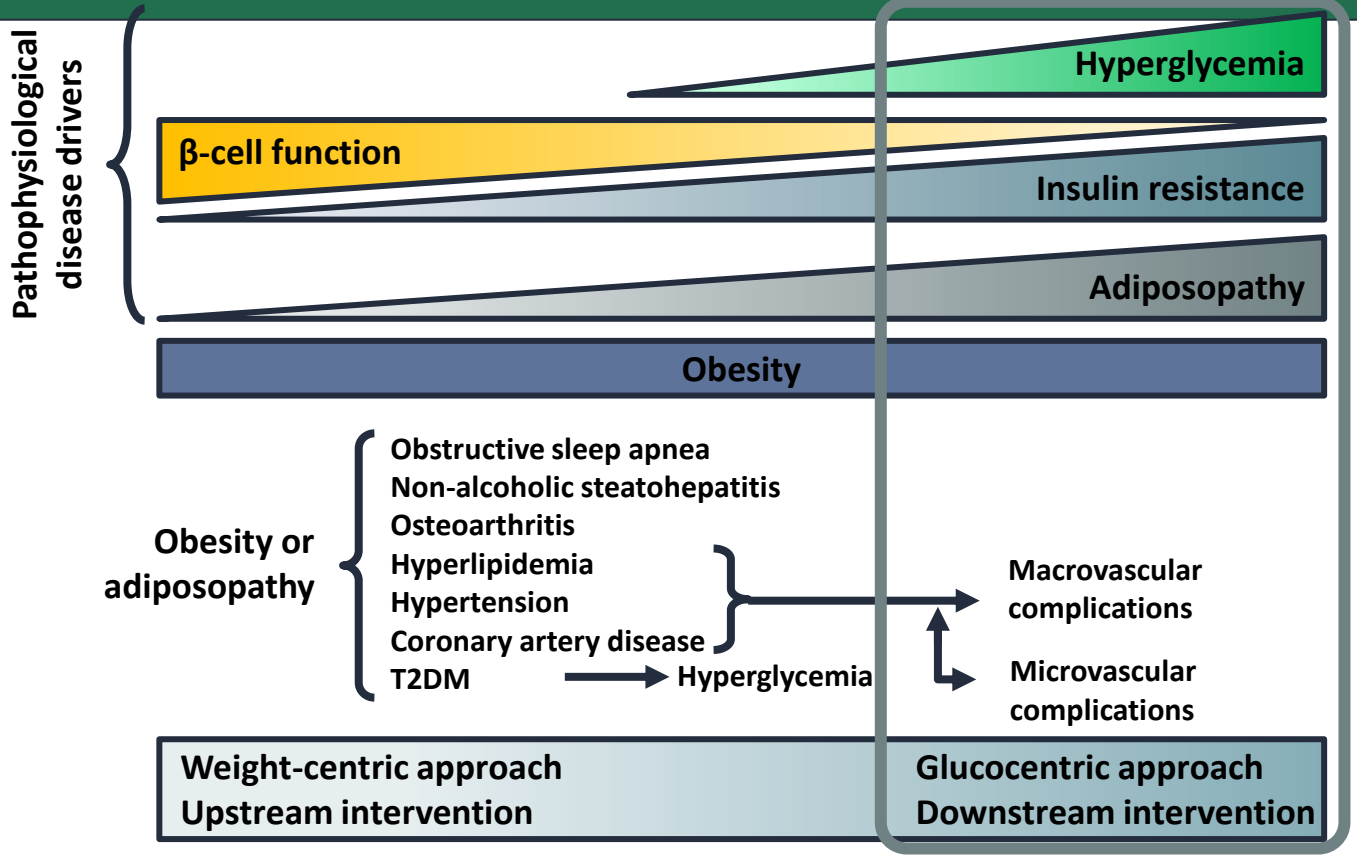
Weight Loss Can Lead to Remission

- At 12 months, 46% of participants in intervention group achieved diabetes remission (HbA1c <6.5% after ≥2 months off all antidiabetic medications) in DiRECT open-label trial
- Greater weight loss was associated with greater odds of remission



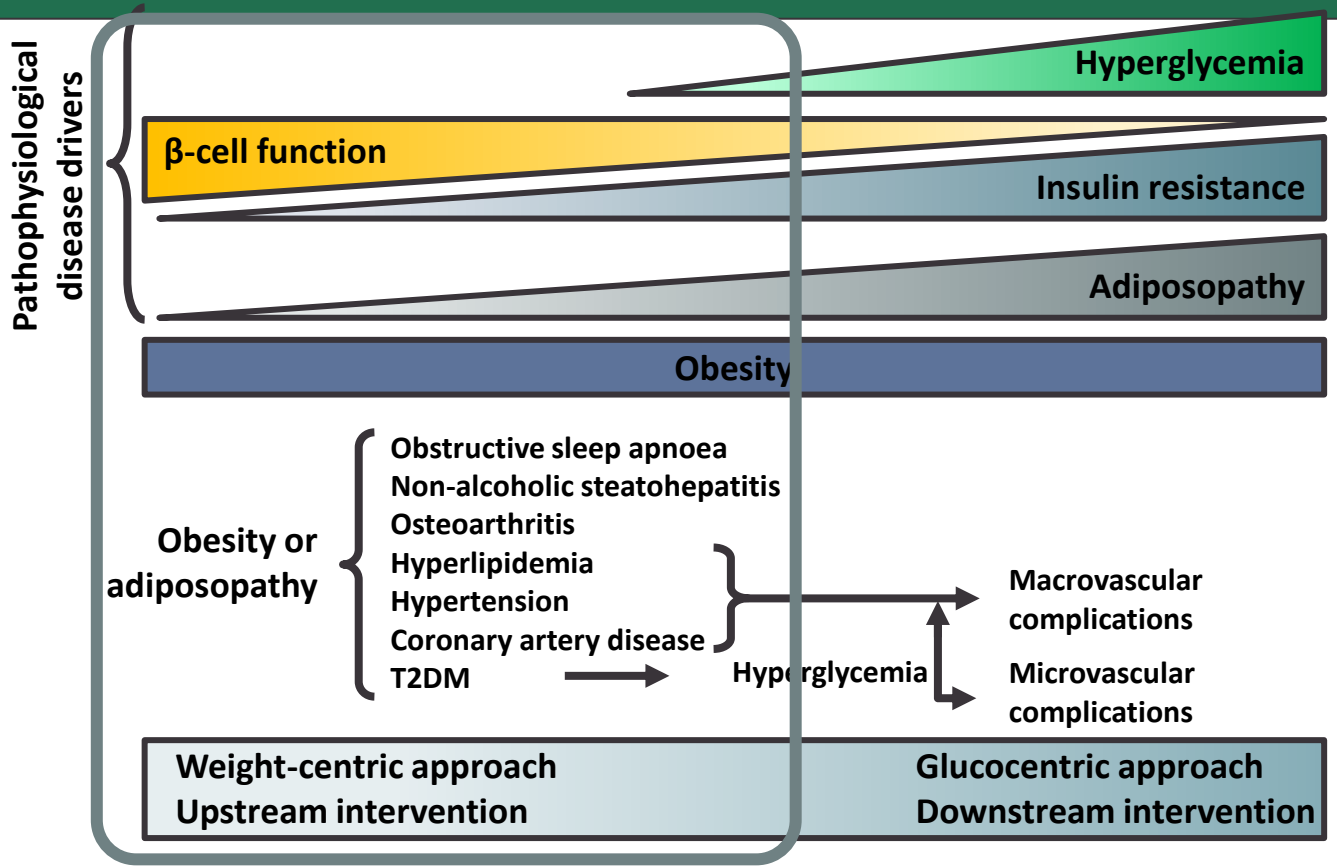
Adapted from Lean MEJ, et al. *Lancet.* 2018;391:541-551.

Diabetes Care Remains Highly Glucose-Centric



- Modified from Lingvay I, et al. *Lancet*. 2022;399:394-405.

Moving Toward Weight-Centric Focus to Treat and Prevent T2DM



- Modified from Lingvay I, et al. *Lancet*. 2022;399:394-405.

How Is Obesity Defined in Adults?

Weight status category	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25.0-29.9
Class 1 obesity	30.0-34.9
Class 2 obesity	35.0-39.9
Class 3 obesity	≥40

- CDC. Defining adult overweight & obesity, 6/3/2022 (https://www.cdc.gov/obesity/basics/adult-defining.html). Accessed 12/19/2022.

