DIABETES UPDATE 2023: CLINICAL PEARLS

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ACP Washington Chapter Meeting, Nov 4, 2023
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METABOLISM, ENDOCRINOLOGY & NUTRITION

Disclosures

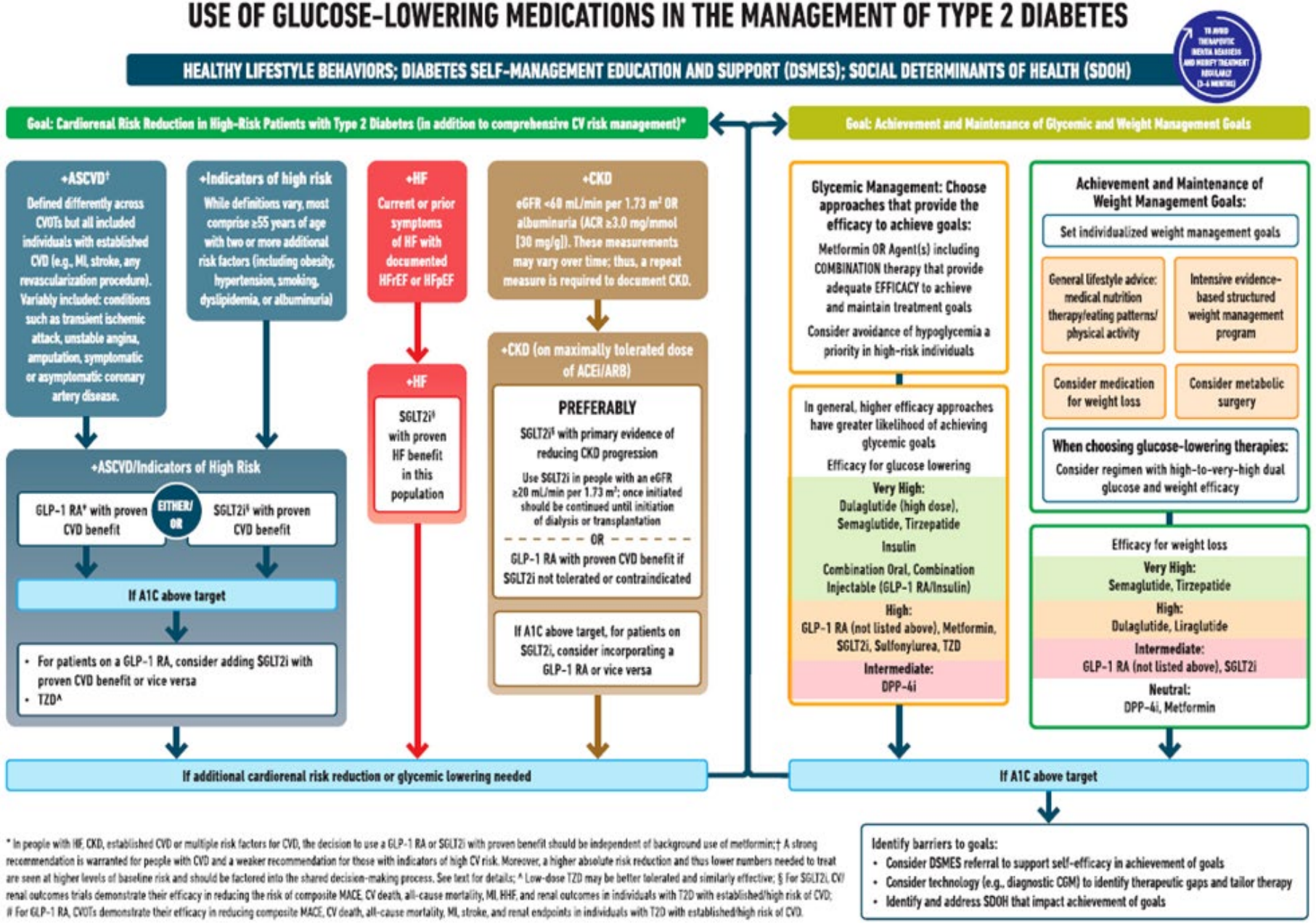
- Advisory boards for Abbott Diabetes Care

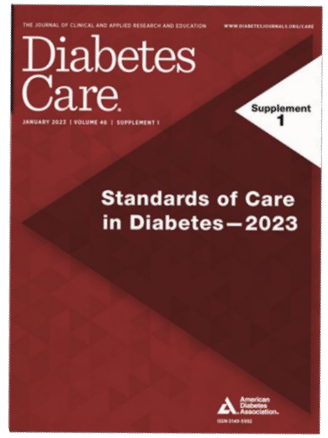
Diabetes management in 2023

1. Appropriate medication selection in individuals with diabetes based on individual characteristics
2. Current issues in prescribing newer medications for diabetes
3. Updates in CGM use
4. Updates in insulin
5. Type 1 diabetes

Scenario 1

- 56 y/o male with Type 2 diabetes treated with metformin 2g daily
- Has gained weight (~15 lbs) due to work-life stressors and decrease in physical activity
- BMI 33
- A1C on day of visit is 8.6%; you notice that A1Cs were 7.9-8.4% the past year
- He is really concerned about the weight gain
- What is the next step?

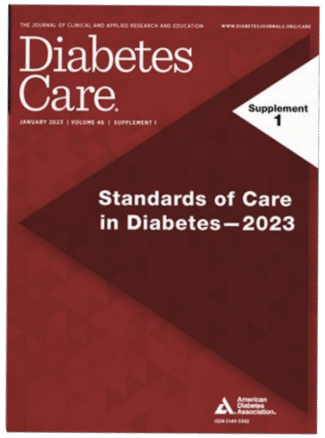




Algorithm for Type 2 Diabetes Treatment – 2023

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

Appropriate Glucose-lowering Medication Selection in type 2 diabetes in 2023



HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

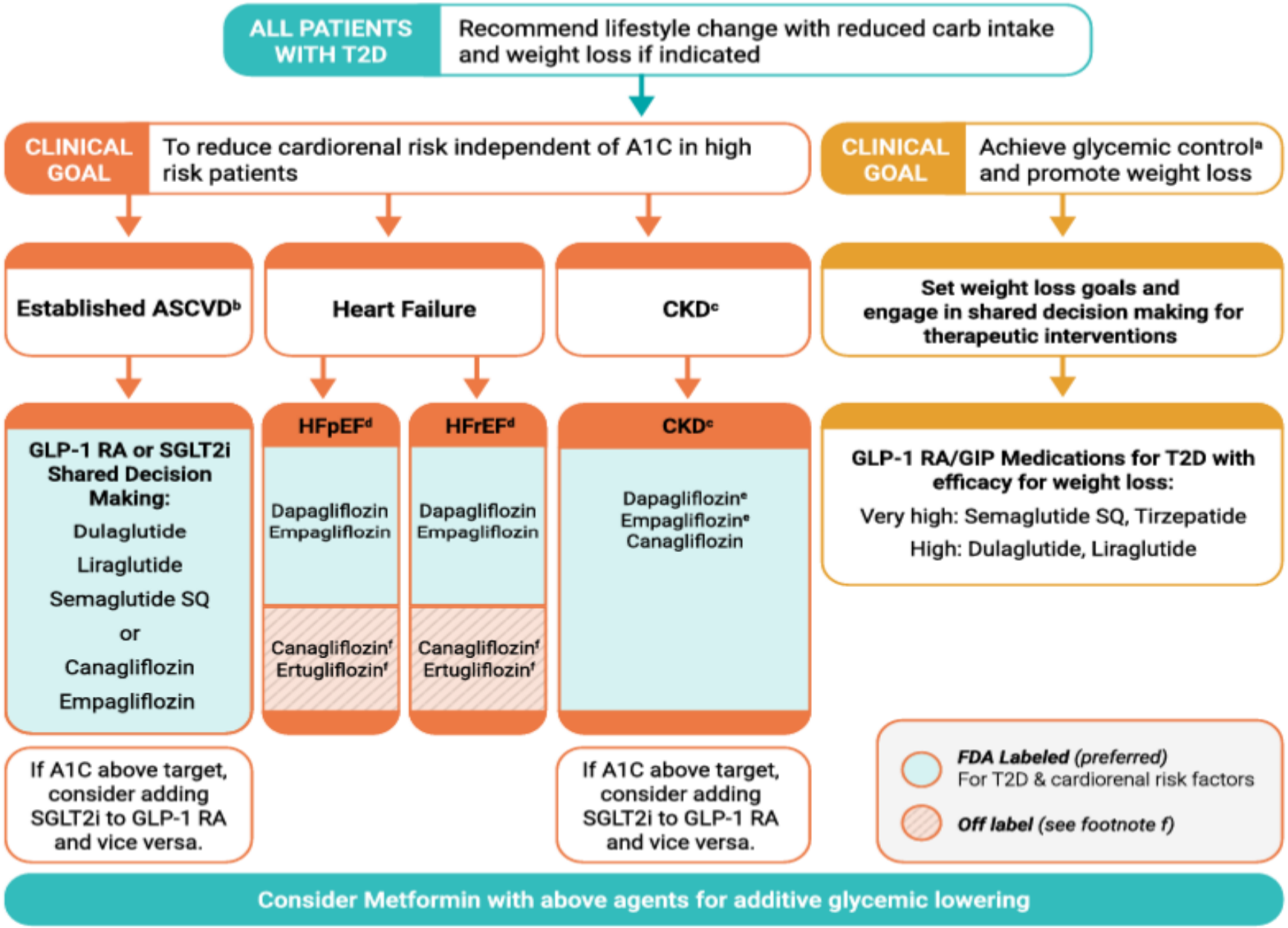
Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

CARDIORENAL RISK REDUCTION

GLYCEMIC AND WEIGHT MANAGEMENT

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

Diabetes algorithm simplified



https://www.mct2d.org/resource-library/mct2d-clinical-decision-aid-sglt2-glp1-for-t2d

Incretin analogs or GLP-1 receptor agonists: The “tides”

