SGLT2 Inhibitors and GLP-1 Agonists: When Should I use them?

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Disclosure

Dr. Clement receives support as a Principal Investigator for a study drug for treatment of NASH, funded by Novo Nordisk. The drug is a GLP-1 agonist.

NASH is not discussed in this presentation

Case Study

- 64 y/o female with no prior h/o diabetes
- PMH: Obesity,
- Syncope while power walking at local shopping mall
- Risk factors for heart disease: high BMI, strong FH for heart disease
- Father died age 55 from complications of MI (possible diabetes)
- P.E.: Height 5’8”, 90.6 kg, BMI 30, heart rate irregular
- Labs:
  - A1C 6.8 FBG 186 mg/dl
  - LDL 246,HDL 41, TG 182
- Diagnosis: STEMI, Multivessel CAD, Aortic Stenosis, Newly discovered type 2 DM

Link Between DM and Heart Disease

- Heart disease is #1 Complication
  - ASCVD
  - MI
  - Heart Failure
  - Sudden Death

Cause for increased CVD risk?

- Metabolic syndrome
- Iatrogenic: Hypoglycemia→ sudden death
- Possible Drug effects?

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Additional copies are available from:

Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
E-mail: druginfo@fda.hhs.gov
Fax: 301-847-8714
(Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

Guidance for Industry. Center for Drug Evaluation and Research (CDER) 2008 Dec

FDA Mandate

- Before submission of new drug application (NDA)/biologic license application:
  - Sponsors should compare the incidence of important cardiovascular events occurring w/ the investigational agent to the incidence of the same types of events occurring w/ the control group

Guidance for Industry. Center for Drug Evaluation and Research (CDER) 2008 Dec

Indiana Jones and the Last Crusade, 1989

Are Diabetes RX's cardioprotective?

- **NO**:
  - Insulin
  - SU's
  - DPP4 inhibitors

- Potential Benefit: ? Metformin

- **YES**:
  - Some SGLT-2 Inhibitors
  - Some GLP-1 agonists

Cardiovascular Disease and Risk Management

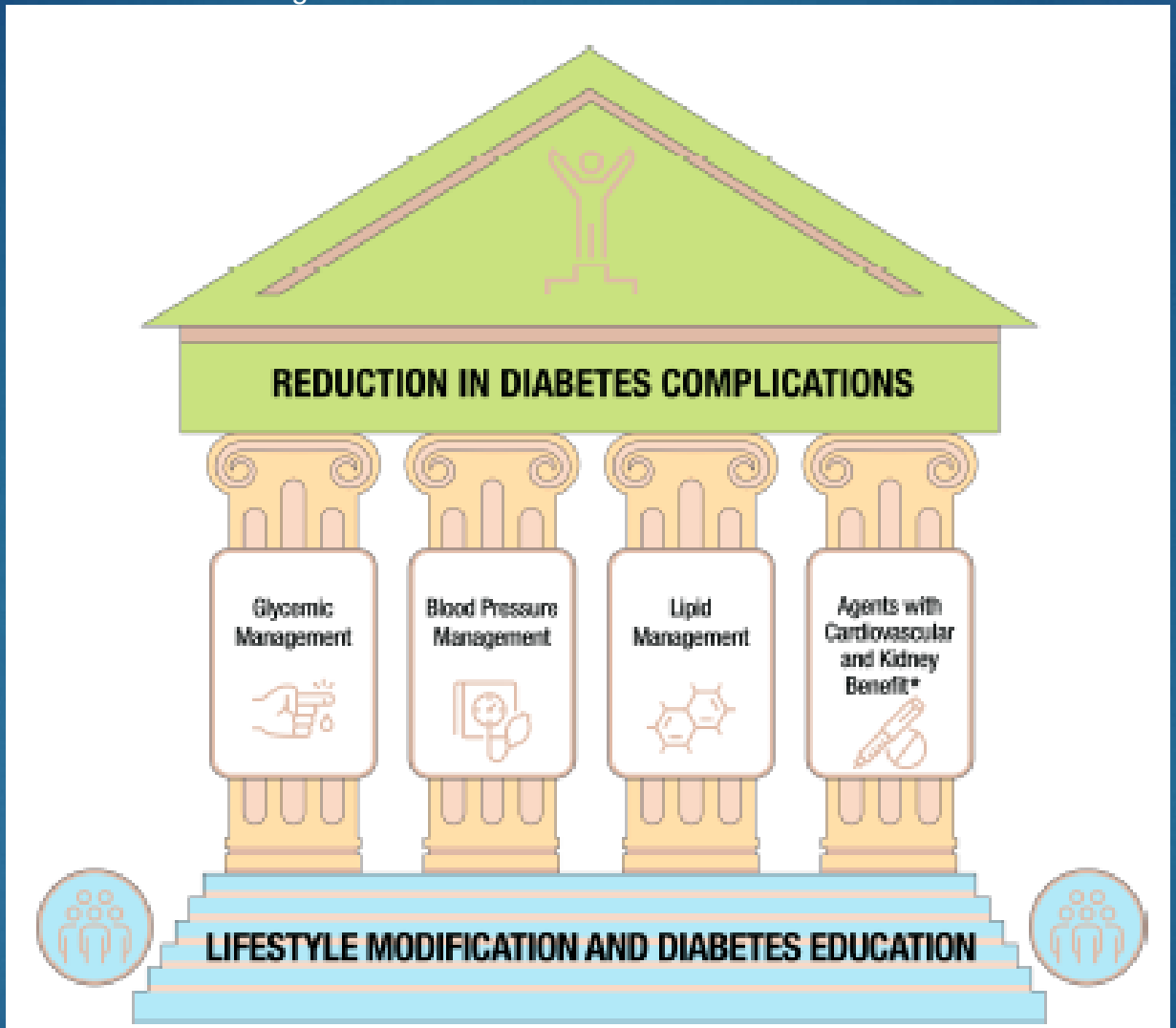


Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

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

American Diabetes Association Guideline

- **Among people w/ Type 2 diabetes who have established atherosclerotic CV disease or established kidney disease, a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist w/ demonstrated CV disease benefit is recommended as part of the comprehensive CV risk reduction and/or glucose lowering regimens. Evidence Level A**

Outline

- Link btw DM and ASCVD
- 2008 FDA Mandate
- **SGLT-2 Inhibitors**
- GLP-1 Agonists
- When to use new Rx's?