Pharmacotherapy

8.14 When choosing glucose-lowering medications for people with type 2 diabetes and overweight or obesity, consider the medication's effect on weight. B

8.15 Whenever possible, minimize medications for comorbid conditions that are associated with weight gain. E

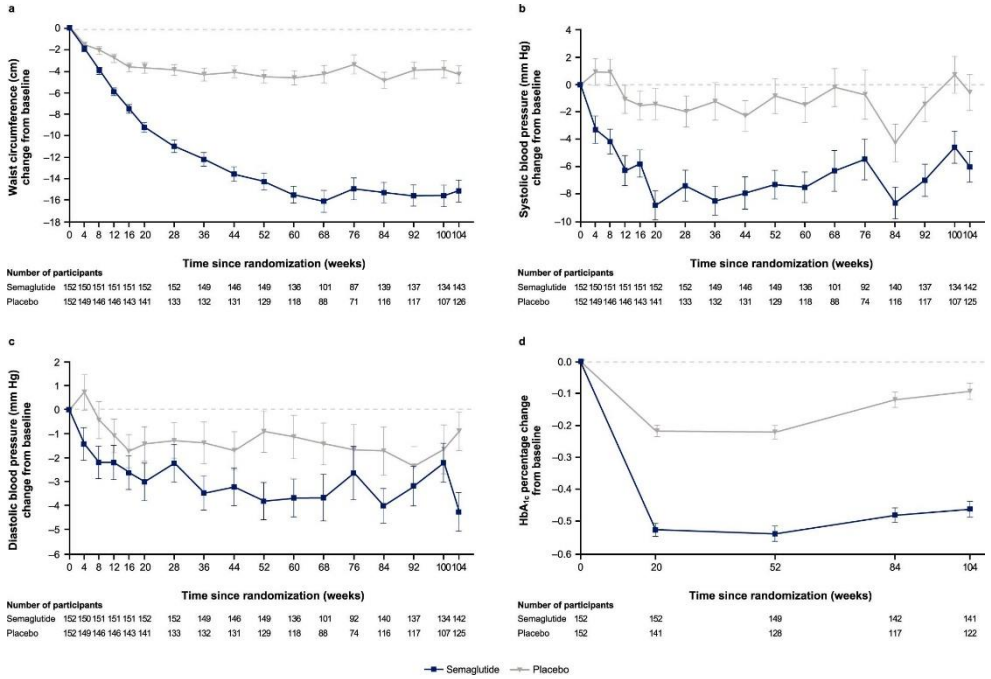
8.16 Obesity pharmacotherapy is effective as an adjunct to nutrition, physical activity, and behavioral counseling for selected people with type 2 diabetes and BMI ≥27 kg/m2. Potential benefits and risks must be considered. A

Nuha A. ElSayed, Grazia Aleppo, Vanita R. Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane Jeffrie Seley, Robert C. Stanton, Robert A. Gabbay, American Diabetes Association; 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: *Standards of Care in Diabetes—2023*. *Diabetes Care* 1 January 2023; 46 (Supplement_1): S128–S139. https://doi.org/10.2337/dc23-S008

Trial	Participant characteristics	PBO-corrected weight loss	≥5% BW loss		≥10% BW loss	
			Liraglutide 3.0 mg	PBO	Liraglutide 3.0 mg	PBO
Astrup et al, 2009	76% women, stable body weight, BMI ≥30 kg/m^2 and ≤40 kg/m^2	-4.4 kg	76.1%	29.6%	28.3%	2.0%
Astrup et al, 2012	76% women, stable body weight, BMI ≥30 kg/m^2 and ≤40 kg/m^2	-5.8 kg	73%	28%	37%	10%
Wadden et al, 2013	81% women, stable body weight, BMI ≥30 kg/m^2 or ≥27 kg/m^2 with dyslipidemia or hypertension; lost ≥5% of initial body weight in low-calorie diet run-in period (4-12 weeks)	-5.9 kg	50.5%	21.8%	6.1%	6.3%
Pi-Sunyer et al, 2015	78% women, stable body weight, BMI ≥30 kg/m^2 or ≥27 kg/m^2 if with dyslipidemia or hypertension	-5.6 kg	63.2%	27.1%	33.1%	10.6%
Davies et al, 2015	50% women, stable body weight, BMI ≥27 kg/m^2; T2D (HbA_{1c} = 7.0%-10.0%) treated with diet and exercise alone or in combination with 1-3 oral hypoglycemic agents	-4.2 kg	54.3%	21.4%	25.2%	6.7%
Blackman et al, 2015	28% women, stable body weight, BMI ≥30 kg/m^2, moderate-to-severe obstructive sleep apnea, unwilling or unable to use CPAP	-4.9 kg	46.4%	18.1%	22.4%	1.5%

- Adapted from Mehta A, et al. *Obes Sci Pract*. 2017;3:3-14. (Complete references for the studies cited can be found in Mehta et al.)

STEP 5 Trial: Two-year effects of semaglutide in adults with overweight or obesity



- Garvey, W.T., Batterham, R.L., Bhatta, M. *et al.* Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nat Med* **28**, 2083–2091 (2022). https://doi.org/10.1038/s41591-022-02026-4
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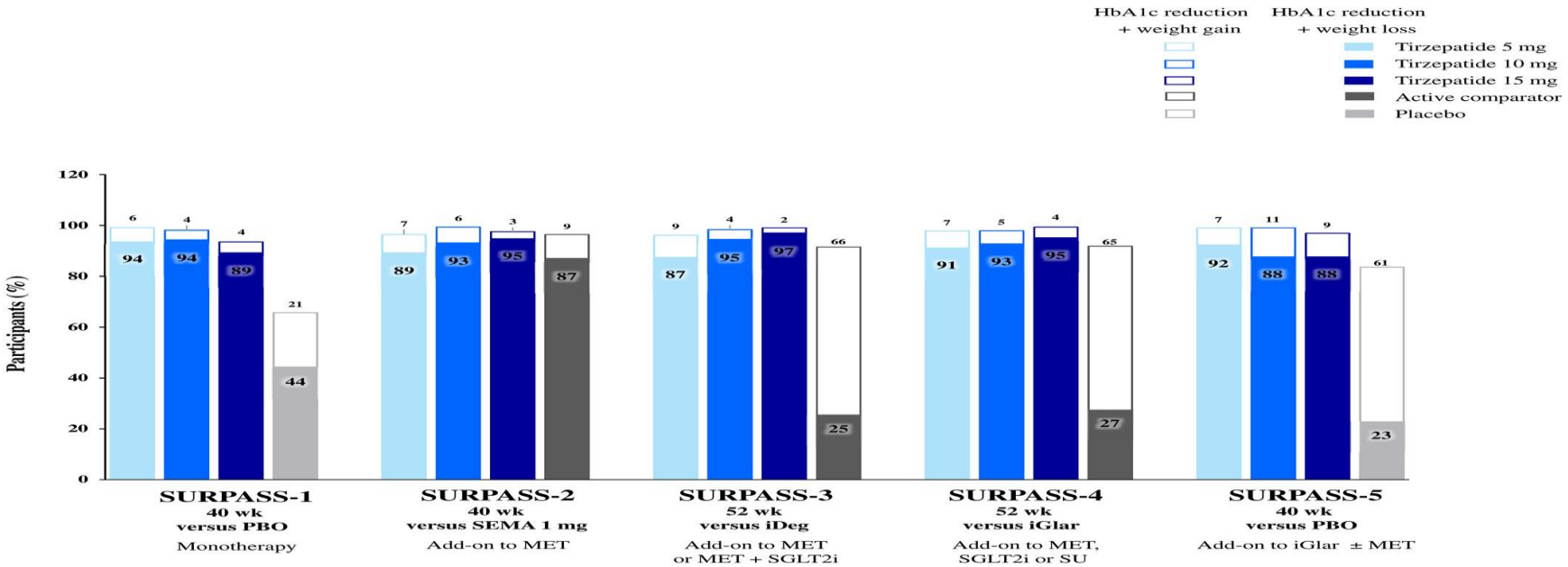
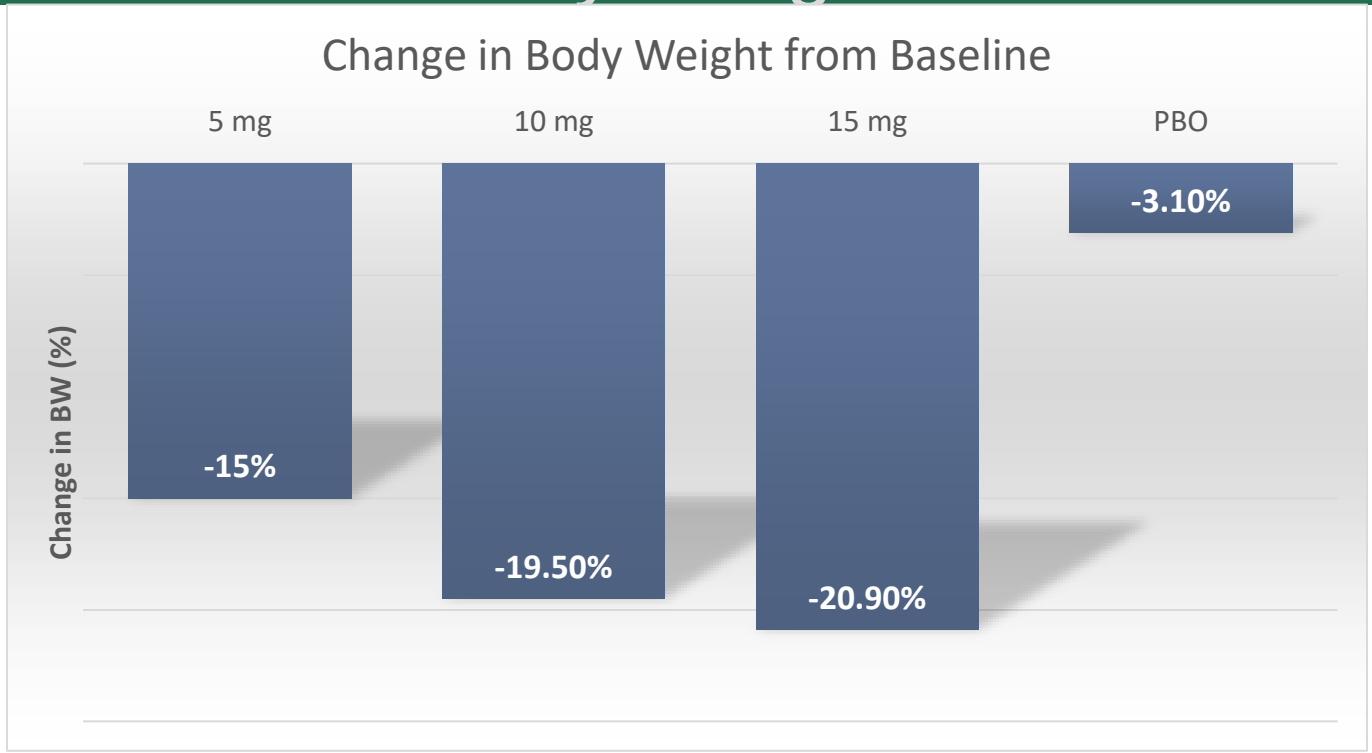
Relationship between body weight change and glycaemic control with tirzepatide treatment in people with type 2 diabetes: A post hoc assessment of the SURPASS clinical trial program