Exenatide IR (Byetta) 5-10 mcg twice daily sc

Exenatide ER (Bydureon) 2mg weekly sc

Liraglutide (Victoza) 0.6 – 1.8 mg daily sc

Semaglutide (Ozempic) 0.25 -2mg weekly sc

Semaglutide (Rybelsus) 3-14 mg daily oral

Dulaglutide (Trulicity) 0.75-4.5 mg weekly sc

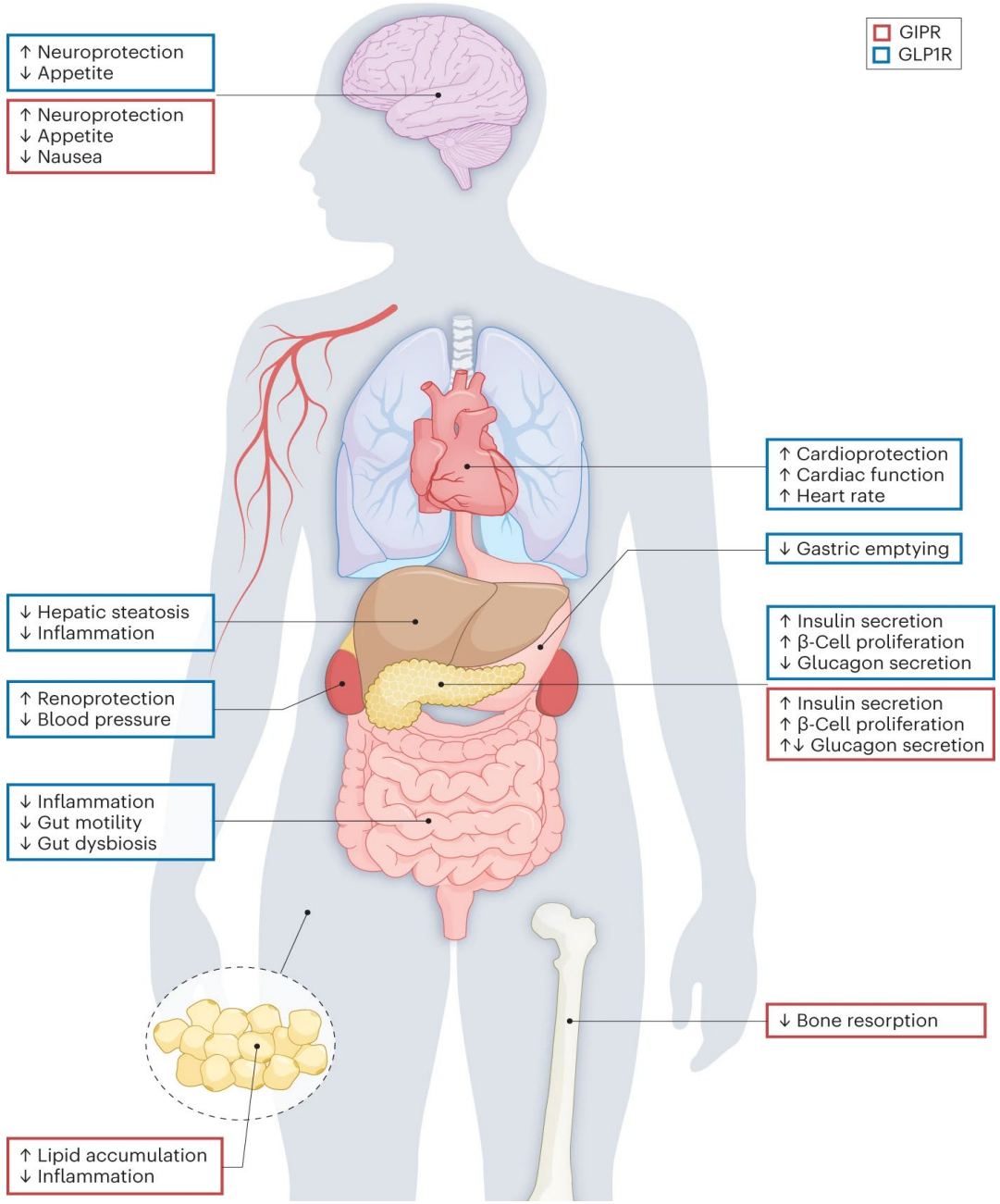
Tirzepatide (Mounjaro) 2.5-15 mg weekly sc

Incretins in type 2 diabetes

- Glucagon like peptide 1 (GLP-1) and Glucose-dependent insulinotropic polypeptide (GIP)

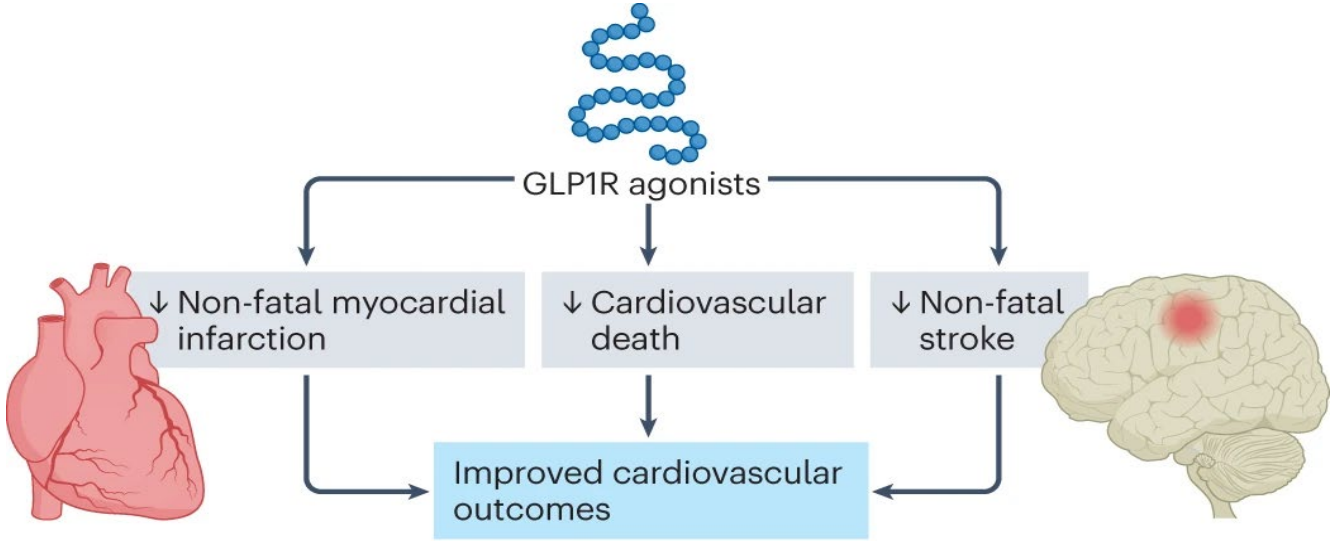
GLP-1 receptors present on

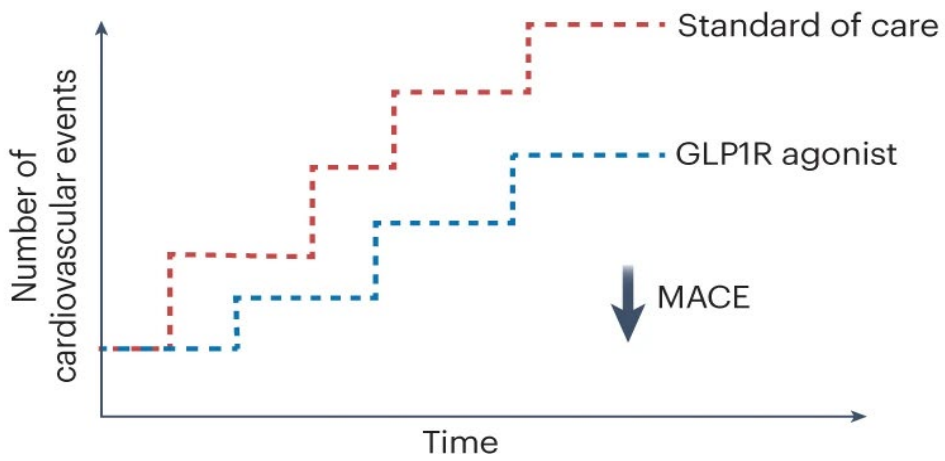
- Pancreatic beta cell – insulin secretion
- Hypothalamus/brain stem – promote satiety
- Vagal neurons – decrease gastric motility
- Pancreatic acinar cells – pancreatitis/ pancreatic cancer?
- Sinoatrial node - tachycardia
- Vascular smooth muscle