SGLT-2 Inhibitors

Sodium-glucose cotransporter 2 Inhibitor

- How do SGLT-2 Inhibitors Work?
- How well do they lower glucose?
- Are they cardio-protective?
- Side Effects
- Best patient to use an SGLT-2 Inhibitor?

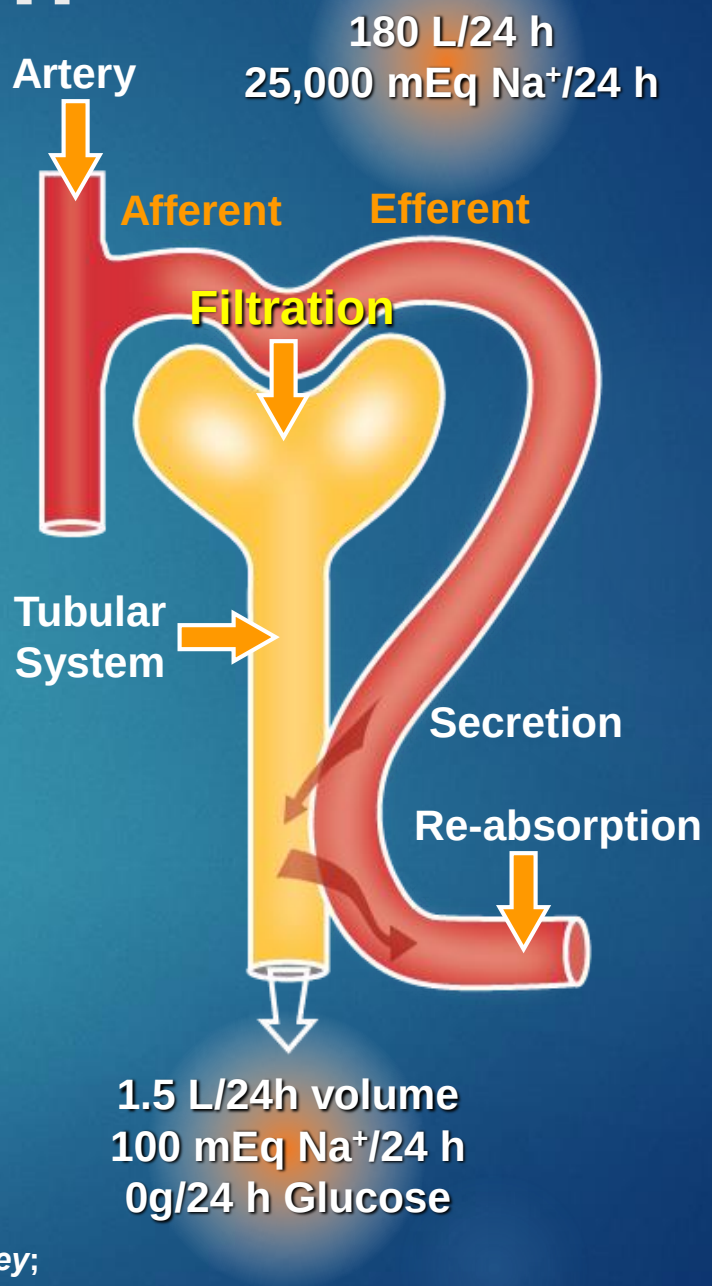
The Renal Corpuscle and Glomerular Filtration

- Glucose, water, salts, small metabolites, and other small molecules are filtered and collect in Bowman's space
- Filtration is a process of passive diffusion
- The total amount of a substance (glucose) filtered is proportional to its plasma concentration

