Cardiovascular effects of non-insulin diabetic medications

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LICKING MEMORIAL HEALTHSYSTEM

Objectives

- Discuss the relationship between diabetic control and cardiovascular complications.
- Review different classes of non-insulin diabetic medications and their mechanisms of action
- Discuss cardiovascular effects of non-insulin diabetic medications

Cardiovascular: ☐ WNL ☒ HTN ☐ CAD ☐ MI
☐ CP/ angina ☐ History of CHF ☐ Arrythmia: _____
☐ Valve DZ/ MVP: _____ ☐ Pacer/ AICD
☐ CABG ☐ Stent ☐ PVD ☐ Depend edema

MET: 1 (Eat/ dress) 2 (Walk/ cook) 3 (Walk 1-2 blocks) 4 (Rake/ garden) 5 or greater (Climb 1 flight)

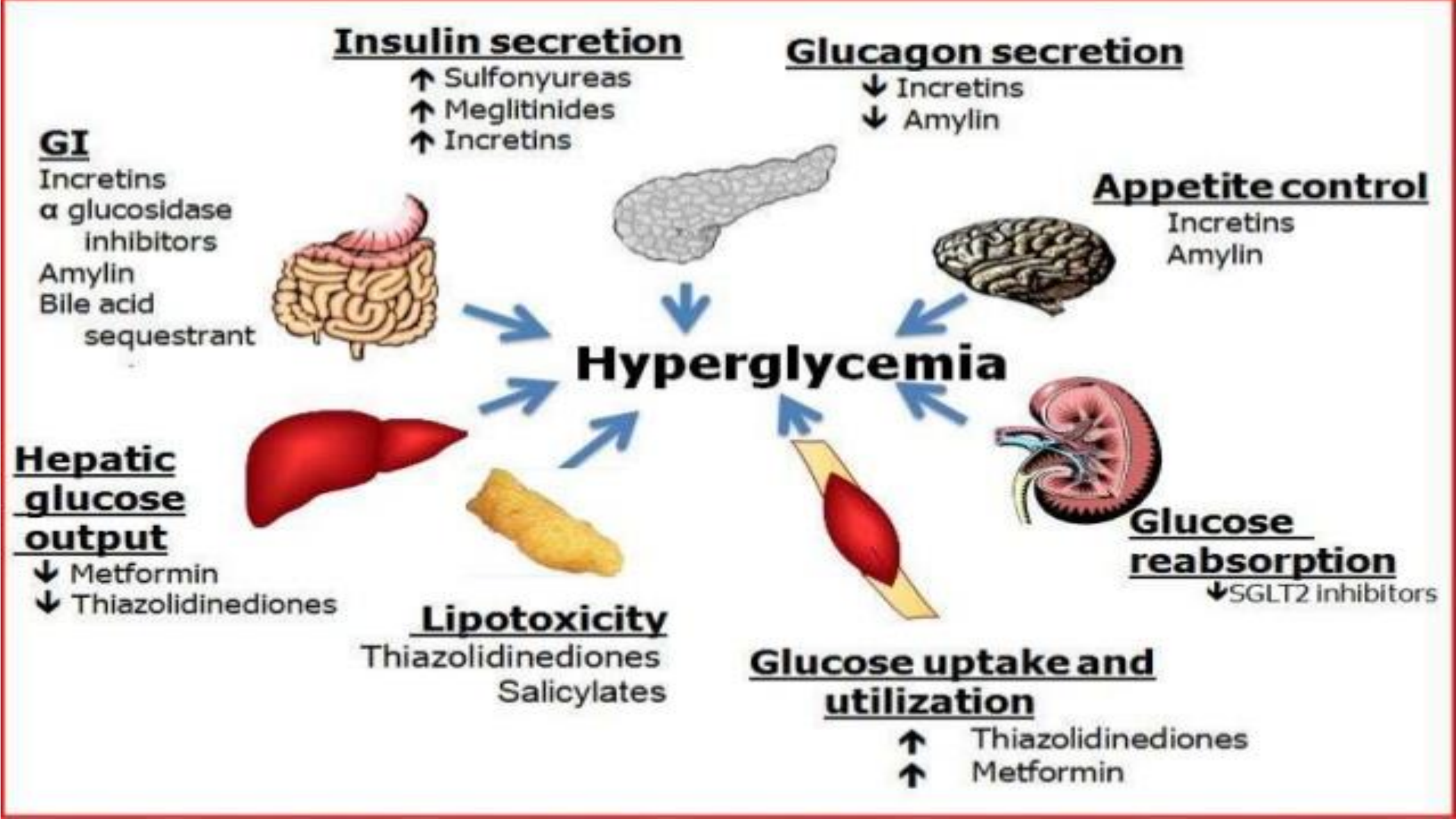
Respiratory: ☐ WNL ☐ Recent URI ☐ Pneumonia
☐ Smoker___ppd, times _____years ☐ Quit: _____
☐ abstained from smoking pre op
☐ COPD/ Emphysema/ Chronic Bronchitis ☐ Asthma
☐ Sleep Apnea ☐ Home CPAP ☐ Home O2

GI/ Hepatic: ☐ WNL ☐ Hiatal hernia/ GERD ☐ PUD
☐ Crohn's ☐ Hepatitis ☐ Cirrhosis ☐ Ascites
☐ Alcohol consumption: _____