Ussher and Drucker. Nat Rev Cardiol 2023

GLP-1 RAs reduce major adverse CV outcomes

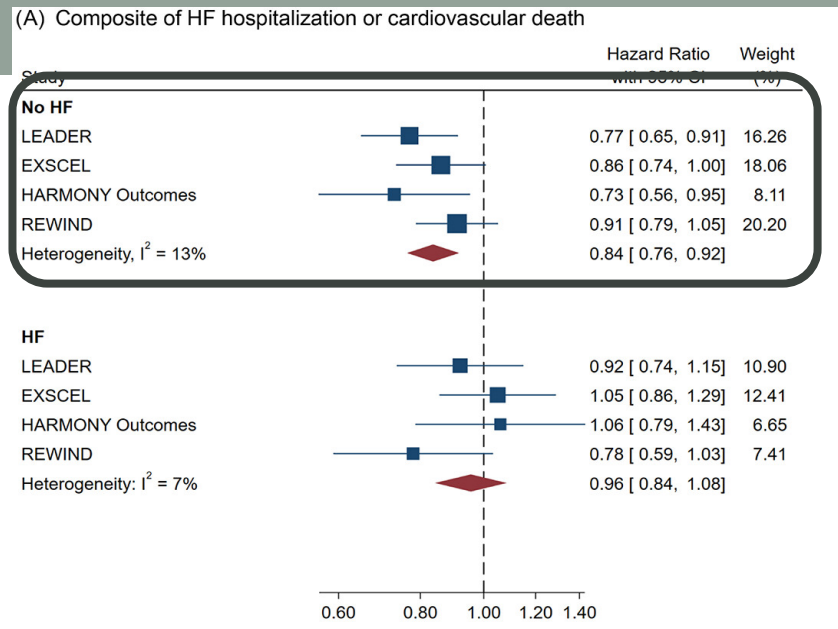


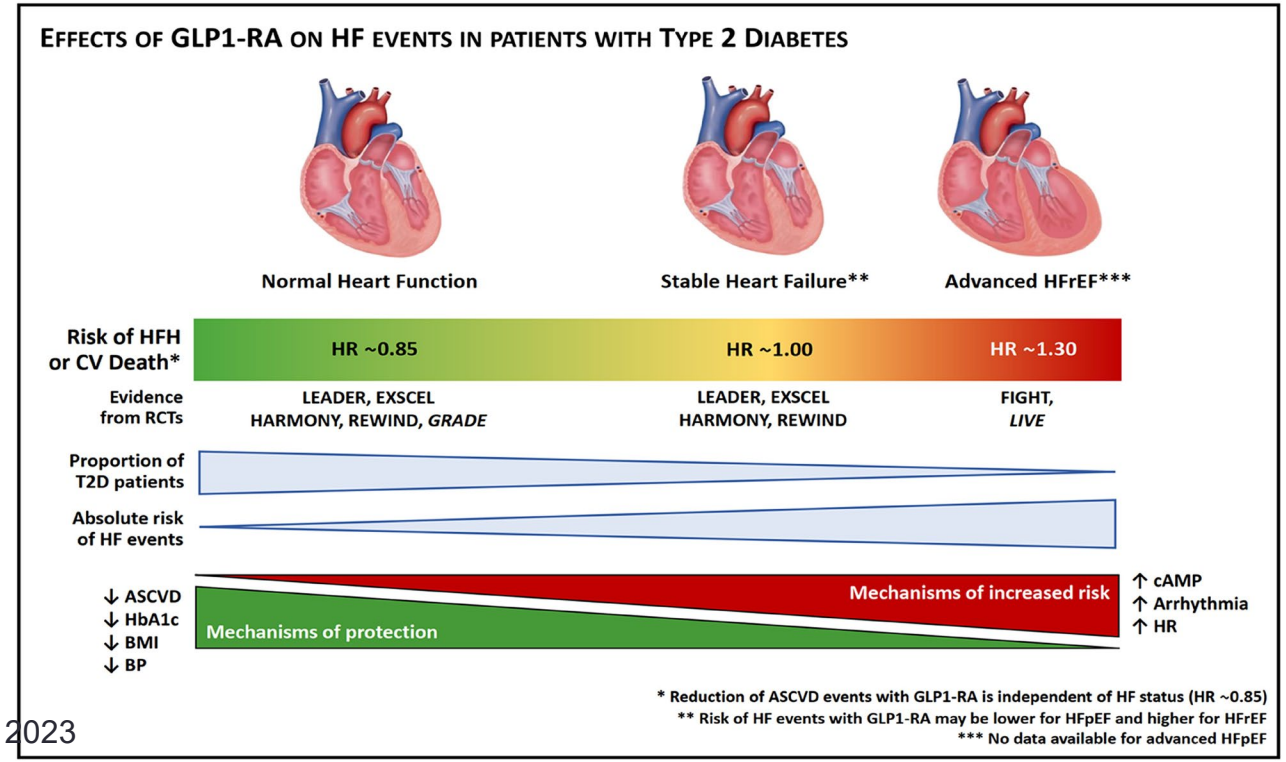


Ussher and Drucker. Nat Rev Cardiol 2023

GLP-1RA and heart failure in diabetes

- In patients with T2D without HF → ↓ HF hospitalizations or CV death
- In patients with stable HFpEF (15-20% of people with T2D)→ no ↓ HF hospitalizations or CV mortality but can ↓ atherosclerotic events
- Patients with HFrEF → maybe harmful; avoid





Ferreira JP et al Diabetes Obesity and Metabolism 2023; Ferreira JP et al JCEM 2023

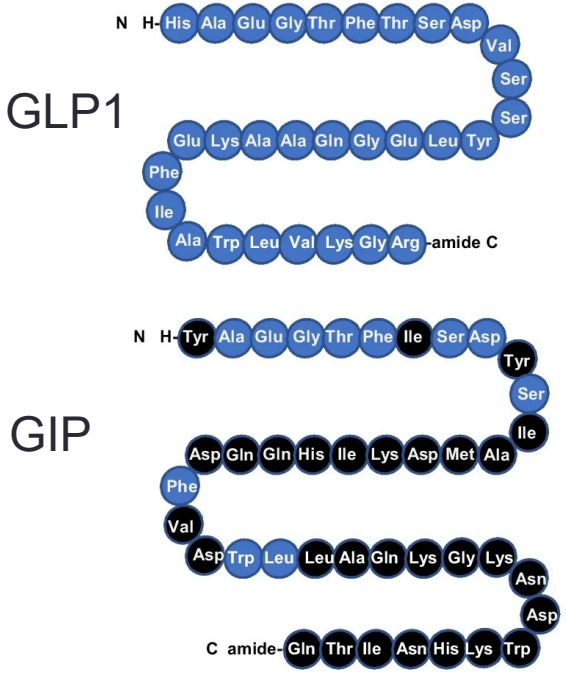
GLP-1RAs and the kidney

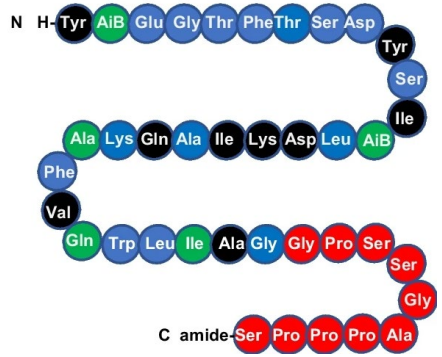
- FLOW study – semaglutide on progression of renal impairment in people with T2D and CKD
- N = ~3500
- To demonstrate whether semaglutide can delay progression of CKD and to decrease kidney and cardiovascular mortality
- Stopped early in Oct 2022 based on recommendations that the study met certain pre-specified criteria

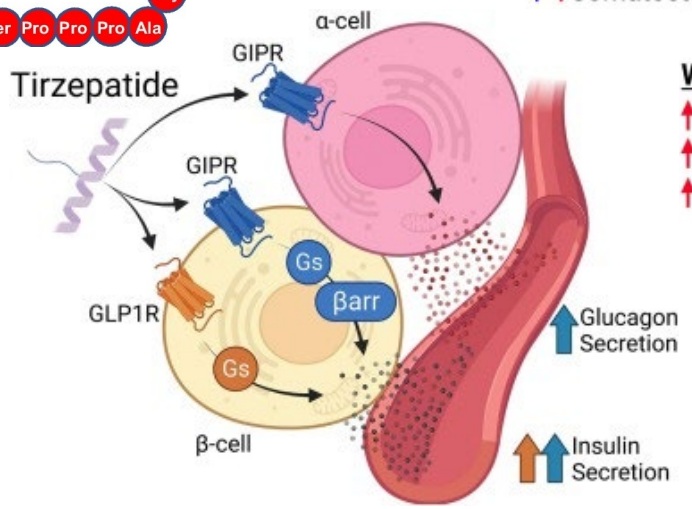
https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=166327

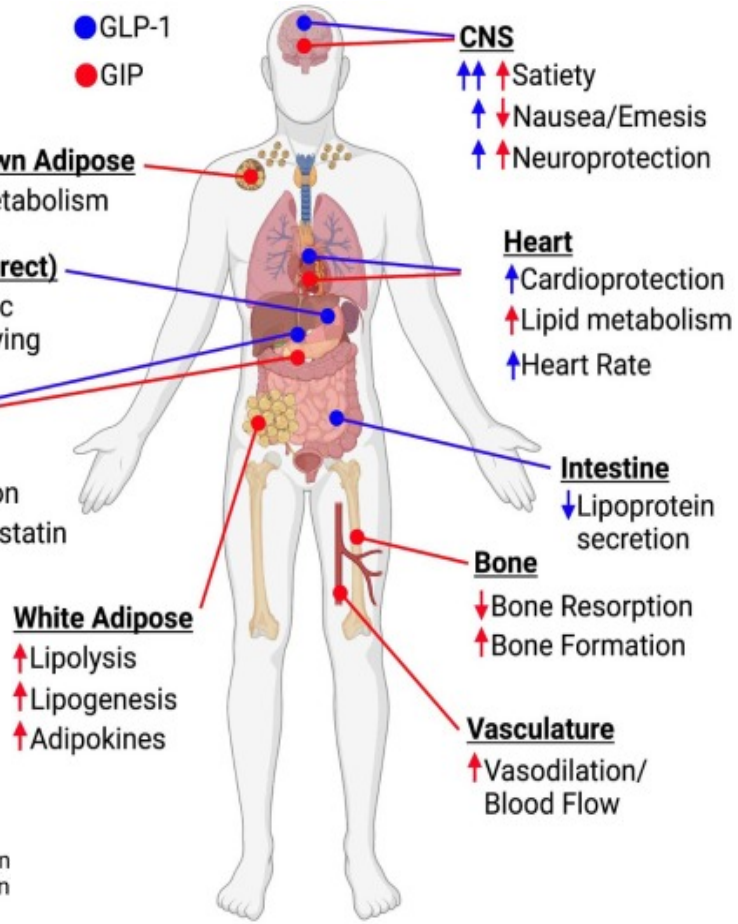
Tirzepatide – a GLP-1 and GIP dual receptor agonist "twincretin"

- Stimulates insulin secretion from beta cell
- Stimulates glucagon secretion from alpha cell