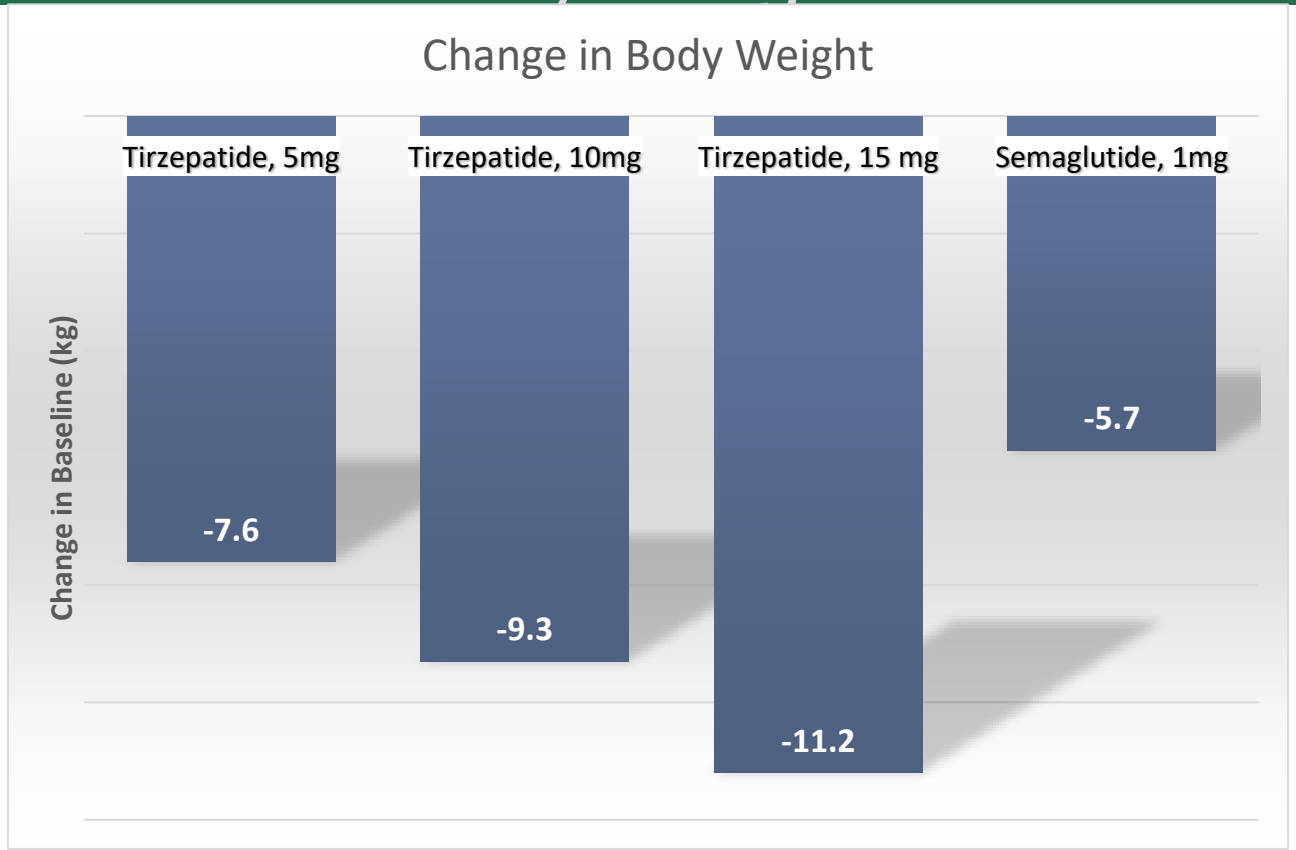
- **Diabetes Obesity Metabolism, Volume: 25, Issue: 9, Pages: 2553-2560, First published: 29 May 2023, DOI: (10.1111/dom.15140)**

Effect of Once-Weekly Tirzepatide vs. Placebo on Body Weight



Adapted from Jastreboff AM, et al. *N Engl J Med*. 2022;387:205-216.

Tirzepatide vs. Semaglutide Body Weight



Adapted from JP Frías et al. N Engl J Med 2021;385:503-515.

Comparing Incretin-Based Therapies

Medication	Dosing	HbA_{1c} lowering*	Weight loss*	ASCVD benefit
GLP-1 RAs				
Dulaglutide	0.75 mg QW 1.5 mg QW 3 mg QW 4.5 mg QW	0.9% 1.5% 1.6% 1.8%	2.7 kg 3.0 kg 3.8 kg 4.6 kg	Yes
Exenatide **Exenatide ER**	10 mcg BID 2 mg QW	0.9% 1.5%	2.6-2.9 kg 2.3 kg	No
Liraglutide	1.2 mg QD 1.8 mg QD	1.0% 1.0%	2.6 kg 2.8 kg	Yes
Lixisenatide	20 mcg QD	0.7%	2.7 kg	No
Semaglutide (injectable)	0.5 mg QW 1 mg QW 2 mg QW	1.3% 1.5% 2.1%	4.2 kg 5.5 kg 6.4 kg	Yes
Semaglutide (oral)	7 mg QD 14 mg QD	1.2% 1.4%	2.3 kg 3.7 kg	No
GLP-1/GIP receptor agonists				
Tirzepatide	5 mg QW 10 mg QW 15 mg QW	2.0% 2.2% 2.3%	7.6 kg 9.3 kg 11.2 kg	TBD

- *In combination with metformin (± other medications) in clinical trials, as reported in product label; duration of treatment varied by trial.
- BID = twice daily; ER = extended release; QD = once daily; QW = once weekly; TBD = to be determined.
- Dulaglutide (Trulicity®) PI 2022 (https://pi.lilly.com/us/trulicity-uspi.pdf). Exenatide (Byetta®) PI 2022 (http://www.astrazeneca-us.com/cgi-bin/az_pi.cgi?product=byetta&country=us&popup=no). Exenatide extended release (Bydureon®) PI 2023 (http://www.azpicentral.com/pi.html?product=bydureon_bcise&country=us&popup=no). Liraglutide (Victoza®) PI 2022 (www.novo-pi.com/victoza.pdf). Lixisenatide (Adlyxin®) PI 2022 (https://products.sanofi.us/Adlyxin/Adlyxin.pdf). Semaglutide injectable (Ozempic®) PI 2022 (www.novo-pi.com/ozempic.pdf). Semaglutide oral

Case 2

- 57-year-old man diagnosed with T2DM 5 years ago
  - A1c is 8.3%
  - BMI 32
  - Currently taking metformin 1000mg BID and Insulin glargine 40 units at bedtime
  - Has gained 35 lbs since starting insulin 2 years ago
  - A1c was 10.5% when insulin was started
  - Reports 2 hypoglycemic events in the past 6 months
  - Concerned about side effects of other injectables since his friend developed pancreatitis on liraglutide

Case 2

- How would you manage this patient?
  - A. No changes
  - B. Add a SGLT2 inhibitor, reduce dose of basal insulin
  - C. Add tirzepatide, reduce dose of basal insulin
  - D. Add liraglutide to current regimen
  - E. Discontinue basal insulin, add dulaglutide

Case 2

- How would you manage this patient?
  - A. No changes
  - B. Add a SGLT2 inhibitor, reduce dose of basal insulin
  - **C. Add tirzepatide, reduce dose of basal insulin**
  - D. Add liraglutide to current regimen
  - E. Discontinue basal insulin, add dulaglutide

Incretin-Based Therapies: Side Effects and Warnings

Side effects

- Nausea
- Vomiting
- Diarrhea
- Dyspepsia
- Constipation
- Injection-site

Warnings

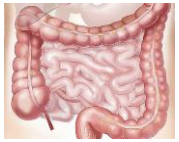
- History of pancreatitis
- Risk factors for pancreatitis
- Gastroparesis
- Personal or family history of:
  - Medullary thyroid cancer
  - Multiple endocrine neoplasia syndrome type 2

- Dulagliutide (Trulicity®) PI 2022 (https://pi.lilly.com/us/trulicity-uspi.pdf). Exenatide (Byetta®) PI 2022 (http://www.astrazeneca-us.com/cgi-bin/az_pi.cgi?product=byetta&country=us&popup=no). Exenatide extended release (Bydureon®) PI 2023 (http://www.azpicentral.com/pi.html?product=bydureon_bcise&country=us&popup=no). Liraglutide (Victoza®) PI 2022 (www.novo-pi.com/victoza.pdf). Lixisenatide (Adlyxin®) PI 2022 (https://products.sanofi.us/Adlyxin/Adlyxin.pdf). Semaglutide injectable (Ozempic®) PI 2022 (www.novo-pi.com/ozempic.pdf). Semaglutide oral (Rybelsus®) PI 2023 (www.novo-pi.com/rybelsus.pdf). Tirzepatide (Mounjaro™) PI 2022 (https://pi.lilly.com/us/mounjaro-uspi.pdf). All URLs accessed 6/7/23.