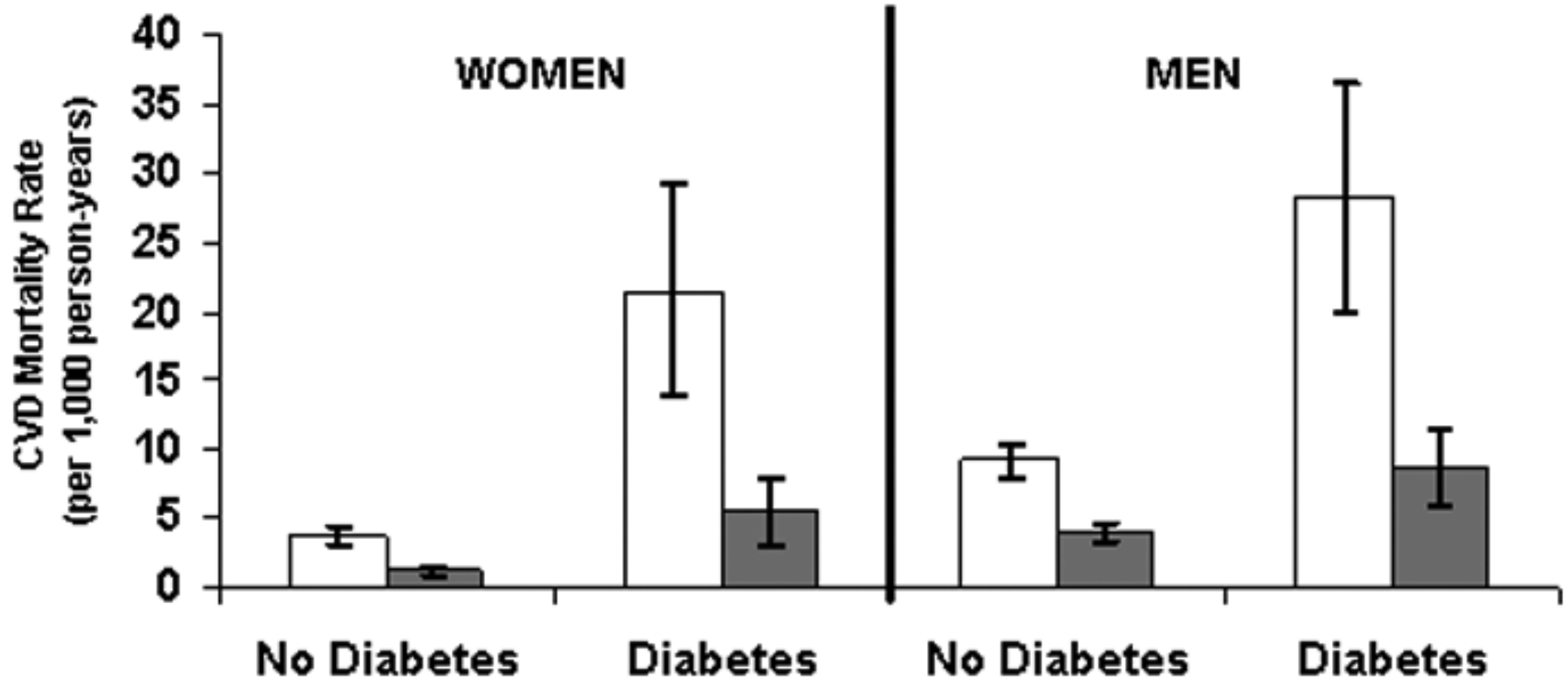
Endocrine/ Metabolic/ Hematologic/ Renal: ☐ WNL
☐ DM I ☒ DM II ☐ DM with complications
☐ Hyperthyroid ☐ Hypothyroid ☐ Sickle cell disease
☐ Hemophilia ☐ Coagulopathy ☐ Renal stones
☐ Anemia ☐ ARF ☐ CRF
☐ Dialysis / last: _____

Neuro/ Musculoskeletal: ☐ WNL ☐ Seizure ☐ Stroke ☐ TIA
☐ Neuromusc disease/ MS/ MD/ MG ☐ Neuropathy ☐ Dementia

Last dose: _____


Insulin secretion
↑ Sulfonyureas
↑ Meglitinides
↑ Incretins
Glucagon secretion
↓ Incretins
↓ Amylin
GI
Incretins
α glucosidase inhibitors
Amylin
Bile acid sequestrant
Appetite control
Incretins
Amylin
Hyperglycemia
Hepatic glucose output
↓ Metformin
↓ Thiazolidinediones
Lipotoxicity
Thiazolidinediones
Salicylates
Glucose reabsorption
↓SGLT2 inhibitors
Glucose uptake and utilization
↑ Thiazolidinediones
↑ Metformin