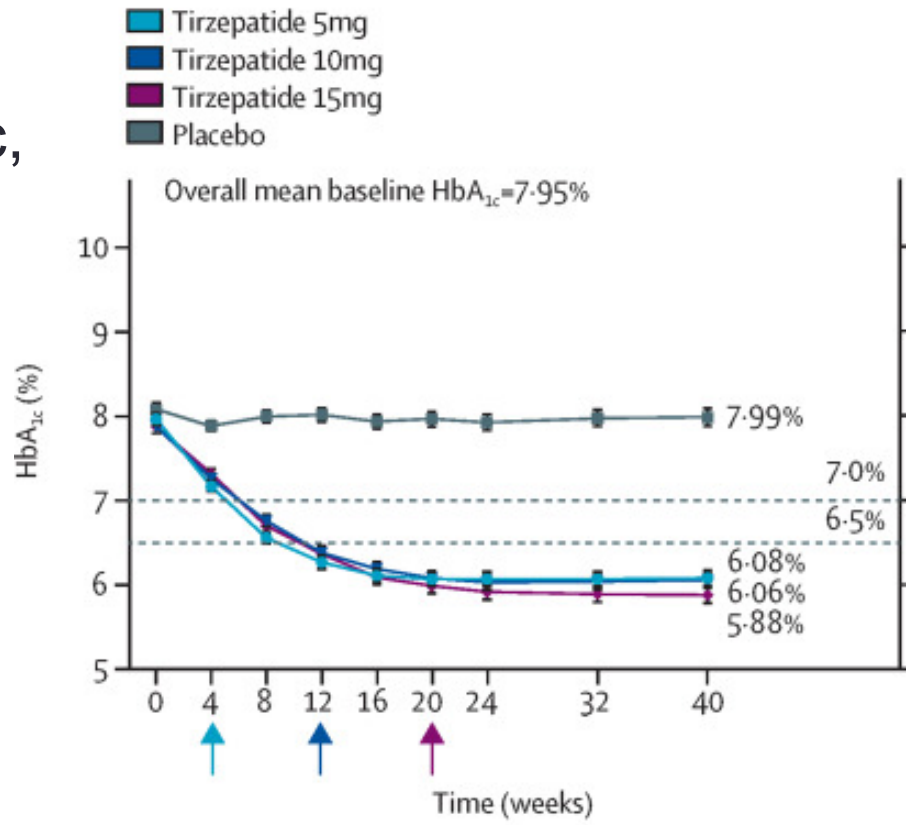


Campbell JE et al Cell Metab Sept 2023

Tirzepatide (Mounjaro)

- SURPASS program - Superior glycemic efficacy to placebo, semaglutide 1mg weekly, insulin degludec, insulin glargine and insulin lispro
- A1C reduction 1.7-2.6%
- Weight reduction of **7-9.5kg**

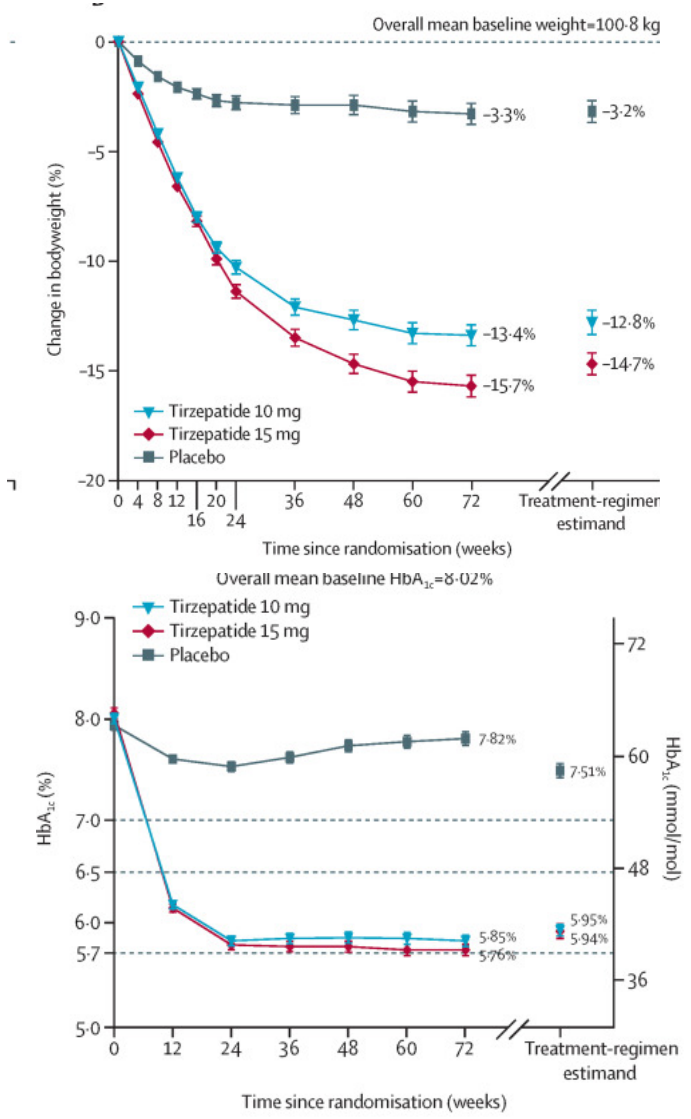
- SURPASS-CVOT trial results expected 2024



Rosenstock J et al, SURPASS-1, Lancet 2021

Tirzepatide in obesity and diabetes – SURMOUNT 2

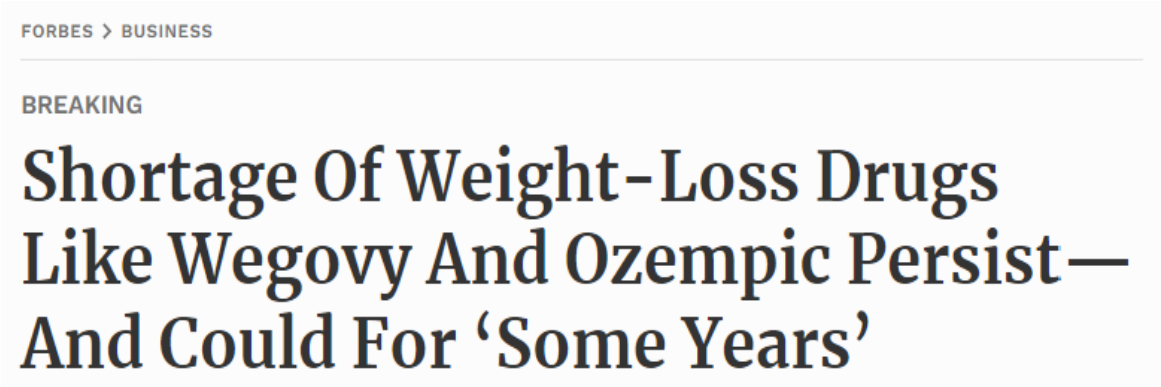
- Tirzepatide 10 or 15 mg weekly for 72 wks
- T2D with BMI ≥ 27kg/m^2
- A1C 7-10%
- 60% Hispanic or Latino
- Mean wt loss ~12-15%
- A1C reduction ~2%
- No increased discontinuation
- More GI side effects (~50% vs 18%)



Garvey T et al SURMOUNT-2 Lancet 2023

Recent issues with GLP-1RA

- Availability/ shortage


FORBES > BUSINESS

BREAKING

Shortage Of Weight-Loss Drugs Like Wegovy And Ozempic Persist—And Could For 'Some Years'

- Critical shortages for 2mg dosing of semaglutide as Ozempic through end of 2023 (via fda.gov)

https://www.forbes.com/sites/brianbushard/2023/09/16/shortage-of-weight-loss-drugs-like-wegovy-and-ozempic-persist-and-could-for-some-years/?sh=e3b5757631ee

Coverage of GLP-1RAs and twincretins in Washington?

- Commercial insurance
  - Typically covered with prior authorizations, Tier 2 or 3
  - There may be a copay (can use Co-pay card)
  - High deductible plan – medication covered only after deductible is met
- Medicare Part D
  - Copay (Copay cards cannot be used)
  - Patient assistance
- WA Medicaid –
  - Liraglutide and Exenatide are “preferred”; weekly are listed as “non-preferred”
  - Type 2 diabetes and “failed” on metformin (at max tolerated dose) and a SGLT2i and 1 preferred GLP-1RA for 90 days (used separately or simultaneously)
  - if ASCVD present - a SGLT2i and 1 preferred GLP-1RA for 90 days (used separately or simultaneously)

Dealing with shortages of GLP-1RAs

- Have patients call around pharmacies; call their health insurance for alternatives
- Have patients keep calling their pharmacy for stock updates
- Switch to a different agent
- Use a lower dose of same agent

Agent	Frequency	Titration Schedule	Equivalent Doses					
Dulaglutide	Weekly	4 week		0.75 mg	1.5 mg	3 - 4.5 mg		
Semaglutide	Weekly	4 week		0.25 mg*	0.5 mg	1 mg	2 mg	
Liraglutide	Daily	1 week	0.6 mg*	1.2 mg	1.8 mg			
Oral Semaglutide	Daily	4 week	3 mg*	7 mg	14 mg			
Tirzepatide	Weekly	4 week				2.5 mg*	5 mg	7.5 - 15 mg

* Sensitizing dose, no glycemic impact

https://www.mct2d.org/resource-library/glp-1-receptor-agonist-shortages-how-to-support-patients

CNN health | Life, But Better | Fitness | Food | Sleep | Mindfulness | Relationships

They took blockbuster drugs for weight loss and diabetes. Now their stomachs are paralyzed

Courtesy Emily Wright

Emily Wright lost 80 pounds on Ozempic and now struggles with gastroparesis

FORBES > INNOVATION

BREAKING

What To Know About Gastroparesis: Lawsuit Claims Ozempic And Mounjaro Causes The Severe Stomach Disorder

J Investig Med High Impact Case Rep. 2021 Jan-Dec; 9: 23247096211051919.
Published online 2021 Oct 18. doi: 10.1177/23247096211051919

PMCID: PMC8529310
PMID: 34663102

Medication-Induced Gastroparesis: A Case Report

M Ammar Kalas, MD,[1] Gian Marco Galura, MD,[1] and Richard W. McCallum, MD, FACG, FACP[1]

Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

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Gastroparesis with GLP-1RA?