Patient Education to Address Potential GI Effects of Incretin-Based Therapies

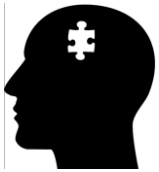
Distinguish satiety and early fullness from nausea and GI AEs

Expected weight loss



Mild-to-moderate GI AEs at initiation or dose escalation

Eating smaller meals, less high-fat food, and small snacks between meals



Identifying triggers and mindfulness about own patterns and responses

Adjusting Other Antihyperglycemic Medications at Initiation of Incretin-Based Therapies

- Sulfonylureas
  - If HbA1c is ≤7.5% or hypoglycemic episodes occur, stop sulfonylurea medication
  - If HbA1c is 7.6-8.5%, decrease sulfonylurea medication by 50%
  - If HbA1c is >8.5%, continue sulfonylurea medication with possibility of future weaning
- Insulin
  - If HbA1c is at or below individualized target or hypoglycemic episodes occur, decrease basal insulin by 20-30%
- DPP-4 inhibitors
  - Discontinue after starting GLP-1 RA or GIP-GLP-1 RA (no interaction, but no benefit)
- Other agents do not require adjustment

Case 3

- 56-year-old male presents to your office for management of type 2 diabetes. He was diagnosed 2 years ago. He reports continued hyperglycemia despite being adherent to his current regimen.
  - HbA1c: 8.2%
  - Weight: 195 lbs
  - Height: 5’ 9”
  - BMI: 28.8
  - Blood Pressure: 124/80 mm Hg
  - Medications: Metformin 1000 mg BID, Lisinopril 10 mg daily, Atorvastatin 20 mg daily

Case 3

- Which of the following treatment options would help improve his glycemic control?
  - A. Add a GLP-1 RA
  - B. Start an SGLT2 inhibitor
  - C. Consider insulin therapy
  - D. Increase the dose of metformin to 1500 mg BID
  - E. Adjust the dose of lisinopril to 20mg daily

Case 3

- Which of the following treatment options would help improve his glycemic control?
  - A. Add a GLP-1 RA
  - **B. Start an SGLT2 inhibitor**
  - C. Consider insulin therapy
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SGLT2 INHIBITORS

SGLT2 Inhibitors

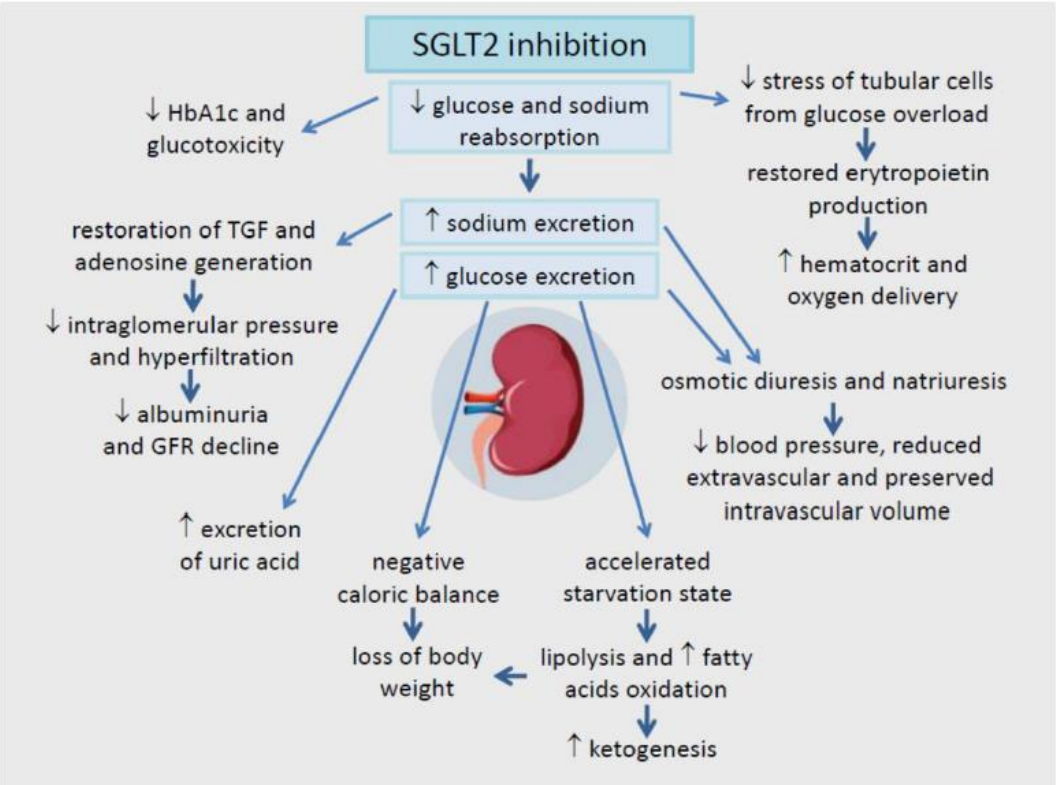


Figure 1. Summary of cardiorenal protective effects driven by inhibition of SGLT2.

Salvatore T, Galiero R, Caturano A, Rinaldi L, Di Martino A, Albanese G, Di Salvo J, Epifani R, Marfella R, Docimo G, et al. An Overview of the Cardiorenal Protective Mechanisms of SGLT2 Inhibitors. *International Journal of Molecular Sciences*. 2022; 23(7):3651. https://doi.org/10.3390/ijms23073651. Used under CC-BY

SGLT2i Trials in T2DM

Table 1. Sodium glucose cotransporter 2 inhibitors (SGLT2i) trials in type 2 diabetes.

Trial (Medication)	Main Outcome HR (95% CI) (*p*-Value)	Key Summary
EMPA-REG OUTCOME [5] (empagliflozin 10 or 25 mg)	↓ MACE, 0.86 (0.74–0.99) ($p = 0.04$) ↓ HHF ↓ All cause death	This was the first SGLT2i trial showing reduction of CV events.
CANVAS Program [6,11] (canagliflozin 100 or 300 mg)	↓ MACE 0.86 (0.75–0.97) ($p = 0.02$)	Canagliflozin reduced CV events and HHF.
DECLARE-TIMI 58 [8] (dapagliflozin 10 mg)	↓ CV death or HHF 0.83 (0.73–0.95) ($p = 0.005$)	Dapagliflozin reduced CV death and HHF. MACE was not reduced.
VERTIS CV [12] (ertugliflozin 5 or 15 mg)	MACE 0.97 (0.75–1.03) ($p < 0.001$ for noninferiority)	Ertugliflozin is non-inferior to placebo in reducing MACE.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, heart failure for hospitalization; MACE, major adverse cardiovascular event.

SGLT2i Trials in CVD

Table 2. SGLT2i trials in cardiovascular disease.

Trial (Medication)	Main Outcome HR (95% CI) (*p*-Value)	Key Summary
DAPA-HF [13] (dapagliflozin 10 mg)	↓ composite of CV death and HHF 0.74 (0.65–0.85) ($p < 0.001$)	Dapagliflozin reduced the risk of worsening HF or CV death in HFrEF patients, regardless of diabetic status.
EMPEROR-Reduced [14] (empagliflozin 10 mg)	↓ composite of CV death and HHF 0.75 (0.65–0.86) ($p < 0.001$)	Empagliflozin shown to reduce HHF and CV death in HFrEF, regardless of diabetic status.
EMPEROR-Preserved [15] (empagliflozin 10 mg)	↓ CV death or HHF 0.79 (0.69–0.90) ($p < 0.001$)	Empagliflozin reduced CV death or HHF in HFpEF patients.
SOLOIST-WHF [16] (sotagliflozin 200 or 400 mg)	↓ CV death and HHF 0.67 (0.52–0.85) ($p < 0.001$)	This was the first major trial of SGLT1/SGLT2 inhibitor in hospitalized patients.
EMPULSE [18] (empagliflozin 10 mg)	↓Death, HF events, time to first HF event, ≥5 change in KCCQ score stratified win ratio, 1.36 (1.09–1.68) ($p = 0.0054$)	Empagliflozin is effective and can be safely initiated in hospitalized patients.
DELIVER [19]/Meta-analysis of DELIVER and DAPA-HF [20] (dapagliflozin 10 mg)	↓ CV death or worsening HF 0.82 (0.73–0.92) ($p < 0.001$)	Patients with HF with mildly reduced or preserved ejection fraction. Dapagliflozin benefits extend to all HF patients across a whole spectrum of EF.