Fawcett. DW. *A Textbook of Histology*. 11th ed. WB Saunders Co.; 1986:757-759

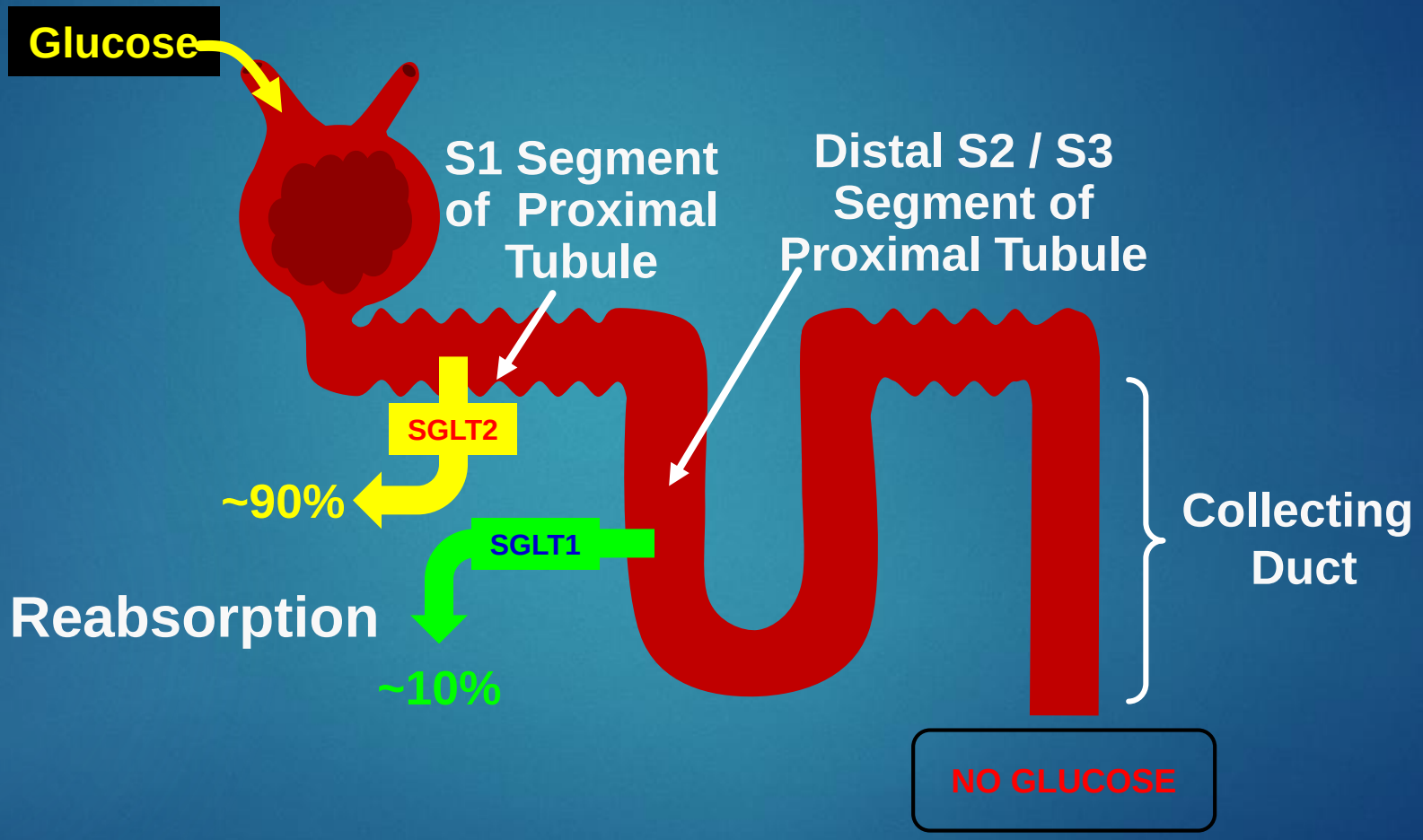
Glomerular Filtration

- 125 mL of filtrate formed/min (180 L/24 h)
  - Urine output 1.5 L/24 h
- 25,000 mEq of Na^+ filtered
  - Urine Na^+ excretion
  - 100 mEq/L
- **144 g glucose filtered/24 h**
  - **Urine glucose excretion = 0**
- Because re-absorption occurs



Mount DB, Yu ASL. In: Brenner BM, ed. *Brenner and Rector's The Kidney*; Abdul-Ghani M and DeFronzo R. *Endocr Pract*. 2008;14:782-90.

Renal Handling of Glucose in a Non-Diabetic Individual



Abdul-Ghani M and DeFronzo R. *Endocr Pract*. 2008;14:782-90.

Selective SGLT2 Inhibitors

- Inhibition of SGLT2-mediated glucose re-absorption in the renal proximal tubule leads to increased glycosuria and reduced plasma glucose levels

- Mechanism of action is independent of insulin resistance or the severity of beta-cell dysfunction

Approved SGLT-2 Inhibitors

- Canagliflozin (Invokana)
- Empagliflozin (Jardiance)
- Dapagliflozin (Farxiga)
- Ertugliflozin (Steglatro)
- Brenzavvy (Bexaglifloxin)

- Class Effect: SGLT-2 Inhibitors reduce A1C by ~0.7 – 1 %

Indications of SGLT-2 I's

Drug	Reduce Major CV Events	Reduce Heart Failure Events	Reduce risk of Renal events from DM nephropathy
Canagliflozin (Invokana)	**Yes**	No	**Yes**
Empagliflozin (Jardiance)	**Yes**	**Yes**	**Yes**
Dapagliflozin (Farxiga)	**Yes**	**Yes**	**Yes**
Ertugliflozin (Steglatro)	No	No	No
Brenzavvy (Bexaglifloxin)	No	No	No

Dose of SGLT-2 I's for Renal Disease

Drug	Normal Renal Function	GFR 30-60	GFR < 30	Hemodialysis or Peritoneal Dialysis
Canagliflozin (Invokana)	100 mg → 300 mg	100 mg GFR 45-60	Avoid Use GFR < 45	Avoid Use
Empagliflozin (Jardiance)	10mg →25mg	10 mg	10 mg GFR 20-30 (off label)	Avoid Use
Dapagliflozin (Farxiga)	5 mg→ 10mg	10mg for GFR 25-45	10 mg (to GFR 25)	Avoid Use
Ertugliflozin (Steglatro)	5mg→15mg	15mg GFR 45-60	Avoid use	Avoid Use
Bexaglifloxin (Brenzavvy)	20mg	20mg	Avoid Use	Avoid Use

Benefits/Limitations of SGLT-2 Inhibitors

- Benefits:
  - Lowers glucose in a *glucose dependent* fashion
  - Modest weight reduction
  - Effect is additive to metformin
  - CV benefits
  - Renal benefits

- Limitations:
  - Effectiveness is dependent on normal GFR
  - Yeast/peroneal infections (Fournier's gangrene)
  - Cases of renal dysfunction, dehydration, near-syncope in elderly
  - Concerns regarding PVD and limb ischemia