- When prescribed for weight loss, GLP-1RA (liraglutide and semaglutide) were associated with increased risk of
  - Gastroparesis
  - Pancreatitis
  - Bowel obstruction

(compared to bupropion-naltrexone)

RESEARCH LETTER

Risk of Gastrointestinal Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss

Sodhi M et al JAMA Sept 2023

GLP-1RA and procedures/ surgeries

June 29, 2023

American Society of Anesthesiologists Consensus-Based Guidance on Preoperative Management of Patients (Adults and Children) on Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

Girish P. Joshi, M.B.B.S., M.D., Basem B. Abdelmalak, M.D., Wade A. Weigel, M.D., Sulpicio G. Soriano, M.D., Monica W. Harbell, M.D., Catherine I. Kuo, M.D., Paul A. Stricker, M.D., Karen B. Domino, M.D., M.P.H., American Society of Anesthesiologists (ASA) Task Force on Preoperative Fasting

- Consider holding on the day of (on daily GLP-1RA) or the week prior (weekly dosing)
- Delay procedure if GI symptoms present on day of procedure for concerns of regurgitation and pulmonary aspiration
- If no GI symptoms, but GLP-1RA not held, use ‘full stomach’ precautions or consider evaluating gastric volume by ultrasound. If stomach is empty, proceed. If stomach is full, consider delaying the procedure or treat the patient as ‘full stomach’.

Scenario

- 38 yo male with type 2 diabetes and moderate hypertriglyceridemia comes for an office visit after a year long hiatus
- On metformin 1500mg
- Established with a functional medicine provider as he was concerned about his weight
- Given compounded semaglutide which he started at a low dose and was increased. He notes that he draws it up weekly from a vial with a syringe. He pays $390 for it monthly

Issues with GLP-1RA

- Compounded semaglutide??

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/medications-containing-semaglutide-marketed-type-2-diabetes-or-weight-loss

FDA U.S. FOOD & DRUG ADMINISTRATION

Are there concerns with compounded semaglutide?

FDA has received adverse event reports after patients used compounded semaglutide. Patients should not use a compounded drug if an approved drug is available to treat a patient. Patients and health care professionals should understand that the agency does no review compounded versions of these drugs for safety, effectiveness, or quality.

Additionally, FDA has received reports that in some cases, compounders may be using sal forms of semaglutide, including semaglutide sodium and semaglutide acetate. The salt forms are different active ingredients than is used the approved drugs, which contain the base form of semaglutide. The agency is not aware of any basis for compounding using the salt forms that would meet the FD&C requirements for types of active ingredients that can be compounded. On April 27, 2023, FDA wrote to the National Association of Boards of Pharmacy expressing the agency's concerns with use of the salt forms in compounded products.

What should patients know?

Patients should be aware that some products sold as 'semaglutide' may not contain the same active ingredient as FDA-approved semaglutide products and may be the salt formulations. Products containing these salts, such as semaglutide sodium and semaglutide acetate, have not been shown to be safe and effective.

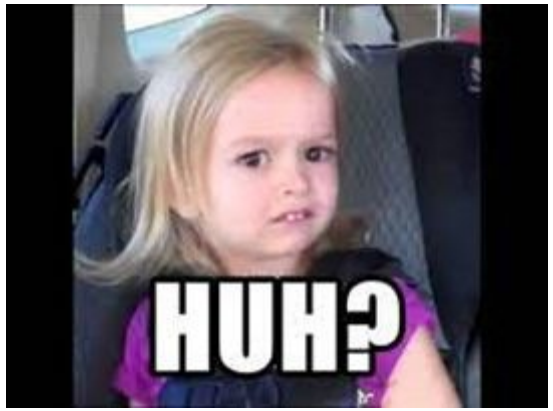
Patients should only obtain drugs containing semaglutide with a prescription from a licensed health care provider, and only obtain medicines from state-licensed pharmacies or outsourcing facilities registered with FDA.

Purchasing medicine online from unregulated, unlicensed sources can expose patients to potentially unsafe products that have not undergone appropriate evaluation or approval, or do not meet quality standards. If you choose to use an online pharmacy, FDA's BeSafeRx campaign resources and tools can assist in making safer, more informed decisions when purchasing prescription medicine online.

Scenario

- MyChart message from a patient June 2023 -

- “Dr S, I am wondering if I would be a candidate for the drug retatrutide for weight loss and maybe I can get it if you prescribe it?”

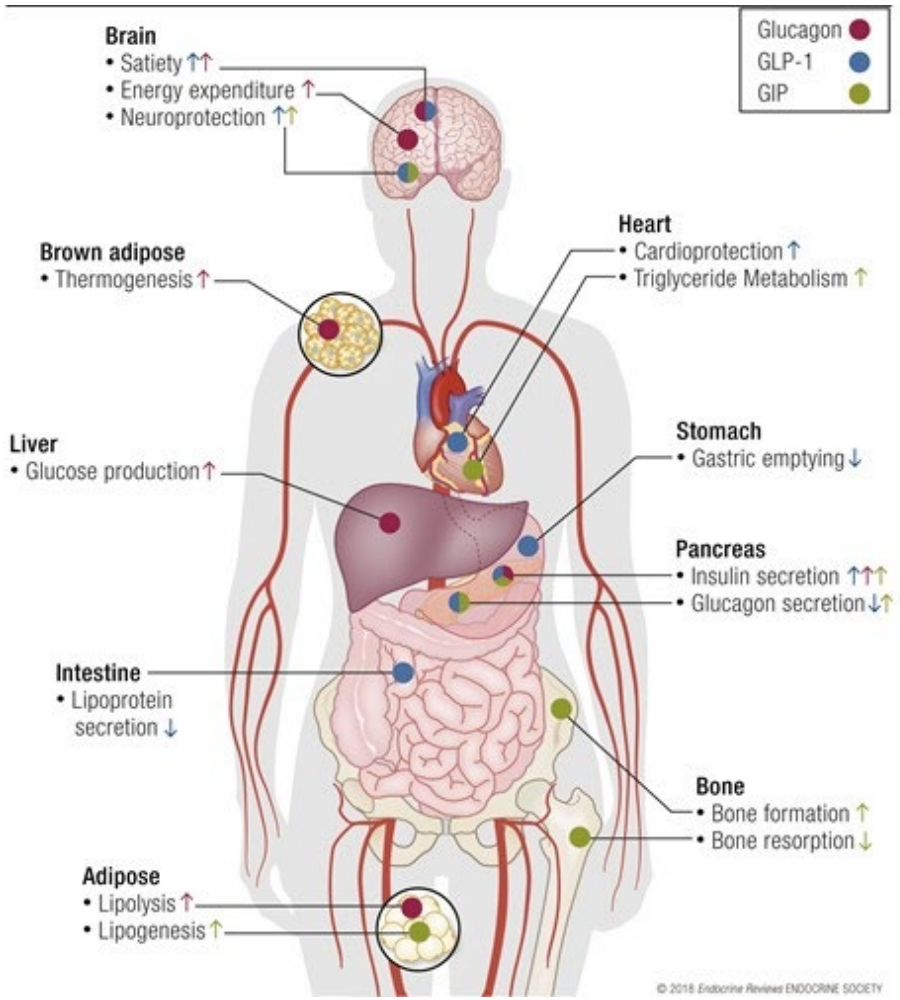


GROCERY
GAMES

Retatrutide (“triple G”)

- An investigational GLP-1, GIP and glucagon receptor tri-agonist
- Two phase 2 studies, obesity and type 2 diabetes
- Dosed weekly
- Nausea is much lesser