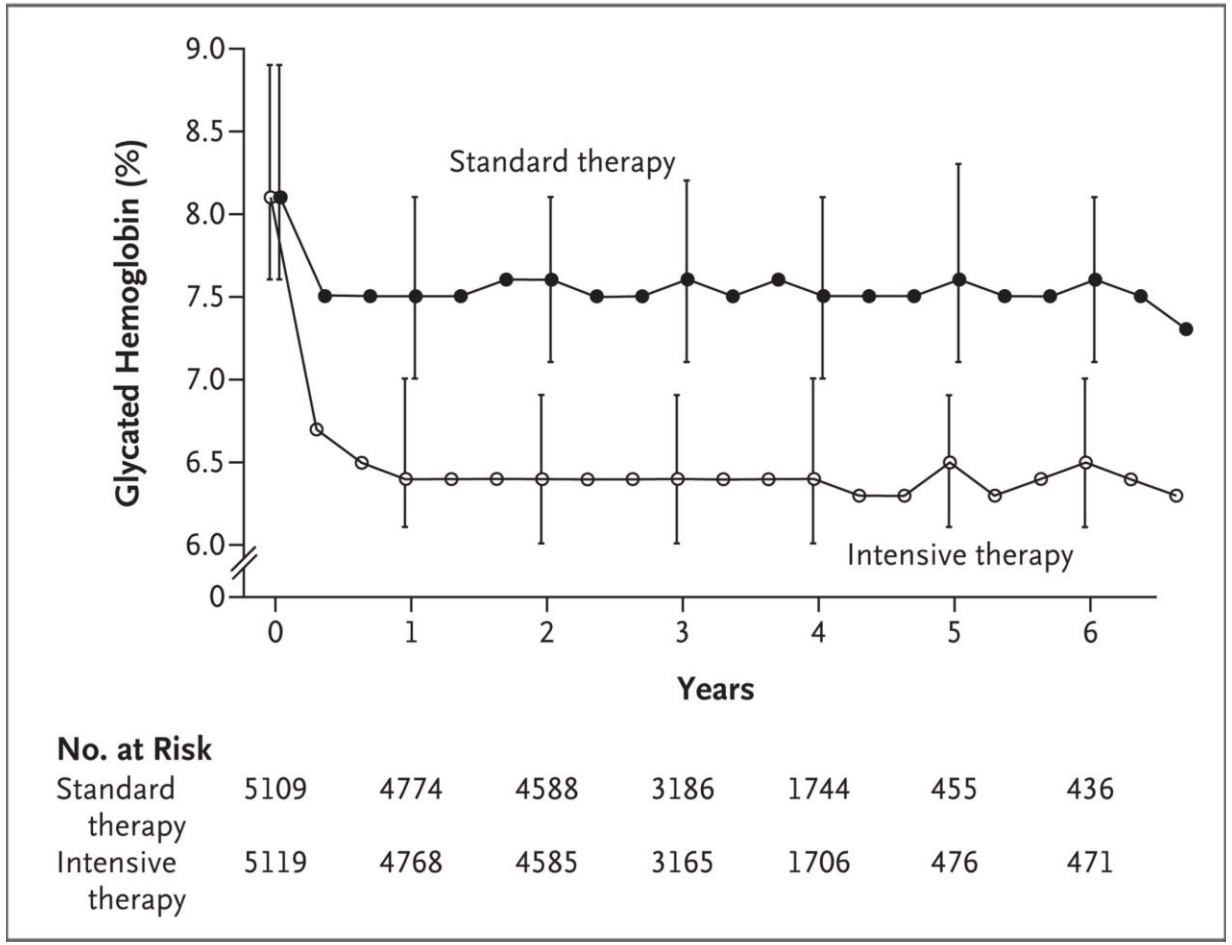
So, although DM is associated with cardiovascular morbidity …



Note: Bars indicate 95% confidence intervals. Rates are adjusted for age in 10-year intervals.

… Better glycemic control is not translated to lower CV mortality.

- Gerstein HC et al. NEJM 2008; 358:2545-59
- 10,251 T2DM patients randomized to intensive vs. standard therapy.
- Primary outcome was a composite of MI, CVA, or death from CV causes.
- After 1 year, stable median HbA1c levels of 6.4% and 7.5% were achieved in the two groups.
- While the primary outcome was not statistically significantly different, all cause mortality was higher in the intensive therapy (HR 1.22, P < 0.04), with frequent episodes of hypoglycemia and weight gain.



Variety of noninsulin drugs for T2DM

- Biguanides
- Sulfonylureas
- Meglitinides
- Thiazolidinediones (TZDs)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like peptide-1 (GLP-1) agonists
- Sodium glucose cotransporter-2 (SGLT-2) inhibitors
- Alpha glucosidase inhibitors
- Bile acid sequestrant
- Dopamine-receptor agonist

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- Metformin
- Inhibits hepatic gluconeogenesis and increases insulin-mediated glucose uptake in peripheral tissues
- Long track record of safety and reduction in sudden death and MI
- Considered the first line therapy in T2DM
- Possible association with lactic acidosis
  - When used with iodinated contrast
  - In a fasting state

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- 1st generation: tolbutamide, chlorpropamide
- 2nd generation: glipizide, glyburide (glibenclamide), gliciazide
- 3rd generation: glimepiride
- Binds and blocks K_{ATP} channels in pancreatic β cells, mediating exocytosis of insulin-containing granules. Mitochondrial K_{ATP} channels are also important in ischemic preconditioning.
- 1st generation sulfonylureas are associated with increased CV mortality. Possibly 2nd as well.
- Gliciazide and glimepiride may be better than older drugs. But weight gain is a concern.
- Considered 2nd line agents for T2DM

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- Repaglinide, nateglinide
- Similar mechanism of action to sulfonylureas in blocking different pancreatic K_{ATP} channels.
- No data on long-term cardiovascular safety.

Variety of noninsulin drugs for T2DM

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- **Thiazolidinediones (TZDs) – "glitazones"**
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- Rosiglitazone (Avandia)
- Pioglitazone (Actos)
- Insulin-sensitizers that act by regulating gene expression through the nuclear transcription factor peroxisome-proliferator-activated receptor γ (PPARγ).