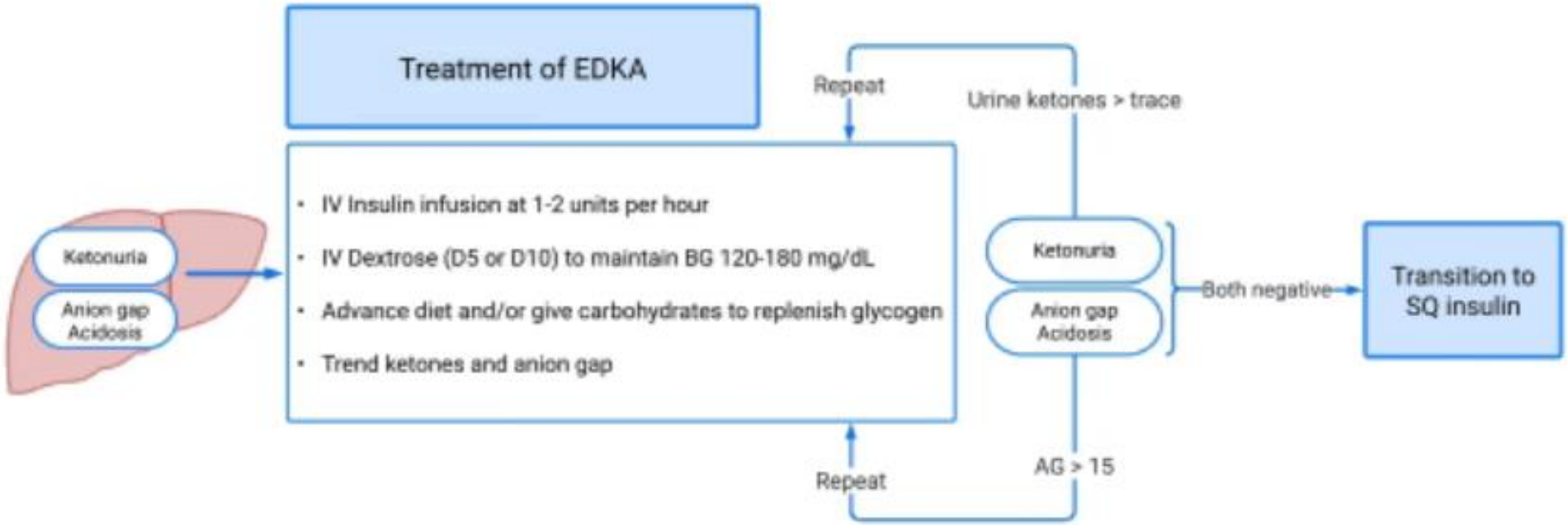
Adverse Events

- Female Mycotic Infections
- UTI, urosepsis
- eDKA (risk factors: low c-peptide level, low carb diet)
- Must withhold drug for 3-5 days prior to surgery
- Increased lower limb amputation (banagliflozin, bexagliflozin)
- Volume depletion
- Necrotizing Fasciitis of the Perineum

Contraindications

- Type 1 DM
- ESRD
- Hypersensitivity to Rx

Euglycemic Diabetic Ketoacidosis (EDKA)
How to Treat?



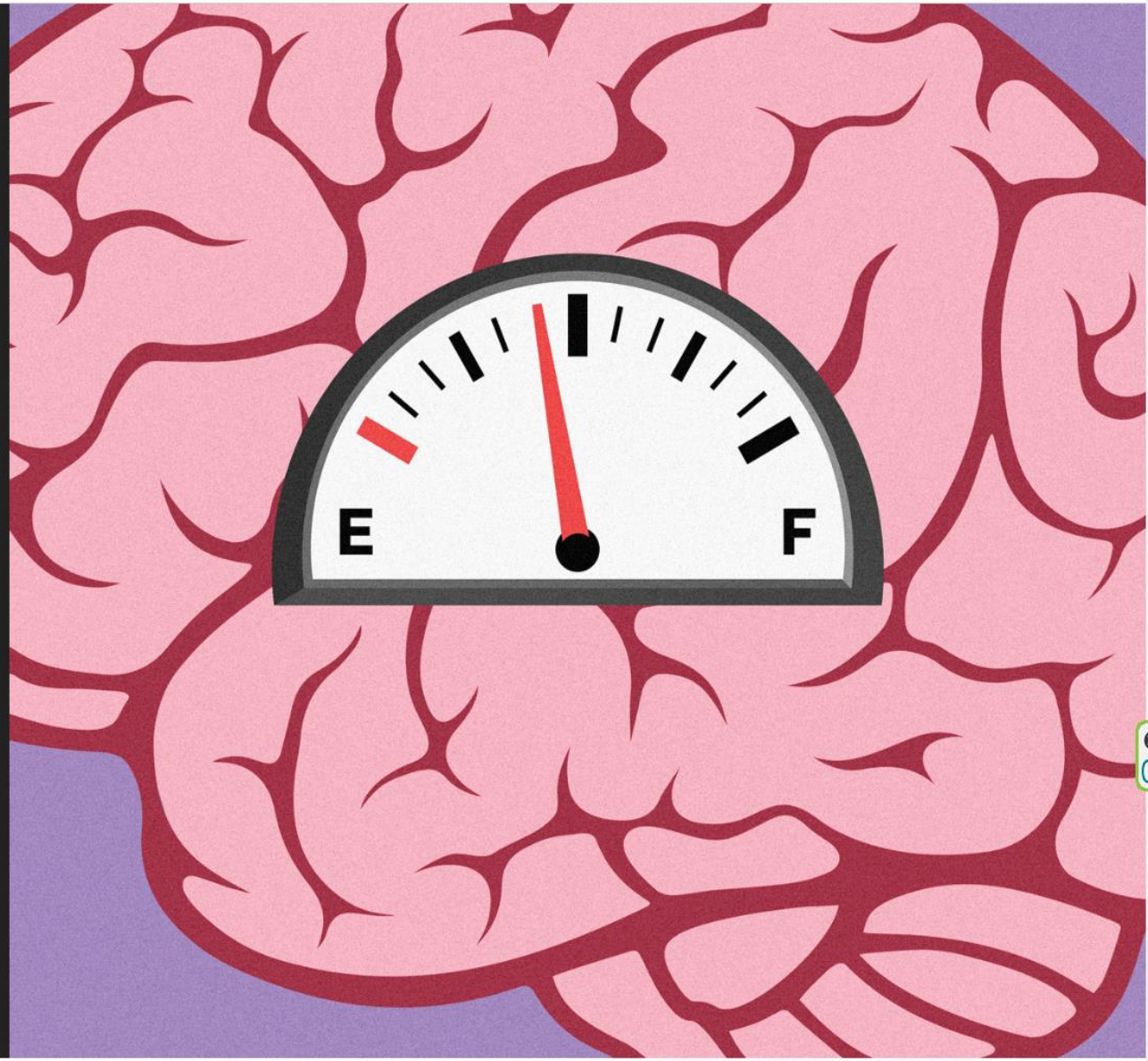
Chow, Clement, Garg. BMJ 2023 (submitted)

GLP-1 Agonists

- How do GLP-1 agonists Work?
- Are they cardio-protective?
- Side Effects
- Best patient to use a GLP-1 agonist?