CV, cardiovascular; EF, ejection fraction; HF, heart failure; HHF, hospitalization for heart failure; HFrEF, heart failure reduced ejection fraction; HFpEF, heart failure preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire Total Symptom Socre.

SGLT2i Trials in Renal Disease

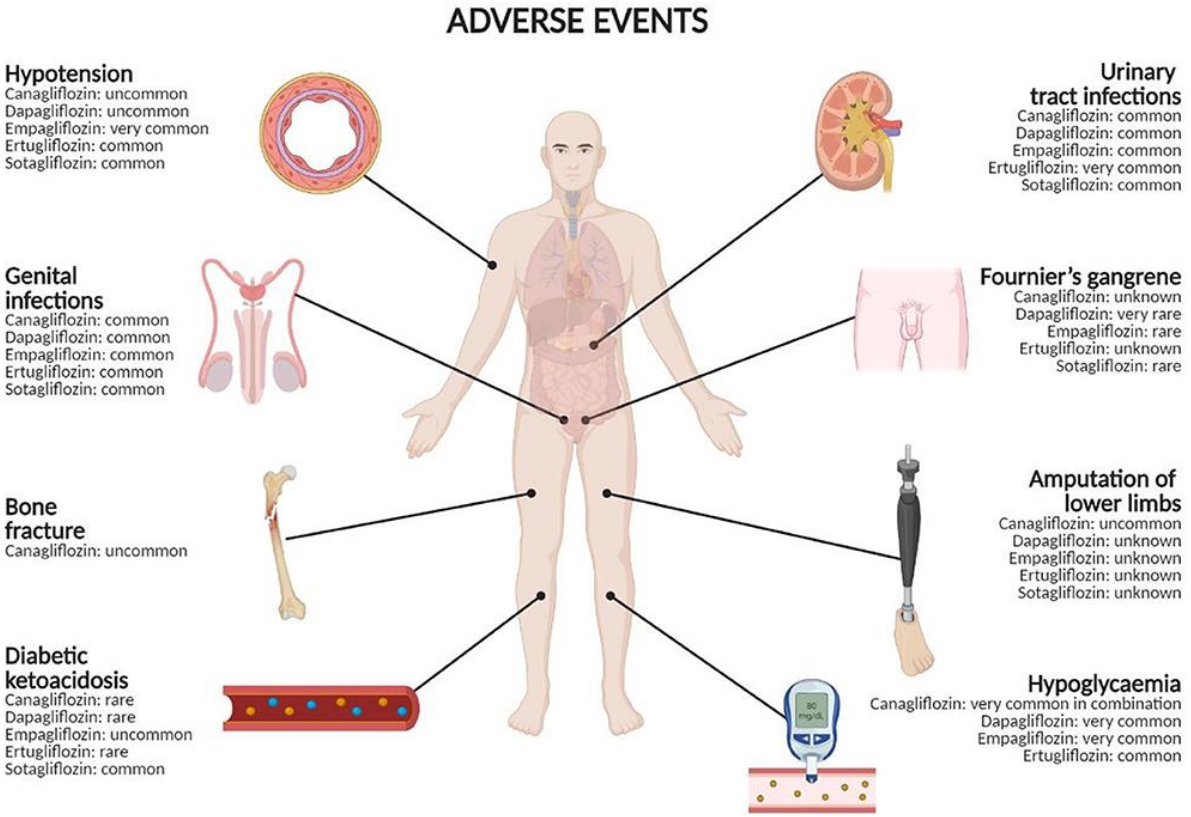
Table 3. SGLT2i trials in renal disease.

Trial (Medication)	Main Outcome HR (95% CI) (*p*-Value)	Key Summary
CREDENCE [21] (canagliflozin 100 mg)	↓ ESRD, doubling of sCr, renal death, or CV death 0.70 (0.59–0.82) ($p = 0.00001$)	CREDENCE was the first trial in more than two decades in improving kidney endpoints.
DAPA-CKD [22] (dapagliflozin 10 mg)	↓ Decline in eGFR, new ESRD, renal death, or CV death 0.61 (0.51–0.72) ($p < 0.001$)	Dapagliflozin reduced the risk of eGFR decline, ESRD, and renal or CV death in CKD patients, regardless of diabetic status.
EMPA-KIDNEY [24] (empagliflozin 10 mg)	↓ ESRD, decrease in eGFR, renal death or CV death 0.72 (0.64–0.82) ($p < 0.001$) ↓ Hospitalization 0.86 (0.78–0.95) ($p = 0.003$)	Empagliflozin reduced ESRD, eGFR decline, and renal or CV death in CKD patients, regardless of diabetic status.

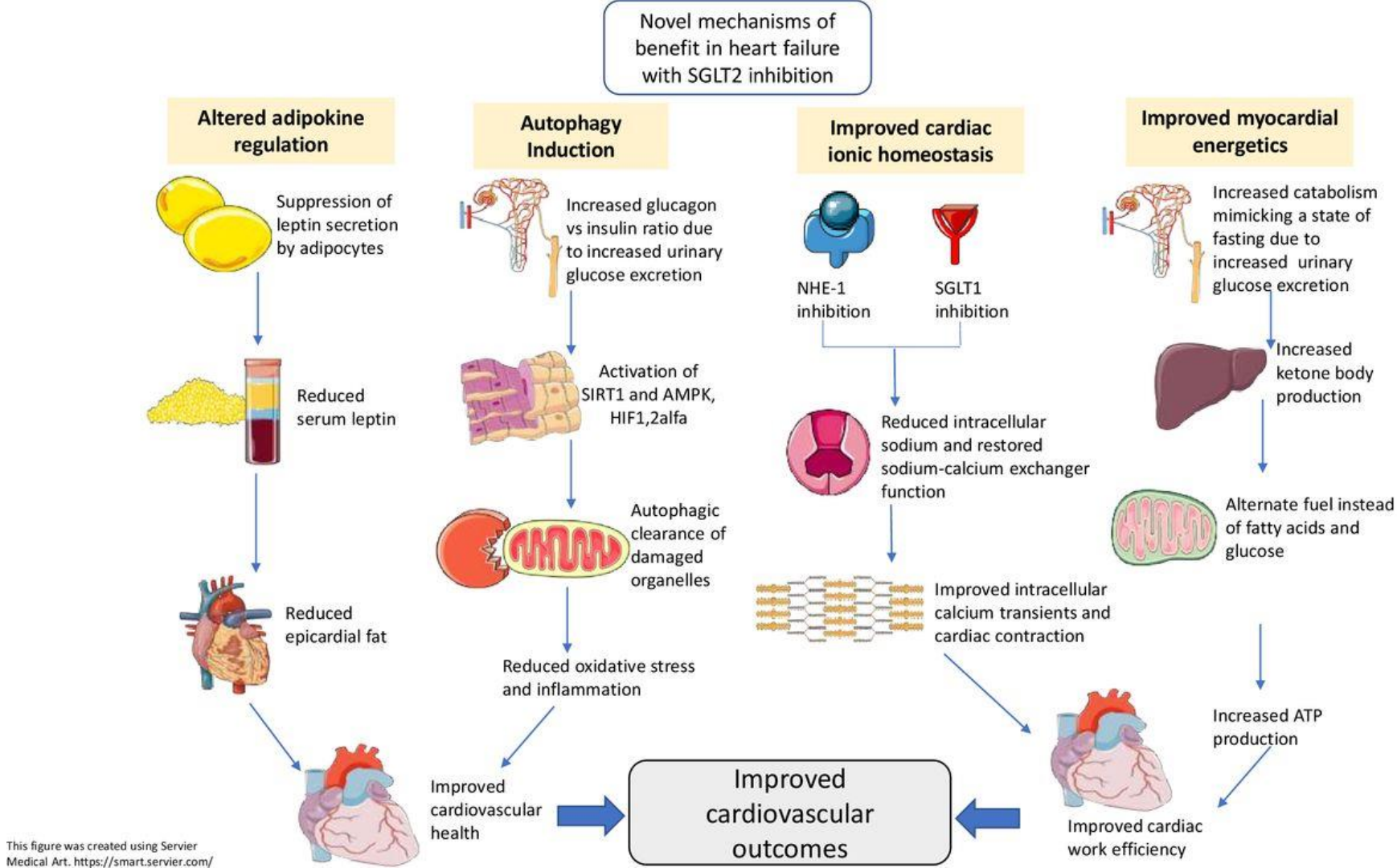
CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLD, glucose lowering drugs; sCr, serum creatinine.