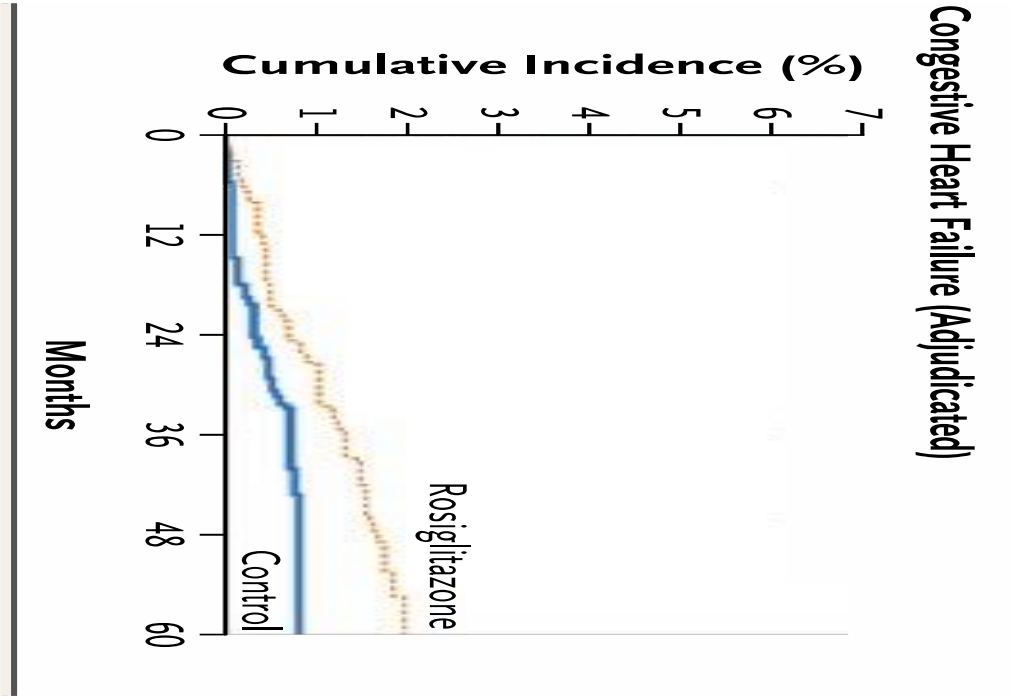
Is rosiglitazone safe? – conflicting data!

- Nissel SE, Wolski K. NEJM 2007
- Meta-analysis of 42 trials on rosiglitazone
- Rosiglitazone was associated with an increase in the risk of
  - MI – OR 1.43 (p=0.03)
  - CV deaths – OR 1.64 (p=0.06)

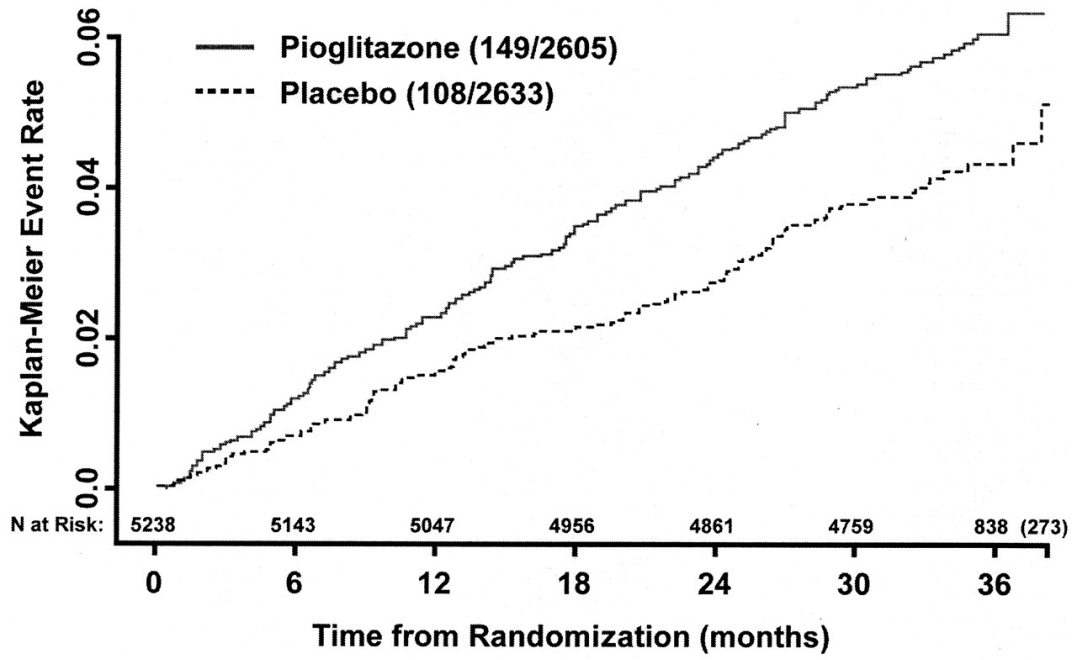
- Home PH et al. NEJM 2007
- RECORD trial of 4447 T2DM patients
- Metformin or sulfonylurea plus rosiglitazone vs. metformin and sulfonylurea
- After a mean follow-up of 3.75 years, there was no increase in MI or CV deaths with rosiglitazone
- BUT there were more patients with heart failure in the rosiglitazone group (HR 2.15, 95% CI 1.35 – 3.27)

TZDs are associated with heart failure.

- RECORD trial



- PROACTIVE trial



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- Dopamine-receptor agonist

- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)
- Alogliptin (Nesina)
- DPP-4's are circulating enzymes that degrade incretins (such as GIP(gastric inhibitory peptide) and GLP-1), insulinotropic gut hormones released in response to food intake. Thus, DPP-4 inhibitors increase the availability of insulin in response to food intake.
- Appear safe in CV endpoints
- ? Of increased HF, mostly with Saxagliptin (HR 1.27, p=0.007 in SAVOR-TIMI53 trial).