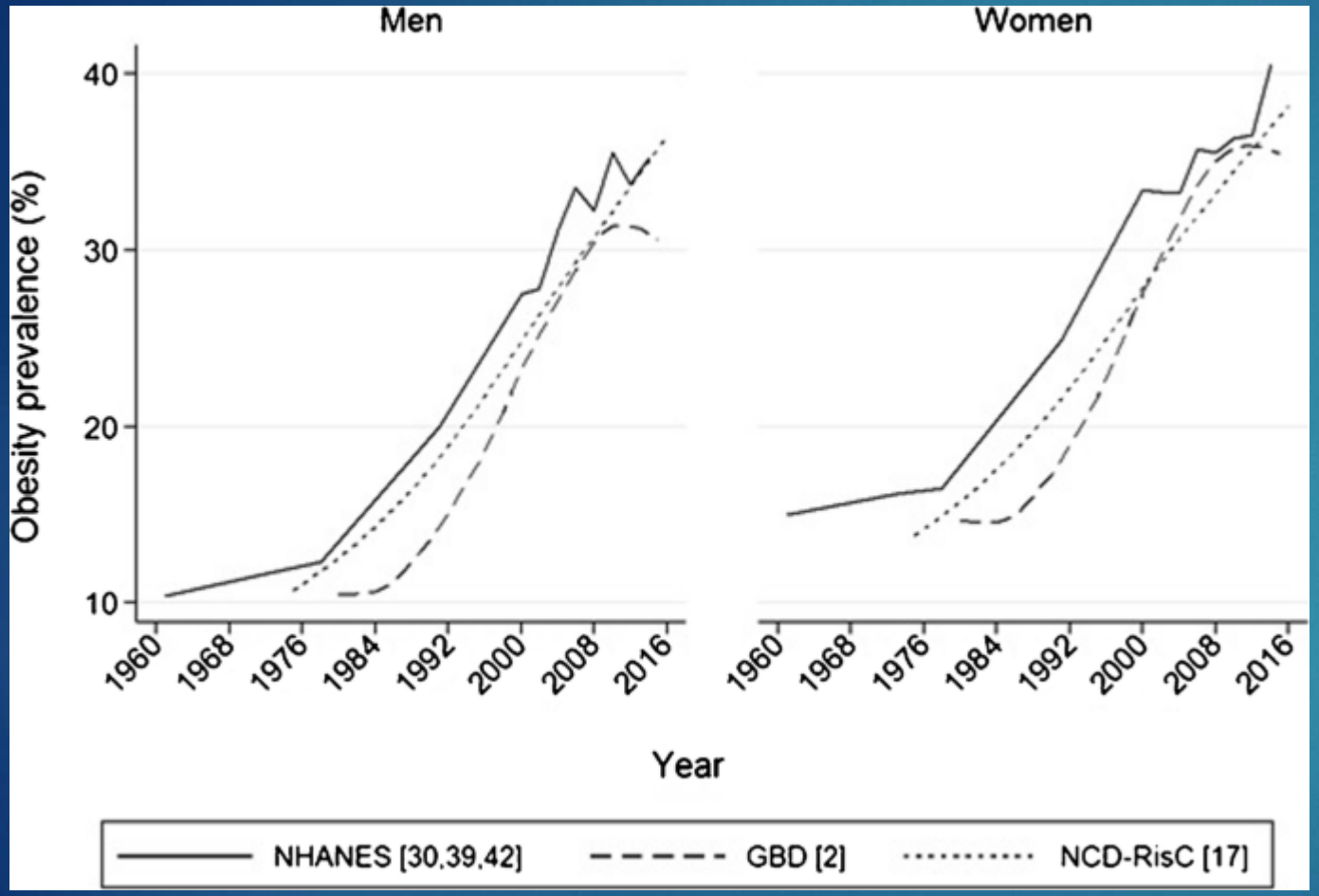
Ozempic Settles the Obesity Debate: It's Biology Over Willpower

Weight-loss drugs affect the brain in ways that help researchers understand how the body regulates weight