	SGLT2i	GLP-1 RA
Benefits	-Reduce MACE (but not stroke) -Reduce hospitalization due to HF - Reduce eGFR decline	-Reduce MACE - Weight loss
Routes of Administration	Oral	Injectable Oral (semaglutide only)
Contraindications	-Type 1 Diabetes -eGFR <25 mL/min/1.73 m2	-Medullary thyroid CA - MEN2
Adverse Effects	Genital mycotic infection	Nausea Vomiting
Rare Adverse Effects	Euglycemic DKA	

SGLT2i Adverse Events

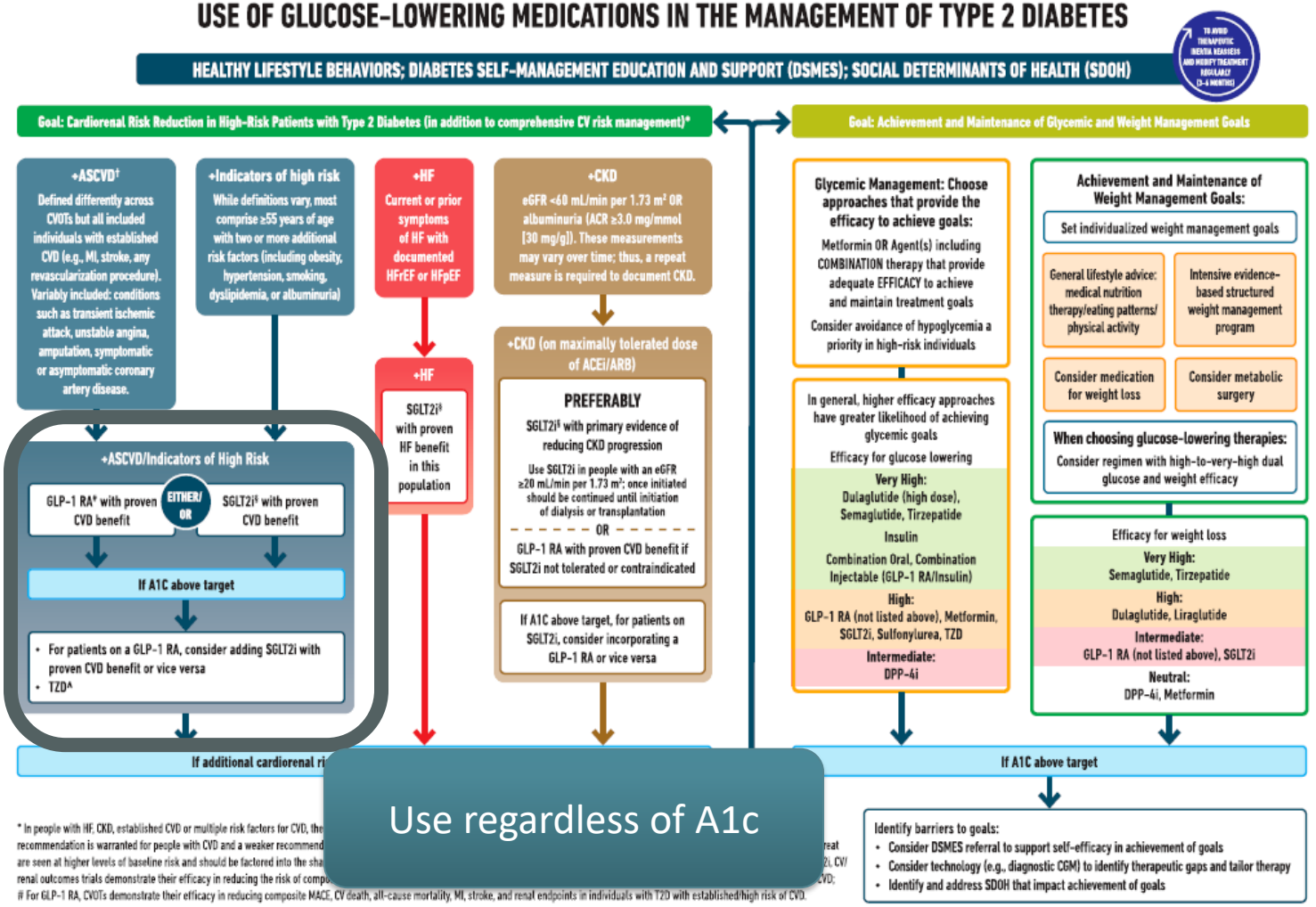


Mascolo A, Di Napoli R, Balzano N, Cappetta D, Urbanek K, De Angelis A, Scisciola L, Di Meo I, Sullo MG, Rafaniello C and Sportiello L (2022) Safety profile of sodium glucose co-transporter 2 (SGLT2) inhibitors: A brief summary. *Front. Cardiovasc. Med.* 9:1010693. doi: 10.3389/fcvm.2022.1010693

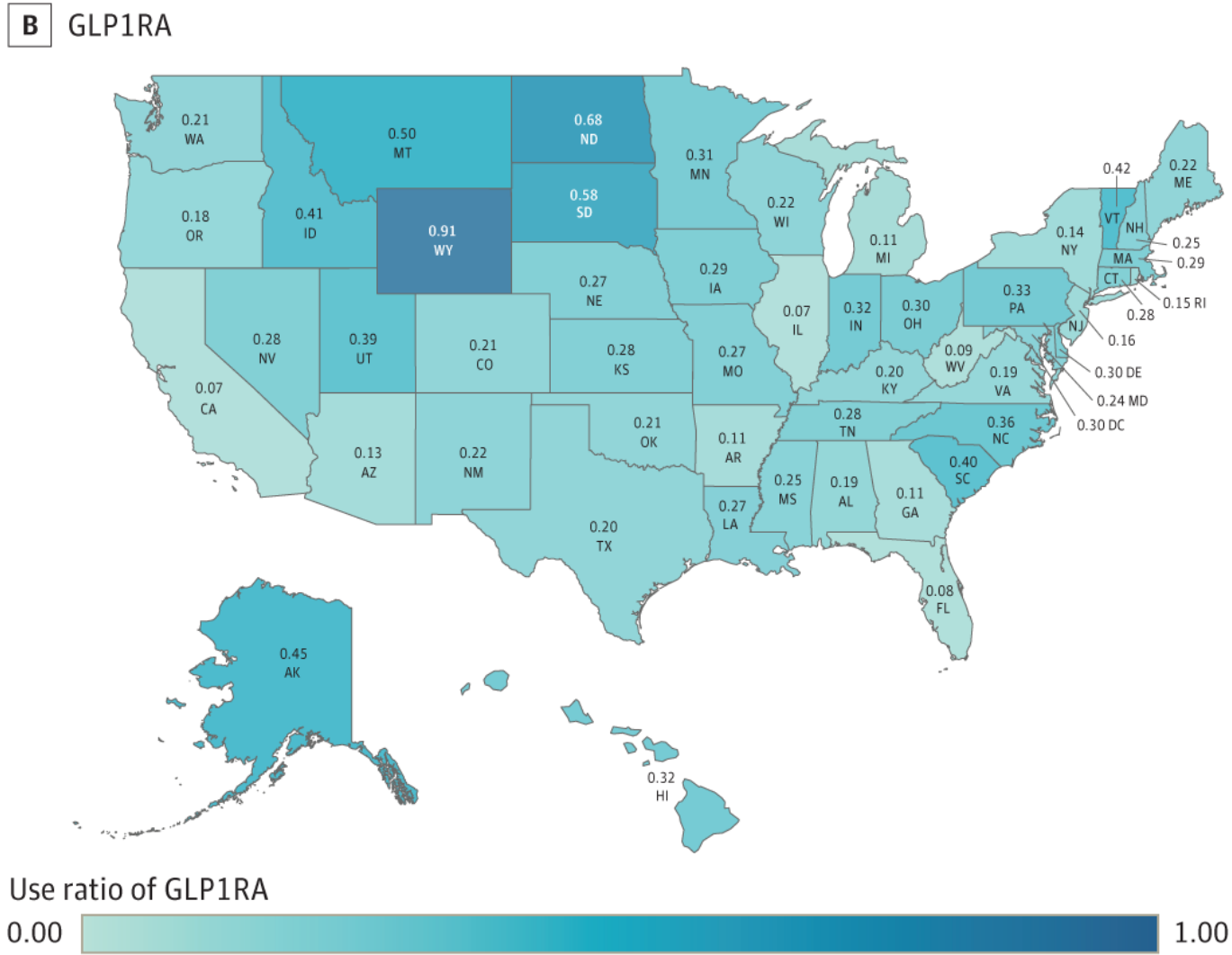


Joshi SS, Singh T, Newby DE, *et al* Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure *Heart* 2021;**107**:1032-1038. Used under CC-BY