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- Exenatide (Byetta) – short-acting (4-6 hrs)
- Liraglutide (Victoza) – intermediate (24 hrs)
- Exenatide ER (Bydureon) – long-acting (7 d)
- Dulaglutide (Trulicity) – long-acting (7 d)
- GLP-1 agonists are incretins that activate the GLP-1 receptor directly and are resistant to degradation by DPP-4.
- Parenterally administered.
- LEADER trial of Liraglutide (NEJM 2016)
  - 9340 T2DM patients with high CV risk
  - Liraglutide reduced MI, CVA, and CV death after a median follow-up of 3.8 years (HR 0.8, $p < 0.001$)

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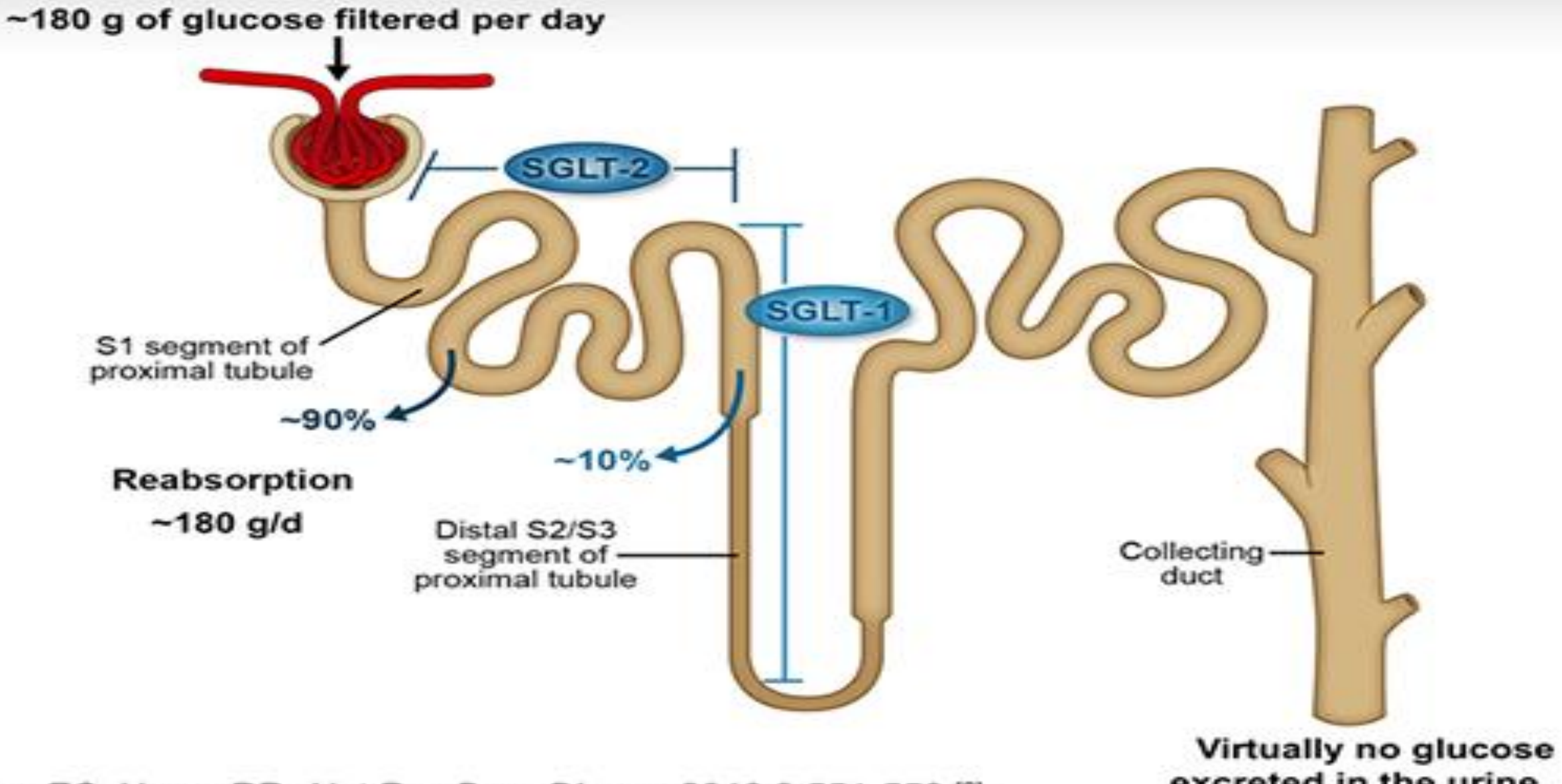
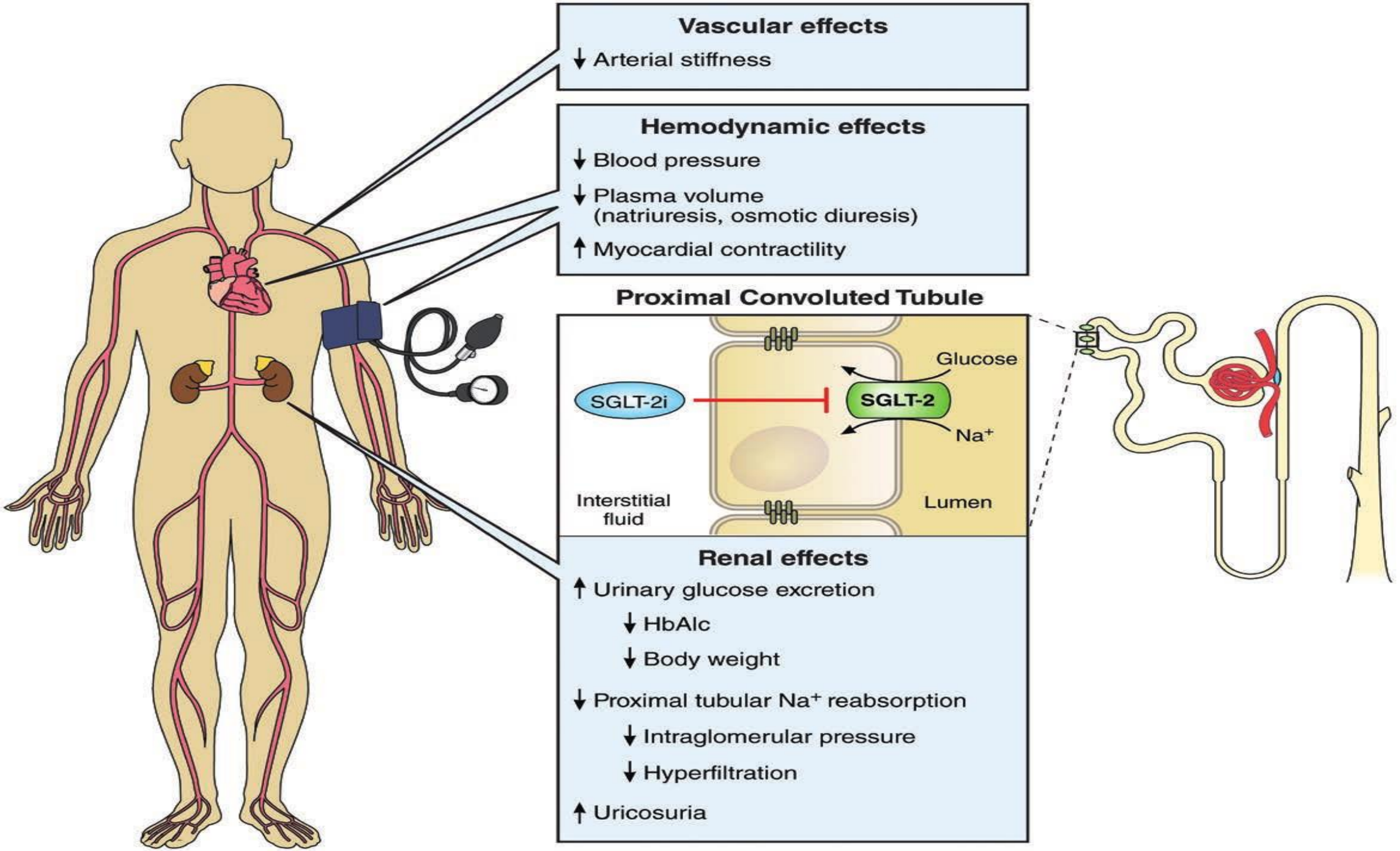
- Glucagon-like peptide-1 (GLP-1) agonists
- **Sodium glucose cotransporter-2 (SGLT-2) inhibitors – "Gliflozins"**
- Alpha glucosidase inhibitors
- Bile acid sequestrant
- Dopamine-receptor agonist