EMIL LENDOF/THE WALL STREET JOURNAL

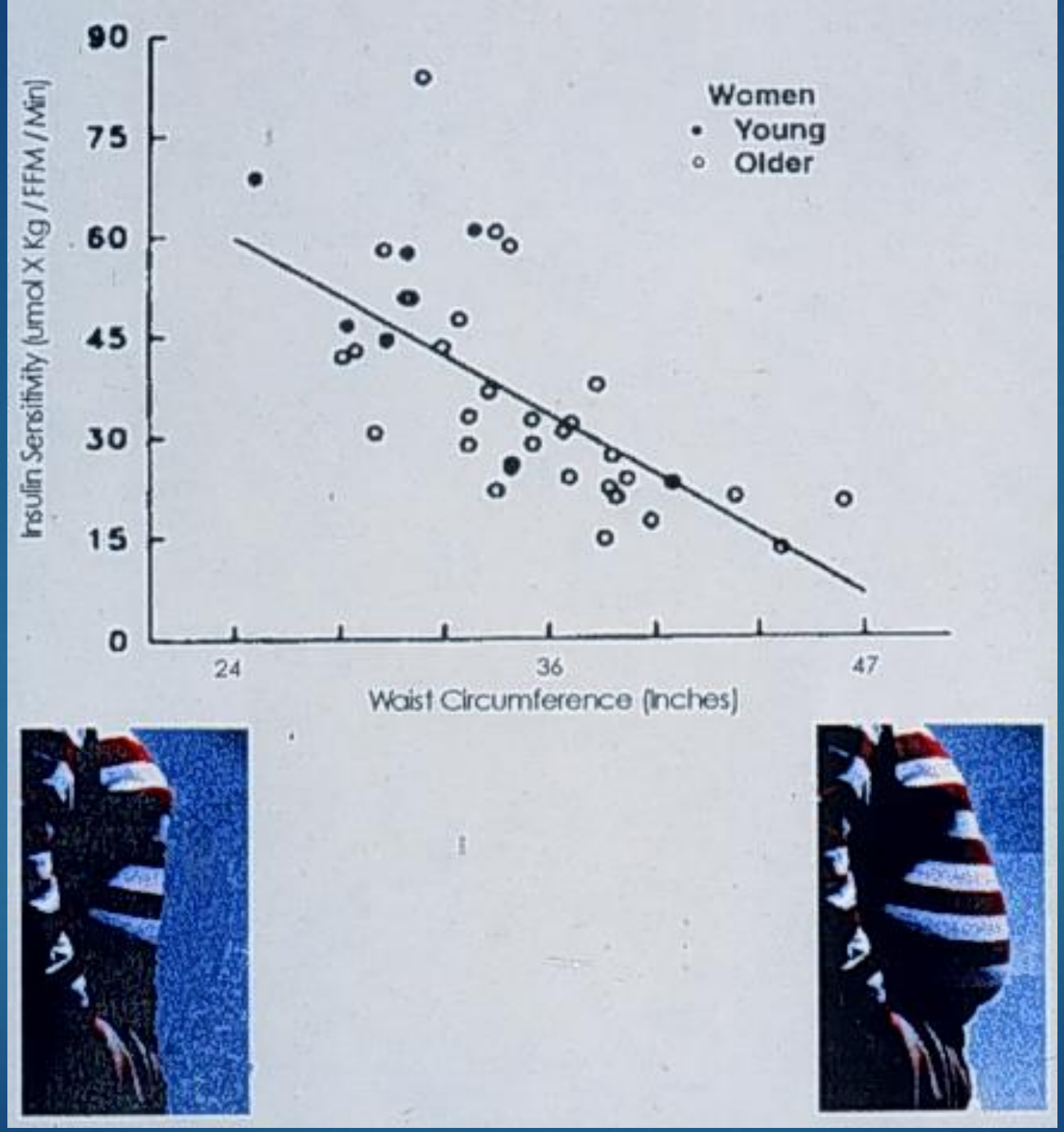
Adult Obesity Trends



Current Prevalence in US: 42%

Inoue et al. Curr Obesity Reports (2018) 7:276-288

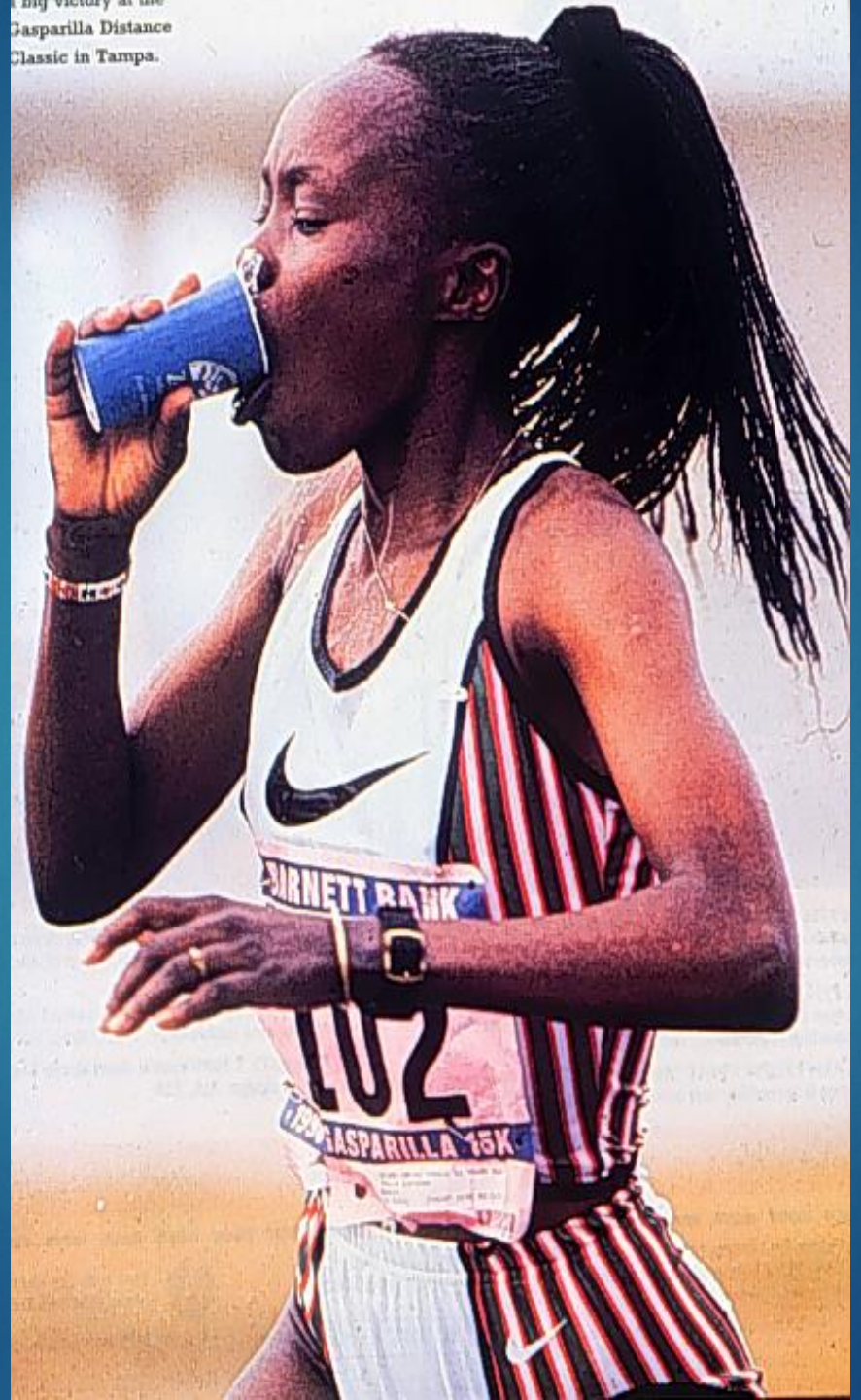

Sweet 'N Low works wonders on a hangover.



Kohrt et al. Diabetes 42:273,1993


Sweet 'N Low works wonders on a hangover.

Gasparilla Distance
Classic in Tampa.