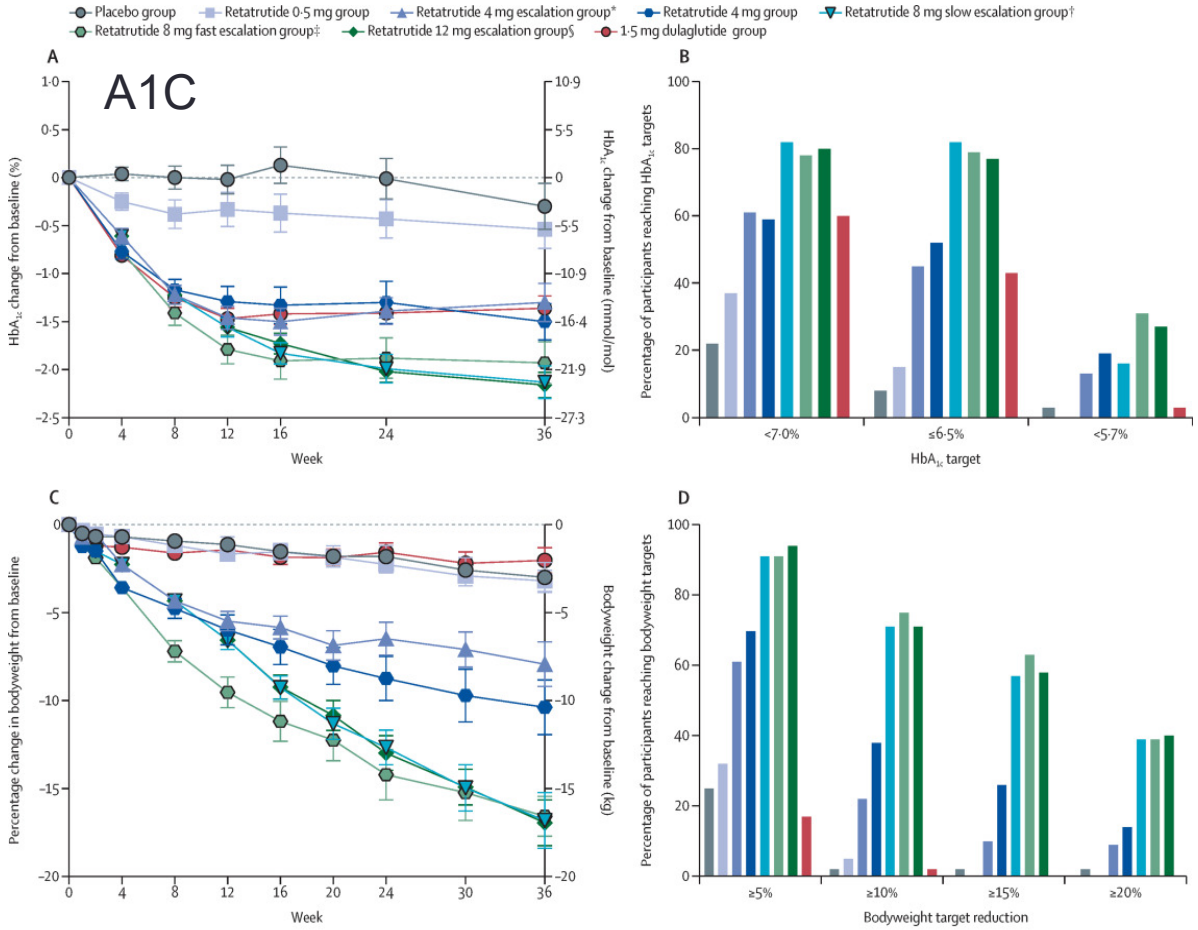
- Phase 3 trials ongoing



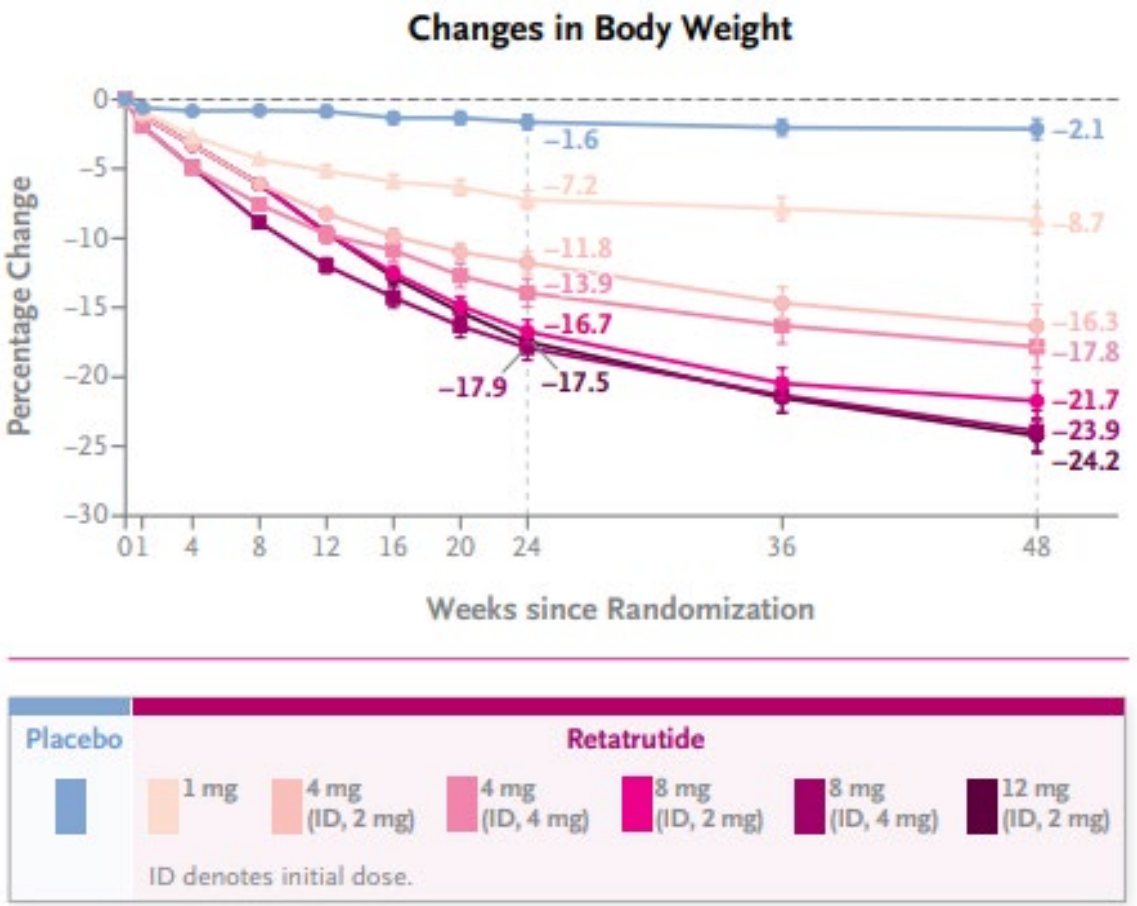
Capozzi M et al Endocrine Review 2018
Rosenstock J et al Lancet Aug 2023

Retatrutide for diabetes and obesity

Diabetes



Obesity



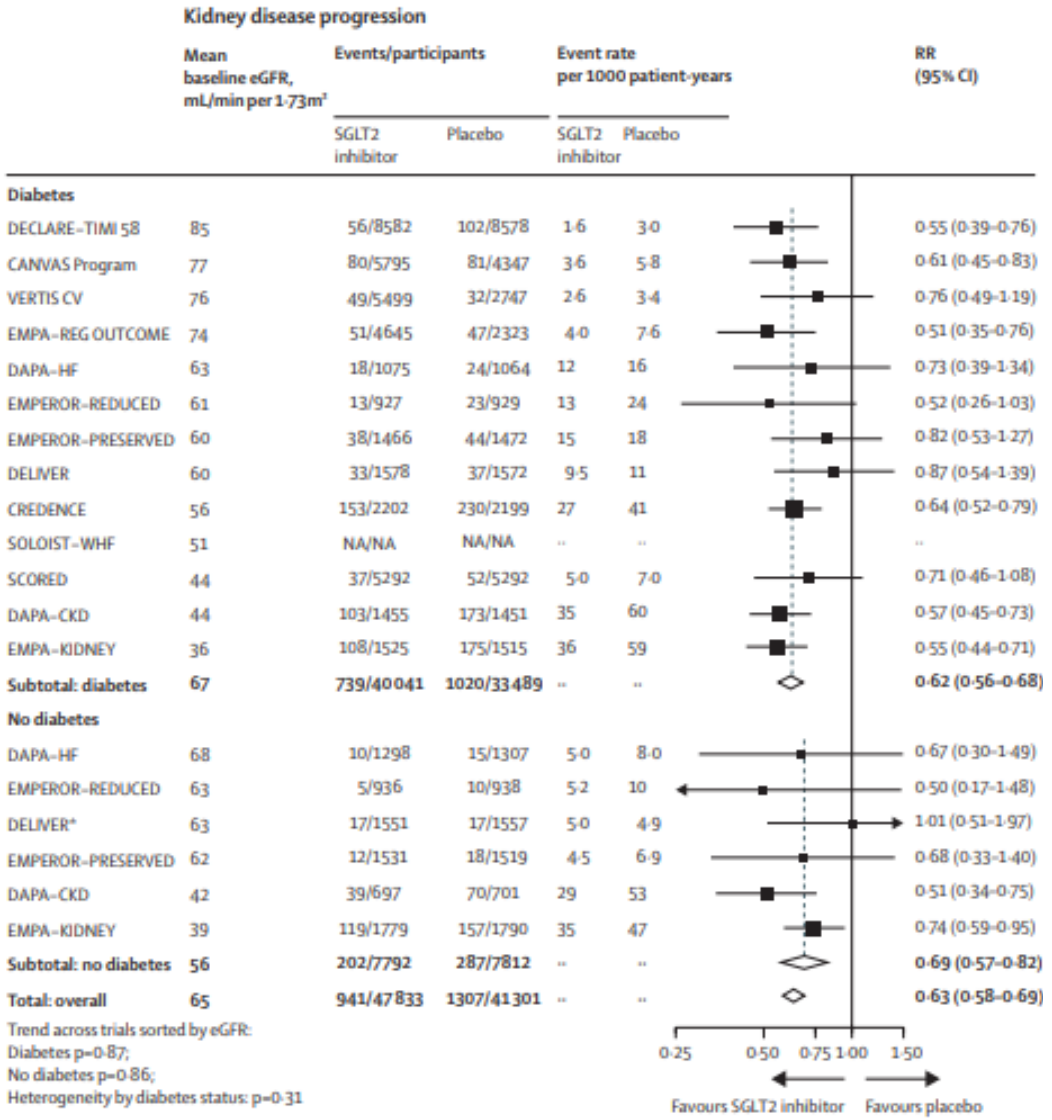
Rosenstock J et al Lancet Aug 2023
Jastreboff AM et al NEJM Aug 2023

SGLT2 inhibitors

	Glucose lowering	CV indication	CKD indication	CV indication without diabetes	CKD indication without diabetes
Canagliflozin	✓	✓	✓		
Dapagliflozin	✓	✓	✓	✓	✓
Empagliflozin	✓	✓	✓	✓	
Ertugliflozin	✓				
Sotagliflozin		✓		✓	
Bexagliflozin	✓				