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- SGLT-2 are channels located on the luminal side of the renal proximal tubules.
- These channels are involved in reabsorption of the filtered urinary glucose load.
- SGLT-2 inhibitors reduce glucose reabsorption by 50 % and act as "glucoretics", with associated natriuresis as well.

The Kidney and Glucose Homeostasis

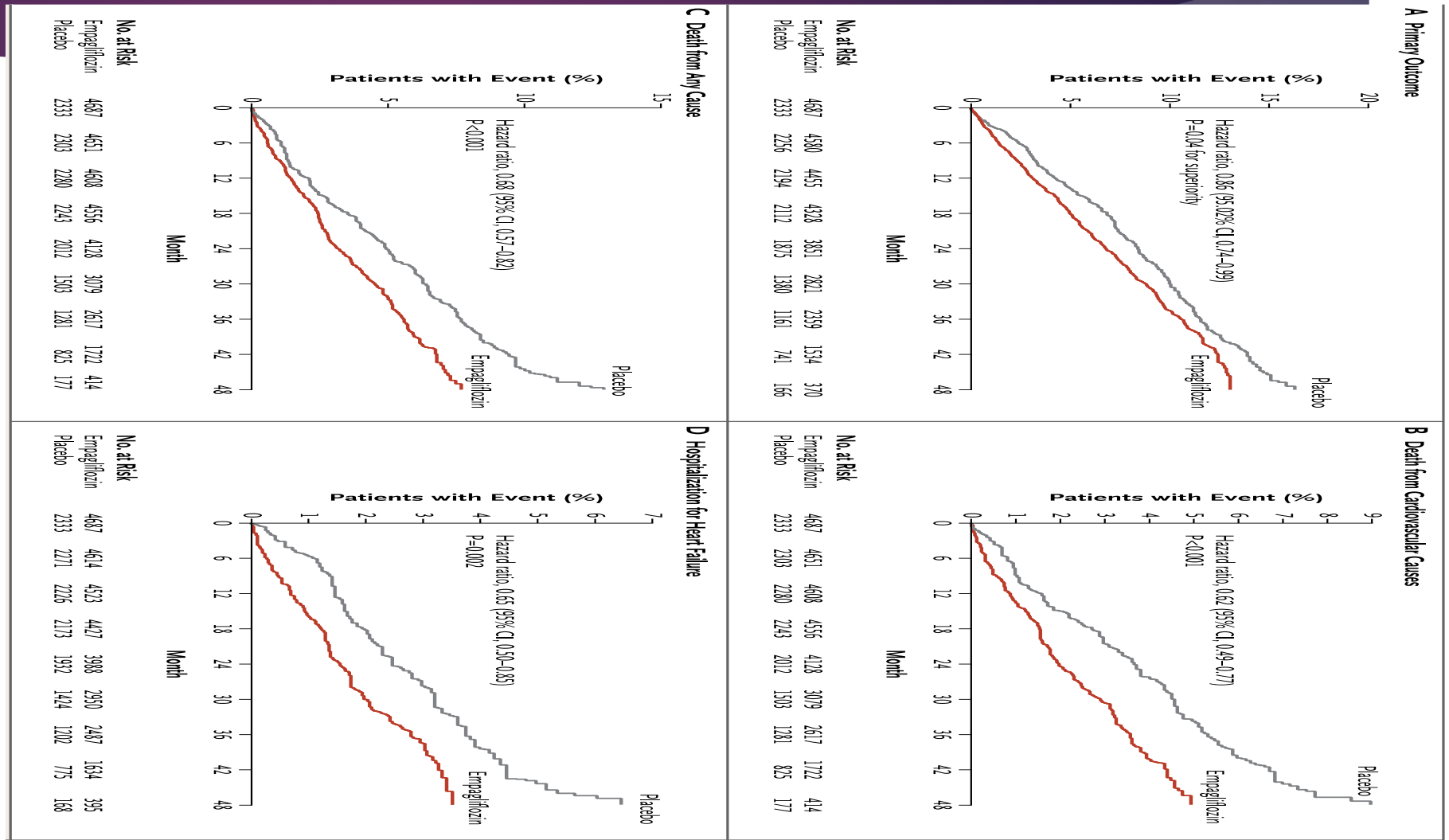


Chao EC, Henry RR. *Nat Rev Drug Discov*. 2010;9:551-559.[2]


Vascular effects
↓ Arterial stiffness
Hemodynamic effects
↓ Blood pressure
↓ Plasma volume
(natriuresis, osmotic diuresis)
↑ Myocardial contractility
Proximal Convoluted Tubule
Glucose
SGLT-2i
SGLT-2
Na+
Interstitial fluid
Lumen
Renal effects
↑ Urinary glucose excretion
↓ HbAlc
↓ Body weight
↓ Proximal tubular Na+ reabsorption
↓ Intraglomerular pressure
↓ Hyperfiltration
↑ Uricosuria

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (Zinman B et al. NEJM 2015)

- EMPA-REG OUTCOME study
- Randomized 7020 T2DM patients to either empagliflozin or placebo.
- Primary outcome: composite of MI, stroke or CV death



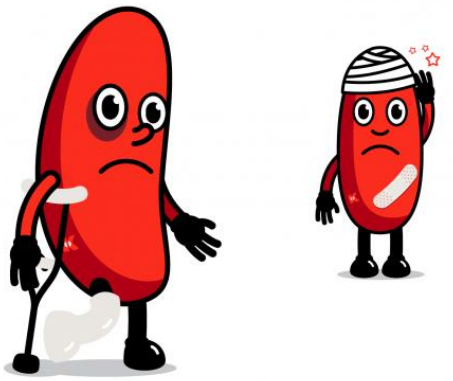
Beneficial glycemic and CV effects of gliflozins

- Comparable lowering of HbA1C to conventional agents like glimepiride
- Less risk of hypoglycemia than glimepiride (2% vs 24%)
  - Glycosuria threshold is usually 180 mg/dL.
- May be used in combination with metformin or insulin
- Also associated with weight loss (2-3 kg over 12 weeks) and ↑ HDL/↓ TG

- Cardiovascular benefits
  - BP lowering without an ↑ in HR
  - ↑ myocardial contractility from Δ in energy substrate utilization
  - ↓ plasma volume →
    - ↓ risk of HF
    - ↓ myocardial stretch → ↓ risk of arrhythmias

Potential adverse effect of gliflozins (1): Volume Depletion

- Volume depletion may be associated with a modest activation of the renin-angiotensin-aldosterone system (RAAS), accentuating the effect of RAAS inhibitors (such as ACE I's)
- May be prone to hypotension in the perioperative setting, due to being NPO preop and losing blood intraop.
- Potential renal injury
  - With contrast agent in the setting of volume depletion
  - With concomitant use of NSAID's
- Gliflozins are not recommended when estimated GFR < 60 ml/min/1.73 m^2.



Cardiovascular: ☐ WNL ☒ HTN ☐ CAD ☐ MI
☐ CP/ angina ☐ History of CHF ☐ Arrythmia: _____
☐ Valve DZ/ MVP: _____ ☐ Pacer/ AICD
☐ CABG ☐ Stent ☐ PVD ☐ Depend edema

MET: 1 (Eat/ dress) 2 (Walk/ cook) 3 (Walk 1-2 blocks) 4 (Rake/ garden) 5 or greater (Climb 1 flight)

Respiratory: ☐ WNL ☐ Recent URI ☐ Pneumonia
☐ Smoker___ppd, times _____years ☐ Quit: _____
☐ abstained from smoking pre op
☐ COPD/ Emphysema/ Chronic Bronchitis ☐ Asthma
☐ Sleep Apnea ☐ Home CPAP ☐ Home O2