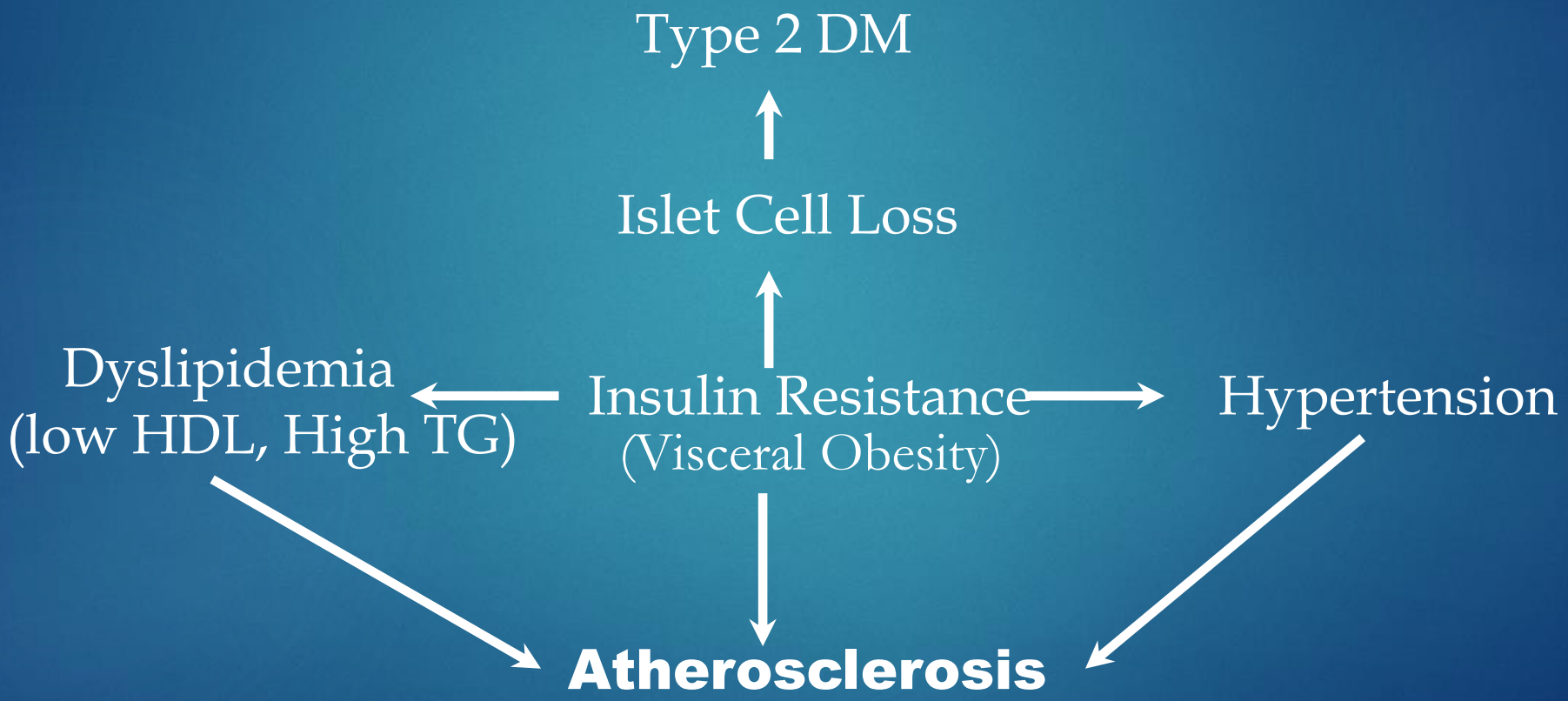


Insulin Resistance and Visceral Fat in Type 2 DM

- Insulin Resistance is an acquired abnormality related to an accumulation of visceral adipose tissue in genetically predisposed persons.

- Visceral Fat releases substrates (e.g., FFA), inflammatory mediators (e.g.TNF alpha) that impair insulin action.

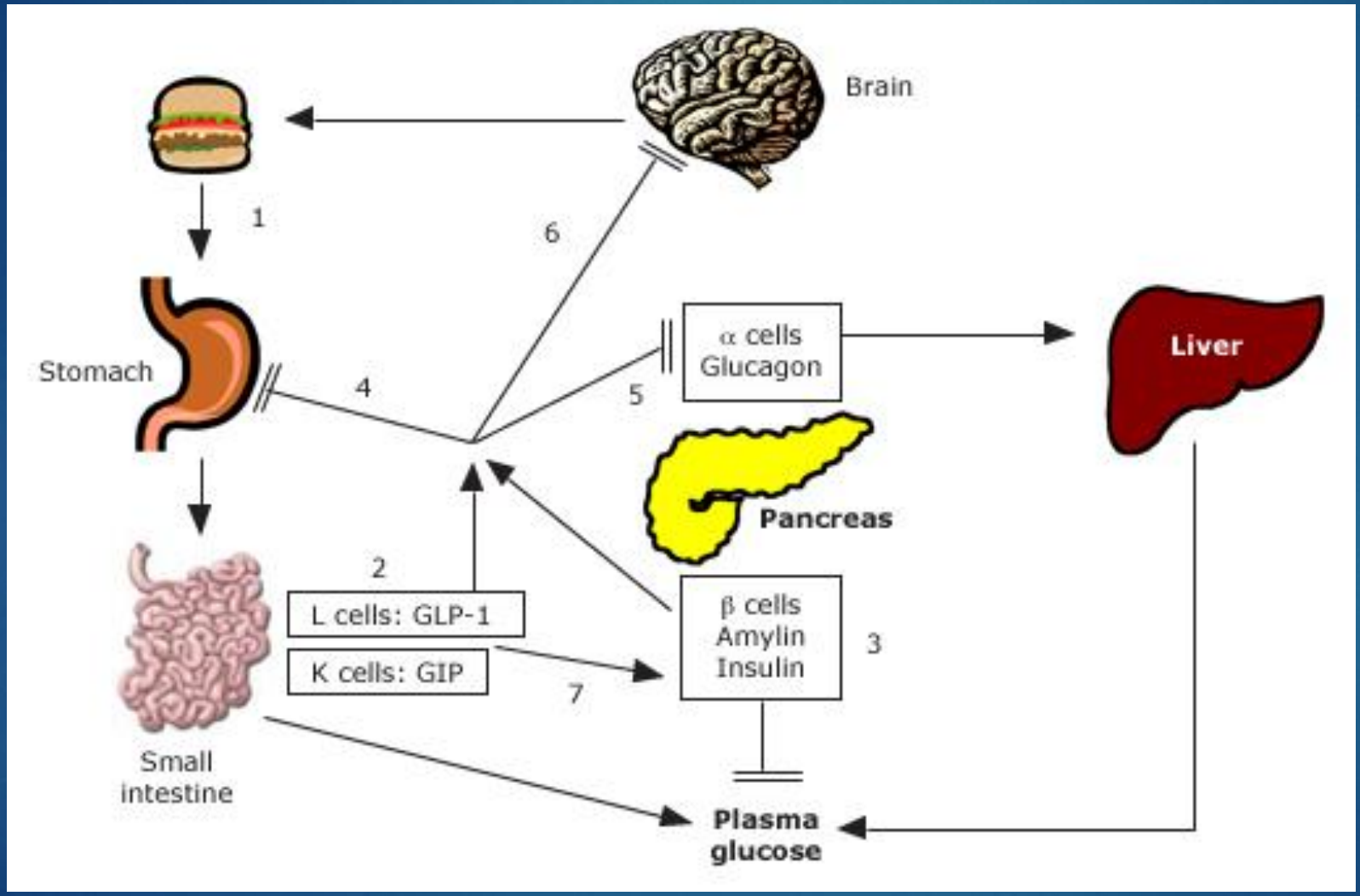
Metabolic Syndrome (Insulin Resistance Syndrome)