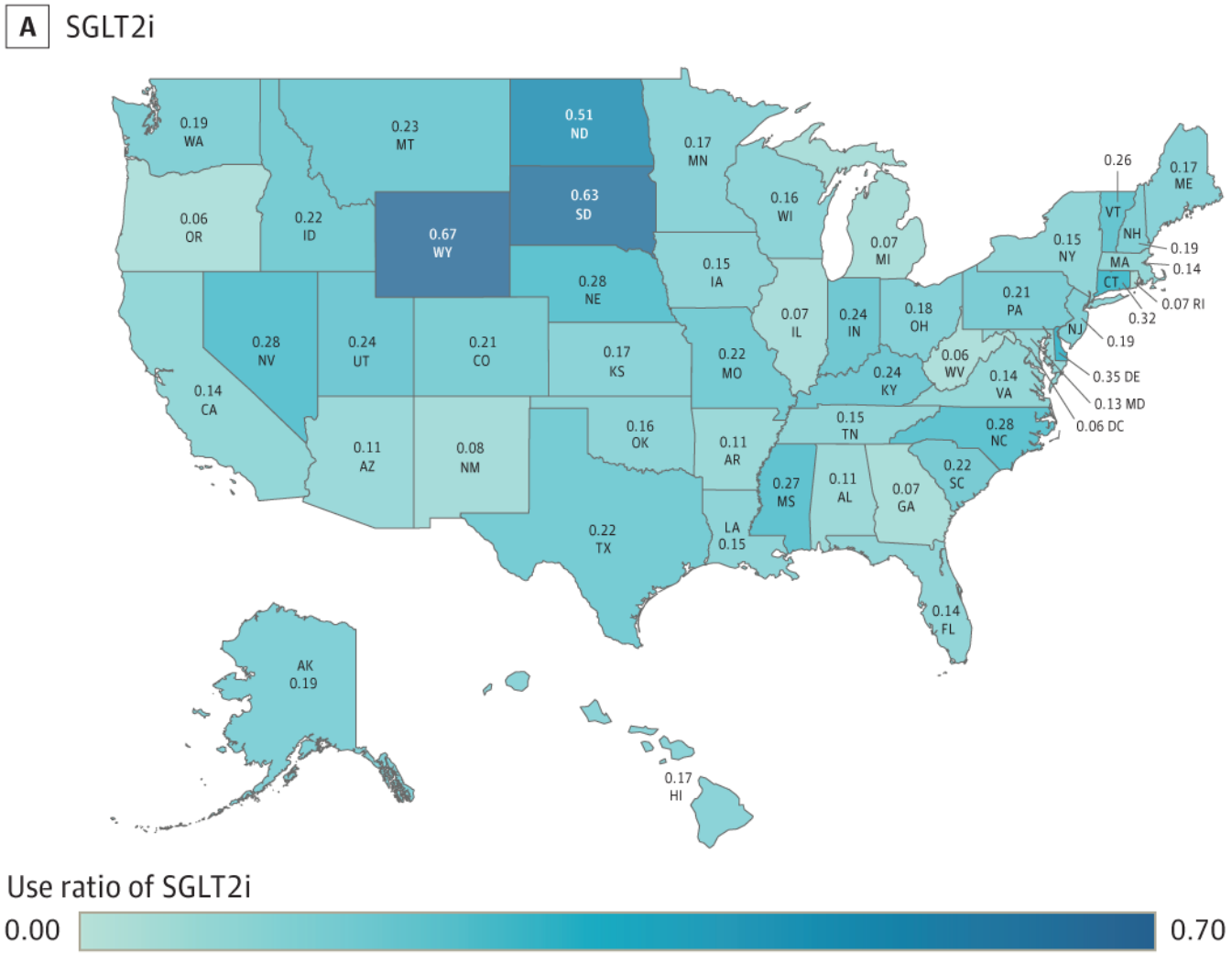
ADA Standards of Care 2023



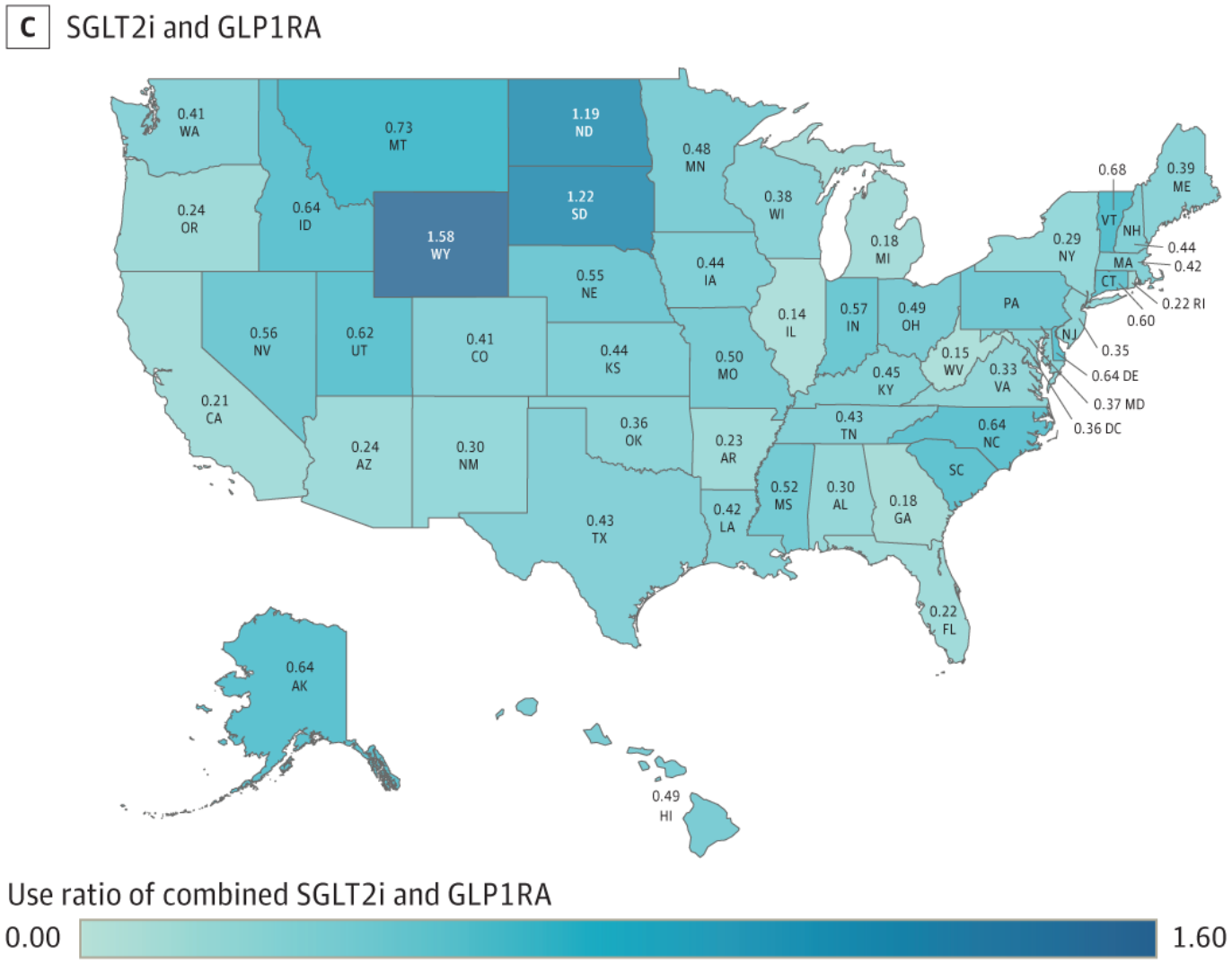
Pharmacologic Approaches to Glycemic Management: *Standards of Care in Diabetes - 2023*. *Diabetes Care* 2023;46(Suppl. 1):S140-S157 Used by permission.



Zhai MZ, Avorn J, Liu J, Kesselheim AS. Variations in Use of Diabetes Drugs With Cardiovascular Benefits Among Medicaid Patients. *JAMA Netw Open.* 2022;5(11):e2240117. doi:10.1001/jamanetworkopen.2022.40117.



Zhai MZ, Avorn J, Liu J, Kesselheim AS. Variations in Use of Diabetes Drugs With Cardiovascular Benefits Among Medicaid Patients. *JAMA Netw Open.* 2022;5(11):e2240117. doi:10.1001/jamanetworkopen.2022.40117.



Zhai MZ, Avorn J, Liu J, Kesselheim AS. Variations in Use of Diabetes Drugs With Cardiovascular Benefits Among Medicaid Patients. *JAMA Netw Open.* 2022;5(11):e2240117. doi:10.1001/jamanetworkopen.2022.40117.