SGLT2 inhibitors and kidney outcomes

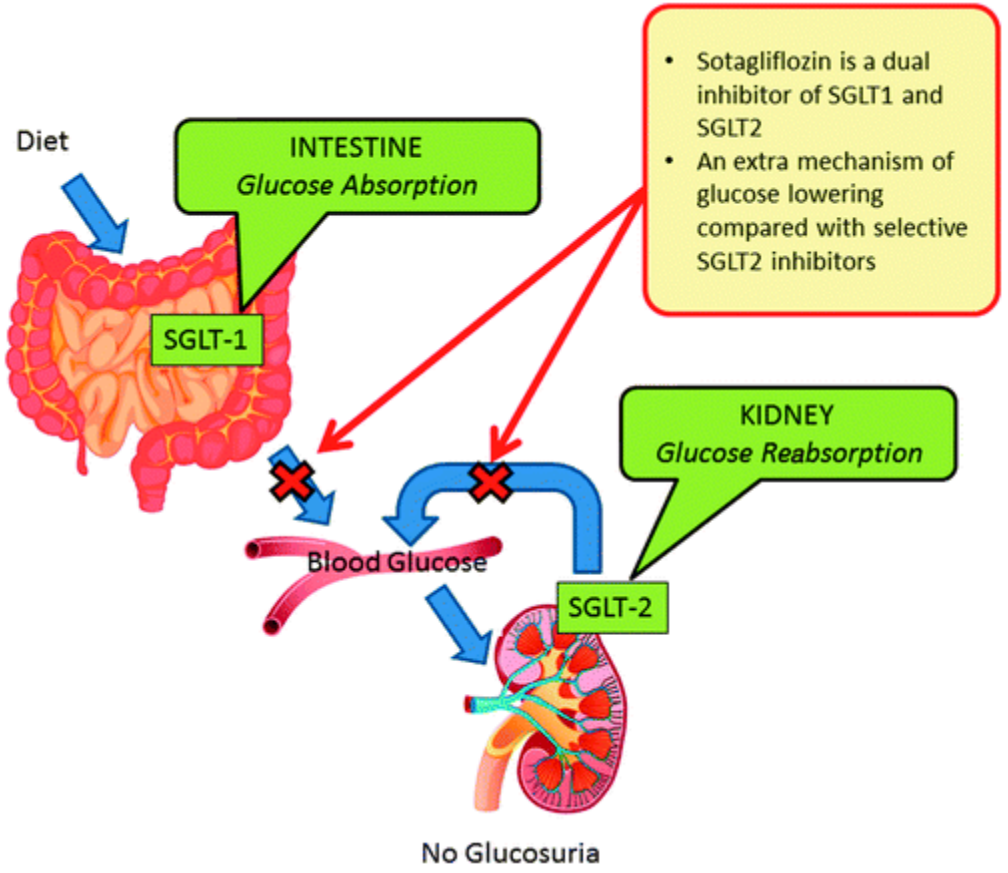
- Large meta-analysis on effects of SGLT2i on CKD progression, as well as cardiovascular (CV) outcomes
- 13 RCTs, 82.7% with diabetes, >90000 pts
- SGLT-2i ↓ risk of CKD progression to a similar degree in people with and without diabetes
- Risk of acute kidney injury or CV death or HF was also lower in patients taking SGLT-2 inhibitors versus those on placebo



Lancet 2022 Nov

Sotagliflozin - SGLT-1 and 2 inhibitor

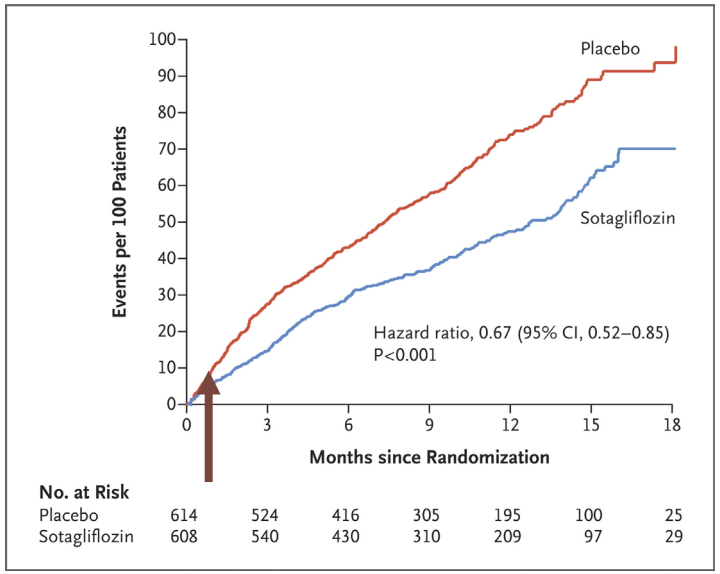
- Initially developed for T1D
- SGLT1 inhibition ↓ glucose absorption in the intestine →blunting of postprandial glycemic excursions and variability → lower need for bolus insulin correction doses → ↓ hypoglycemic risk.
- A1C reduction ~0.5%
- Rejected by the FDA for safety concerns in 2019 (DKA)
- Approved in the EU for use in T1D but not marketed there (Zynquista)



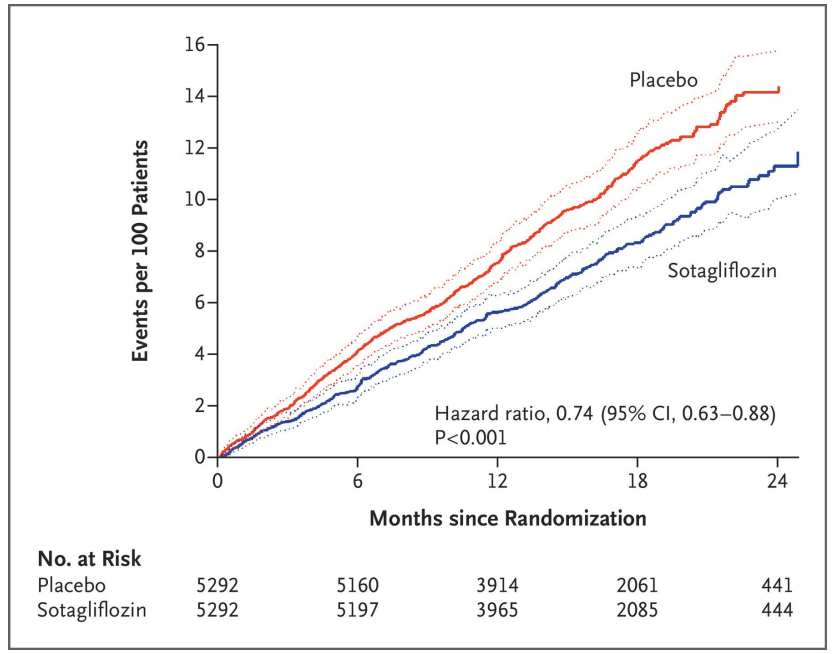
Danne T et al Diabetes Tech Ther 2018

Sotagliflozin for heart failure (SOLOIST-WHF and SCORED)

- Sotagliflozin in T2D and CHF
- Drug initiated during hospitalization for heart failure or within 3 days of discharge (200-400mg/d); N= 1222
- Prim endpoint - Deaths from CV causes and hospitalizations and urgent visits for heart failure



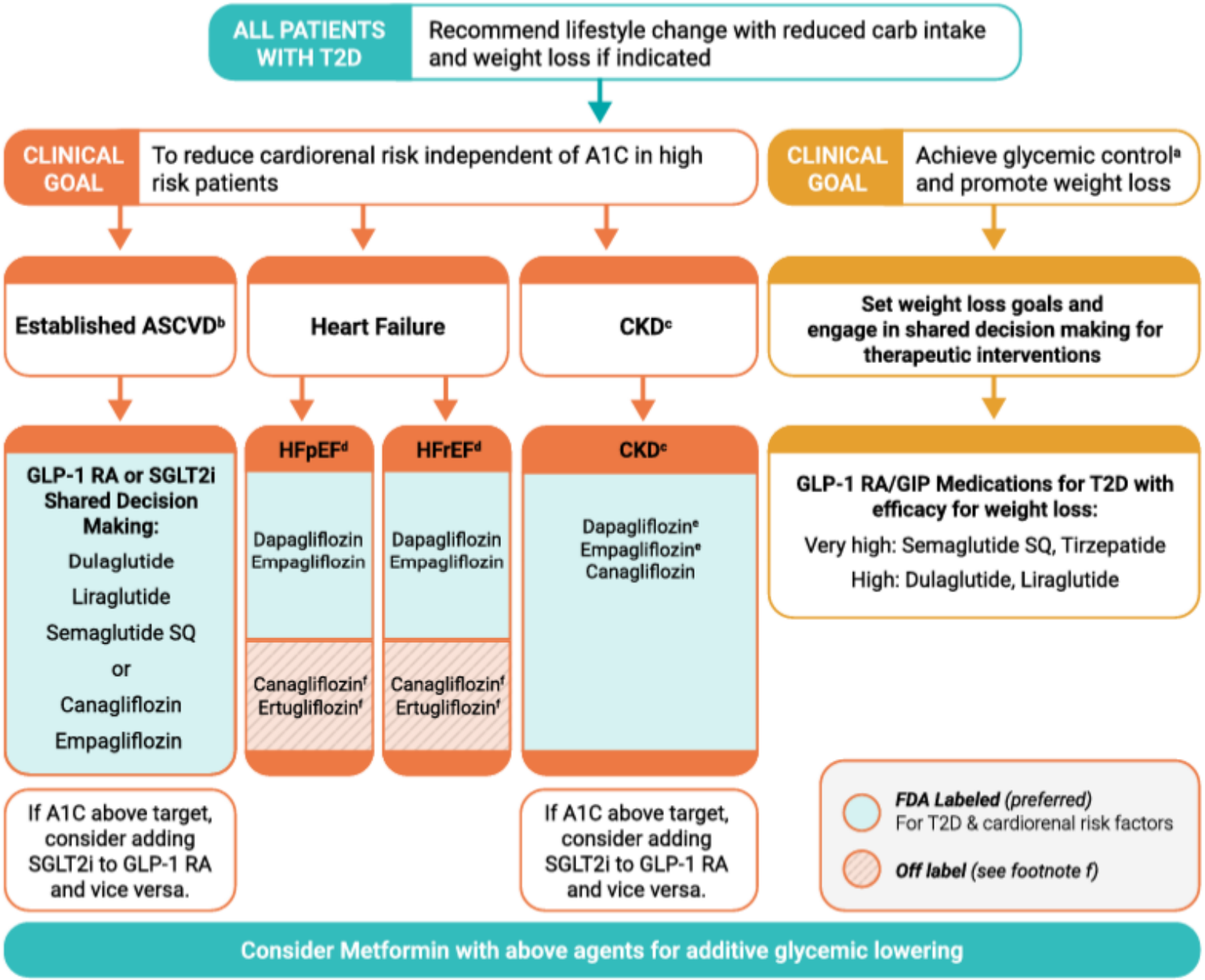
- Sotagliflozin in T2D and CKD (eGFR 25-60) with addition risk factors
- N= 10584
- Prim endpoint - Deaths from CV causes and hospitalizations and urgent visits for heart failure



Bhatt DL et al NEJM 2021; Bhatt DL et al NEJM 2021

Sotagliflozin for heart failure

- FDA approval in May 2023 in patients without or with diabetes
- Marketed as Inpefa



https://www.mct2d.org/resource-library/mct2d-clinical-decision-aid-sglt2-glp1-for-t2d