Approved GLP-1/Dual Receptor Agonists

Drug	Receptor	Reduce Major CV Events	Reduce CHF Events	Reduce Renal Events
Dulaglutide (Trulicity)	GLP-1	**Yes**	No	**Yes**
Semaglutide (SC) (Ozempic)	GLP-1	**Yes**	No	**Yes**
Semaglutide (PO) (Rebelsus)	GLP-1	No	No	No
Liraglutide (Victoza)	GLP-1	**Yes**	No	**Yes**
Exenatide (Bydureon BCISE)	GLP-1	No	No	No
Tirzepatide (Mounjaro)	GLP-1 GIP	?	?	?

Multihormone Regulation of Meal Incretin Effect



GLP-1 agonists lower A1C .5-2.0%

Weight loss 5-20%

UpToDate 2023

Adverse Effects of GLP-1/Dual Agonists

- Risk for C-cell tumors
- Acute Kidney Injury
- Gallbladder disease
- Pancreatitis
- GI events
  - Nausea
  - Vomiting
  - Diarrhea
  - Ileus

Monitoring

- Glycemic Control/hypoglycemia
- Kidney Function
- Screening Retinal Exam (for semaglutide)
- Hypersensitivity (rare)

Contraindications of GLP-1 and Dual agonists

- h/o pancreatitis
- Type 1 DM
- Severe GI disease or gastroparesis
- Personal or FH of medullary thyroid cancer or MEN2
- eGFR < 30 (Lixisenatide, exenatide)

Outline

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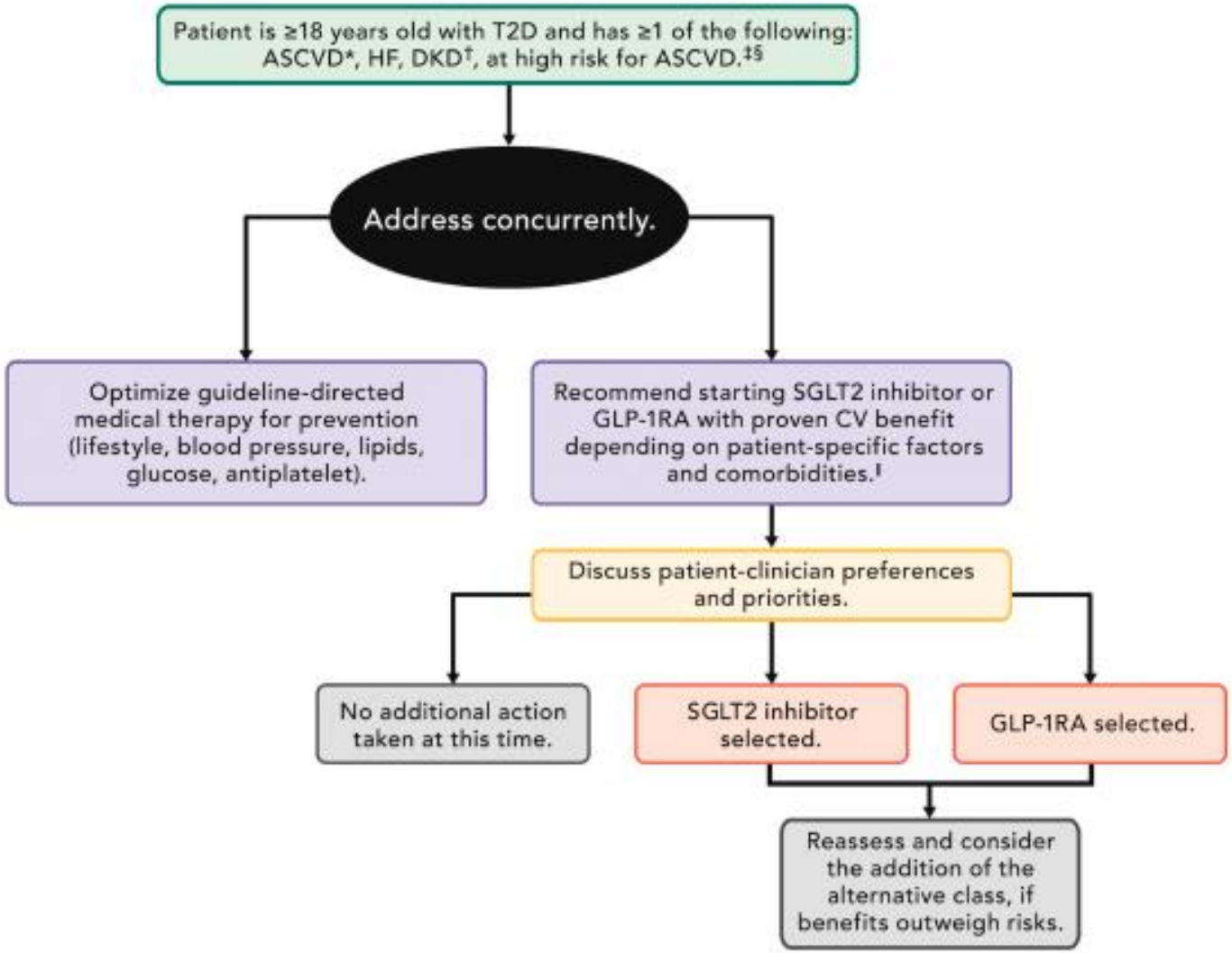
- 2008 FDA Mandate
- SGLT-2 Inhibitors
- GLP-1 Agonists
- **When to use new Rx's?**



Approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy

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

My patient (continued)

- Diagnosis: Newly discovered type 2 DM associated with ischemic and valvular heart disease
- Covered diabetes with IV insulin and transitioned to daily glargine and premeal lispro
- Home diabetes Rx:
  - Lantus 15 units q AM
  - Metformin 500 mg bid
  - Empagliflozin 10 mg daily

Acknowledgements

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- To Piedmont Health Care
- To Stephen Leichter MD
- To my patient who allowed me to tell her story