Case 4

- 78-year-old female presents for care of type 2 diabetes. She was diagnosed 10 years ago. In the past month she had 2 episodes of hypoglycemia that she treated appropriately with glucose tablets.
  - Weight: 150 lbs
  - Height:5’ 3”
  - BMI: 26.6
  - Blood pressure: 126/78
  - HbA1c: 7.5%
  - eGFR: 85 mL/min/1.73m2
  - Medications: Metformin 1000 mg daily, Glipizide 10 mg daily, Alendronate 70 mg

Case 4

- What would be the best treatment option to help her improve her glycemic control?
  - A. Increase glipizide to 20 mg daily
  - B. Add a GLP-1 RA to current regimen
  - C. Start a DPP-4 inhibitor, stop glipizide
  - D. Consider insulin therapy
  - E. Discontinue alendronate due to potential interactions

Case 4

- What would be the best treatment option to help her improve her glycemic control?
  - A. Increase glipizide to 20 mg daily
  - B. Add a GLP-1 RA to current regimen
  - **C. Start a DPP-4 inhibitor, stop glipizide**
  - D. Consider insulin therapy
  - E. Discontinue alendronate due to potential interactions

DPP-4 Inhibitors

- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin
- Vildagliptin-not available in the US

- Benefits:
  - Lowers A1c 0.5-1%
  - Weight neutral
  - Low risk of hypoglycemia
  - CVOT-> Neutral
- Cautions
  - Saxa and Alo should not be used in HF
  - Avoid use with GLP-1 RA

Clinical Feature	Effect on Metformin
Hyperglycemia	Improves glycemic control in T2DM, reduces progression of prediabetes to T2DM
Insulin resistance	Reduces hepatic glucose output, improves peripheral glucose disposal, increases anaerobic glucose metabolism
Hyperinsulinemia	Reduces fasting hyperinsulinemia
Abdominal obesity	Stabilizes body weight, may cause weight loss (4kg)
Dyslipidemia	May modestly improve blood lipid profile in some with hypertriglyceridemia and hypercholesterolemia
Blood pressure	No significant effect but often improvements with weight loss
Proinflammatory state	May reduce CRP and some adipocytokines
Procoagulant state	Some antithrombotic activity
Atherosclerosis	Reduced CV mortality and all-cause mortality in T2DM

Case 5

- Mrs. Miller is a 33-year-old female who presents with increased thirst and urination and unintentional weight loss over the past month.
  - Weight: 157lbs
  - Height:5’ 7”
  - BMI: 24.6
  - Blood pressure: 120/80
  - HbA1c: 10.5%
  - Fasting blood glucose: 300 mg/dL

Case 5 Question 1

- What would you prescribe as her initial therapy?
  - A. Metformin
  - B. SGLT2i
  - C. GLP-1 RA
  - D. Insulin
  - E. Lifestyle changes alone

Case 5 Question 1

- What would you prescribe as her initial therapy?
  - A. Metformin
  - B. SGLT2i
  - C. GLP-1 RA
  - **D. Insulin**
  - E. Lifestyle changes alone

Case 5 Question 2

- What further testing would you like?
  - A. None
  - B. C-peptide
  - C. Lipids
  - D. GAD antibodies

Case 5 Question 2

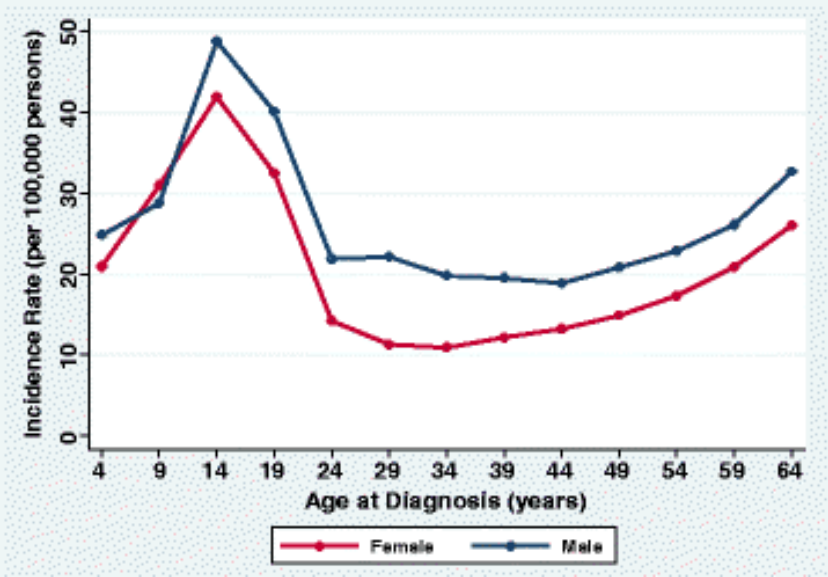
- What further testing would you like?
  - A. None
  - B. C-peptide
  - C. Lipids
  - **D. GAD antibodies**

Type 1 Diagnosis in Adults

- 40% initially diagnosed as having T2DM when developed after age 30
- Age less than 35 at diagnosis
  - Lower BMI (<25 kg/m^2)
  - Unintentional weight loss
  - Ketoacidosis
  - Glucose >360 mg/dL at presentation
- Rapid progression to insulin treatment (<3 years)
- C-peptide
  - May have residual at diagnosis
  - Random testing beyond 3 years of diagnosis if uncertain

Incidence

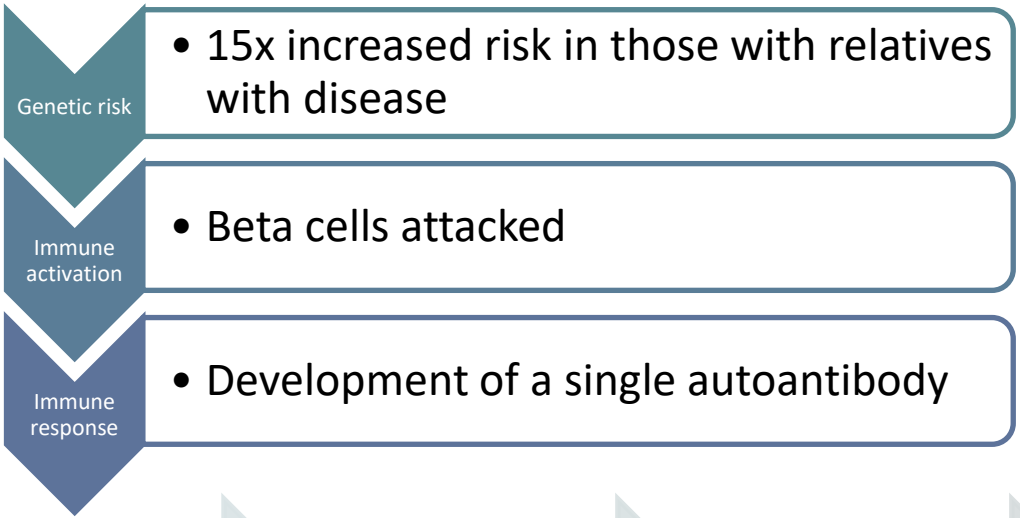
- 15 per 100,000 across all age groups

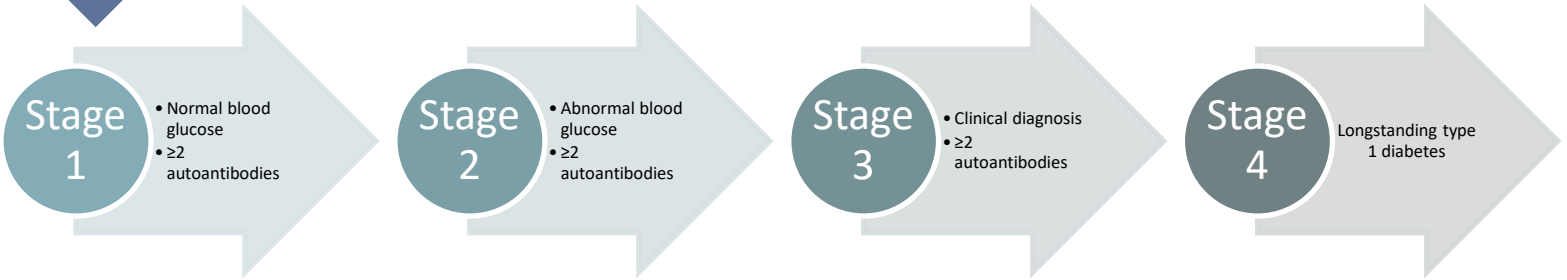


Prevalence

- 5.9 per 10,000 worldwide across all age groups
  - 20 million worldwide
  - 1-3 million in the U.S
  - Rising incidence suggests that number may triple by 2050
- Currently, more adults living with type 1 than children
  - New onset as adults
  - Living longer after diagnosis

Natural History of Type 1 Diabetes





Adapted from Greenbaum CJ, Speake C, Krischer J, et al. Strength in numbers: opportunities for enhancing the development of effective treatments for type 1 diabetes—the TrialNet Experience. *Diabetes* 2018; published online May 16 DOI:10.2337/db18-0065

Antibody Markers of Type 1 Diabetes

- Glutamic Acid Decarboxylase (GAD) Antibodies
- Islet Cell Antibodies (ICA)
  - No longer recommended in testing
- Insulin Auto Antibodies (IAA)
- Islet Tyrosine Phosphatase (IA2 or ICA-512) Antibodies
- Zinc Transporter 8 Antibodies (ZNT8)

Treatment

- Insulin!
  - Multiple daily doses
- May have a “honeymoon” period of requiring less insulin
- Important to highlight in the medical record

Conclusions

1. Incretin therapy can be used as indicated for the treatment of type 2 diabetes, CV risk reduction, and overweight/obesity
2. Patient education should be given to minimize adverse events and side effects
3. SGLT2i show benefits in T2DM, CVD, HF, and renal disease
4. GLP-1 RA and/or SGLT2i should be used in accordance with guidelines in those with T2DM and ASCVD risk regardless of A1c
5. Although type 2 diabetes is the most common form in adults, type 1 diabetes should also be considered in certain clinical pictures.

QUESTIONS?

THANK YOU

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