Scenario

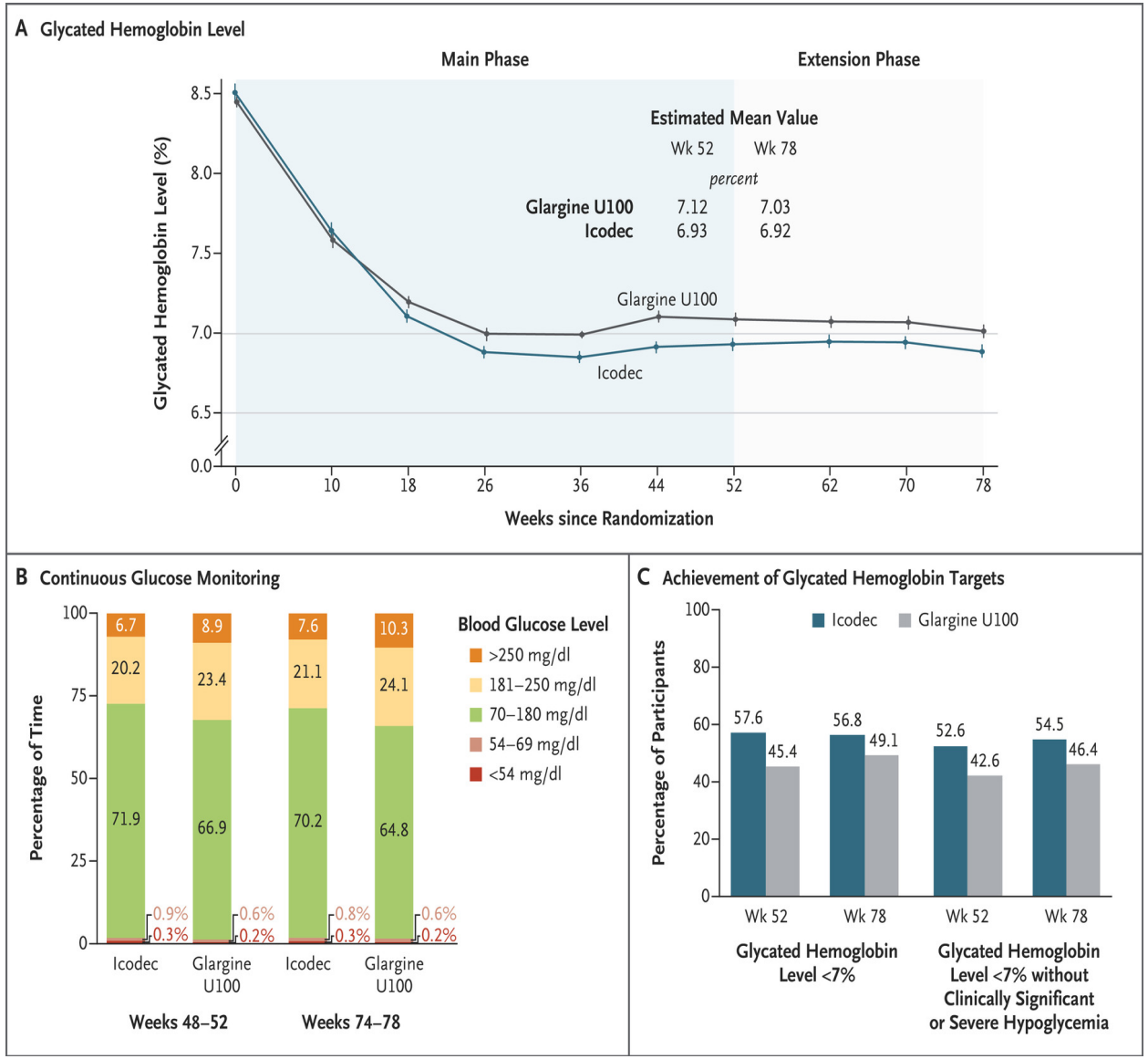
- 36 year old woman with type 2 diabetes; on metformin, empagliflozin, dulaglutide. BMI 37. Most recent A1C is 10.2% (9-10% in the past year)
- Does not want to take daily insulin injections

Once weekly basal insulin – insulin icodec

- Insulin molecule modified so that it tightly binds to albumin
- Provides basal insulin coverage over a full week after a single sc injection
- ONWARDS-1, Phase 3 a study, open label
- N = 984; baseline A1C 7-11%

70u/wk and titrated

10u/day and titrated



Nishimura et al 2021; Rosenstock J et al NEJM July 2023

Continuous glucose monitoring

- Libre 2
  - Requires scanning every 8h
  - Measures every minute and stores every 15 min

- Libre 3
  - No scanning
  - Smaller sensor
  - Sends data every minute
  - Reader available

- Dexcom G6
  - Realtime CGM
  - No scanning
  - Measures every 5 min
  - Sensor, transmitter and receiver/app

- Dexcom G7
  - No scanning
  - Measures every 5 min
  - No transmitter

Revised Medicare coverage for CGM (April 2023)

- Taking insulin (any kind)
- Have type 1 or type 2 diabetes
- Severe hypoglycemia or recurrent non-severe hypoglycemia despite attempts to modify treatment plan
- Document adherence every 6 months

- Medicare requires a DME supplier
- Medicaid – some plans still ask for 3+ injections of insulin, but pharmacy benefit

Scenario

- 51 year old male presents to you for an annual exam. On levothyroxine for hypothyroidism.
- A1C 7.6%
- BMI 24.6
- Started metformin but A1C in 3 months was 9.5% (100% adherence)
- Electronic consultation is placed

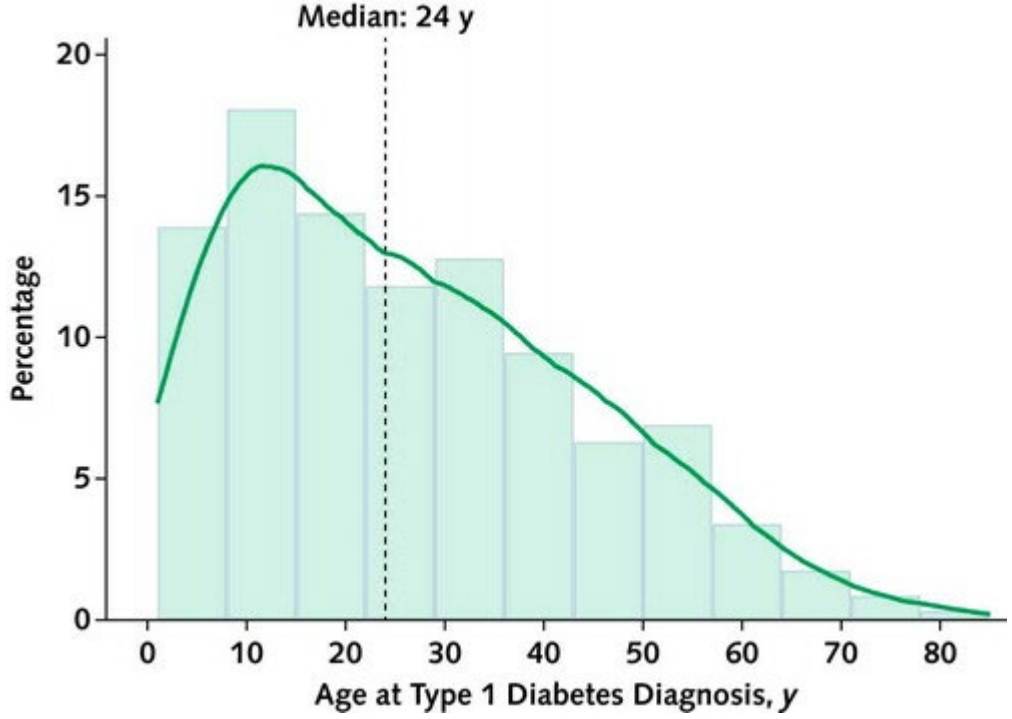
- Recommendation – Check GAD65abs →positive

https://jamanetwork.com/journals/jama/fullarticle/2810571

Age at Diagnosis in U.S. Adults With Type 1 Diabetes

Michael Fang, PhD, MHS, Dan Wang, MS, Justin B. Echouffo-Tcheugui, MD, PhD, Elizabeth Selvin, PhD, MPH

- National Health Interview Survey - nationally representative survey of the noninstitutionalized U.S. population
- Survey cycles from 2016-2022
- N = 947 adults
- Median age of T1D diagnosis is ~24y
- Men are diagnosed later in life than women
- Racial/ethnic minority adults diagnosed later than non-Hispanic white adults (age 26-30y)
- 37% people reported diagnosis with T1D after age 30



Fang M et al Ann Int Med 2023

Semaglutide in T1D?

CORRESPONDENCE

Semaglutide in Early Type 1 Diabetes

September 7, 2023
N Engl J Med 2023; 389:958-959

- Newly diagnosed adults with antibody confirmed T1D
- N=10
- All on basal -bolus insulin
- Semaglutide weekly initiated 0.125 → 0.5mg wkly
- Prandial insulin eliminated in all, basal insulin in 7 pts over 1 year
- Rise in C-peptide

Insulin affordability and pricing

- Since 2002, the cost of insulin has tripled
- Insulin rationing is very common in the US (71% are under age 65)

- As of early 2023, price of insulin under the Inflation Reduction Act of 2022, is capped at $35/ type of insulin for Medicare beneficiaries

- For the uninsured, underinsured people-
- Insulinaffordability.com → coupon for $35 insulin (via Lilly)

Key takeaways

- Type 2 diabetes management in 2023 is based on individual patient characteristics, assessing cardiorenal risk
- GLP-1 RAs and GLP1/GIP RAs are highly effective newer agents for weight loss but shortages are limit use in late 2023
- Sotagliflozin an SGLT1/2 inhibitor is approved for use in patients with diabetes and heart failure
- Once weekly insulin may become available in the near future
- Continuous glucose monitoring technology is now an important aspect of management of type 2 diabetes
- Caps on insulin pricing offer hope for our patients

KEEP
CALM
AND
CARRY
TESTING STRIPS, ALCOHOL SWABS,
NEEDLES, GLUCOSE MONITOR,
INSULIN AND,
SNACKS.

THANK YOU!