GI/ Hepatic: ☐ WNL ☐ Hiatal hernia/ GERD ☐ PUD
☐ Crohn's ☐ Hepatitis ☐ Cirrhosis ☐ Ascites
☐ Alcohol consumption: _____

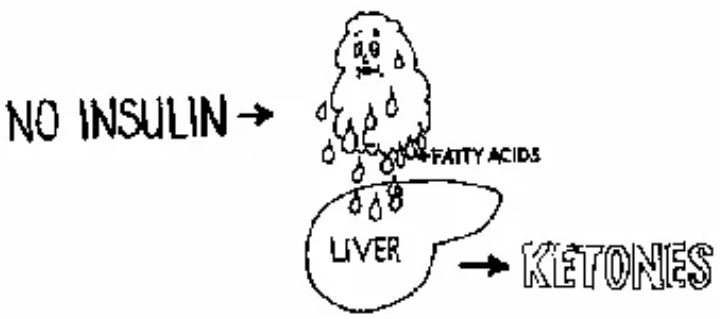
Endocrine/ Metabolic/ Hematologic/ Renal: ☐ WNL
☐ DM I ☒ DM II ☐ DM with complications
☐ Hyperthyroid ☐ Hypothyroid ☐ Sickle cell disease
☐ Hemophilia ☐ Coagulopathy ☐ Renal stones
☐ Anemia ☐ ARF ☐ CRF
☐ Dialysis / last: _____

Neuro/ Musculoskeletal: ☐ WNL ☐ Seizure ☐ Stroke ☐ TIA
☐ Neuromusc disease/ MS/ MD/ MG ☐ Neuropathy ☐ Dementia

Last dose: _____

Potential adverse effect of gliflozins (2): Diabetic ketoacidosis (DKA)

- Cases of DKA have been reported with gliflozins, either with hyperglycemia or with euglycemia (blood glucose < 15 mmol/L or 270 mg/dL), in T2DM.
- However, none of these cases were with gliflozin monotherapy.



- Potential mechanism
- Gliflozins may inhibit SGLT-2 in pancreatic a cells, leading to ↑ glucagon secretion.
  - This promotes a shift from carbohydrate to lipid metabolism, resulting in lipolysis, ketogenesis, and ↑ β-hydroxybutyrate production.
  - Also increases hepatic gluconeogenesis and ketogenesis.

Potential adverse effect of gliflozins (3): Infections

- Genital and urinary tract infections are relatively more common in those on gliflozins.
  - Genital infections; OR of 5.06
  - UTI's: OR of 1.42
- This could be a concern in major joint replacement surgeries or surgeries with implants.

Table 2. Considerations for SGLT2i Use in the Perioperative Period

	Considerations	Management Issues/Suggestions
Preoperative	Diabetes history	Detailed history for cardiac and renal risk factors (SGLT2i use prioritized in patients with cardiac and renal disease).
	Blood glucose control	SGLT2is generally have low risk for hypoglycemia.
	Age	Elderly patients may be more prone to hypotension and hypovolemia with SGLT2is.
	Concurrent medications (ie, diuretics, antihypertensives)	SGLT2i may predispose to volume loss, assess and optimize volume status
		Consider holding SGLT2is, 1 day before surgery in appropriate clinical settings (fasting patient, major surgery).
	Surgical considerations	Evaluate risk of blood loss and volume shifts intraoperatively given surgical plan, recognizing SGLT2is may predispose to volume depletion
		Ensure adequate prehydration prior to contrast exposure for cases involving fluoroscopy to minimize the risk for contrast-induced nephropathy.[24]
		Consider arterial line for pulse pressure variation monitoring and blood draws
		Anticipate potential hemodynamic changes, which may be more pronounced at specific intervals such as laparoscopic insufflation in patients who might be relatively more hypovolemic from fasting alone.[25]
Perioperative	Blood glucose control	Rare cases of DKA, which may present as euglycemic DKA, have been associated with SGLT2is.
		Have a low index of suspicion for DKA, and closely monitor plasma ketone levels if patient demonstrates any hemodynamic instability, seems unwell, or has metabolic acidosis.[22]
		Manage as per institutional DKA protocol or *Diabetes Canada: Clinical Practice Guideline for Hyperglycemic Emergencies in Adults.*[27]
	Maintenance of fluids	SGLT2i use may predispose to volume depletion.
		Ensure appropriate fluid resuscitation.
	Maintenance of electrolytes	Risk for hyperkalemia may be increased in patients with impaired renal function or those predisposed to hyperkalemia with some SGLT2is.[26]
		Closely monitor electrolytes as per local management algorithm.
Postoperative	Resumption of medication	After tolerating oral diet and clinically indicated.
		Assess renal function, consult specific prescribing indications for SGLT2i in renal impairment.

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- Biguanides
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- Dipeptidyl peptidase-4 (DPP-4) inhibitors
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- Sodium glucose cotransporter-2 (SGLT-2) inhibitors
- **Alpha glucosidase inhibitors**
- Bile acid sequestrant
- Dopamine-receptor agonist

- Acarbose (Precose)
- Competitively blocks intestinal a-glucosidases, which convert complex carbohydrates into monosaccharides. This leads to a slower rise in post-prandial blood glucose.
- When used in patients with impaired glucose tolerance, acarbose reduced the development of NIDDM and hypertension after a mean follow-up of 3.3 years.
- No long-term study on CV morbidity and mortality.

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- Colesevelam (Welchol)
- Mechanism of action for lowering blood glucose levels is not known.
- Other effects
  - Weight neutrality
  - Reduction in LDL
  - No serious CV events

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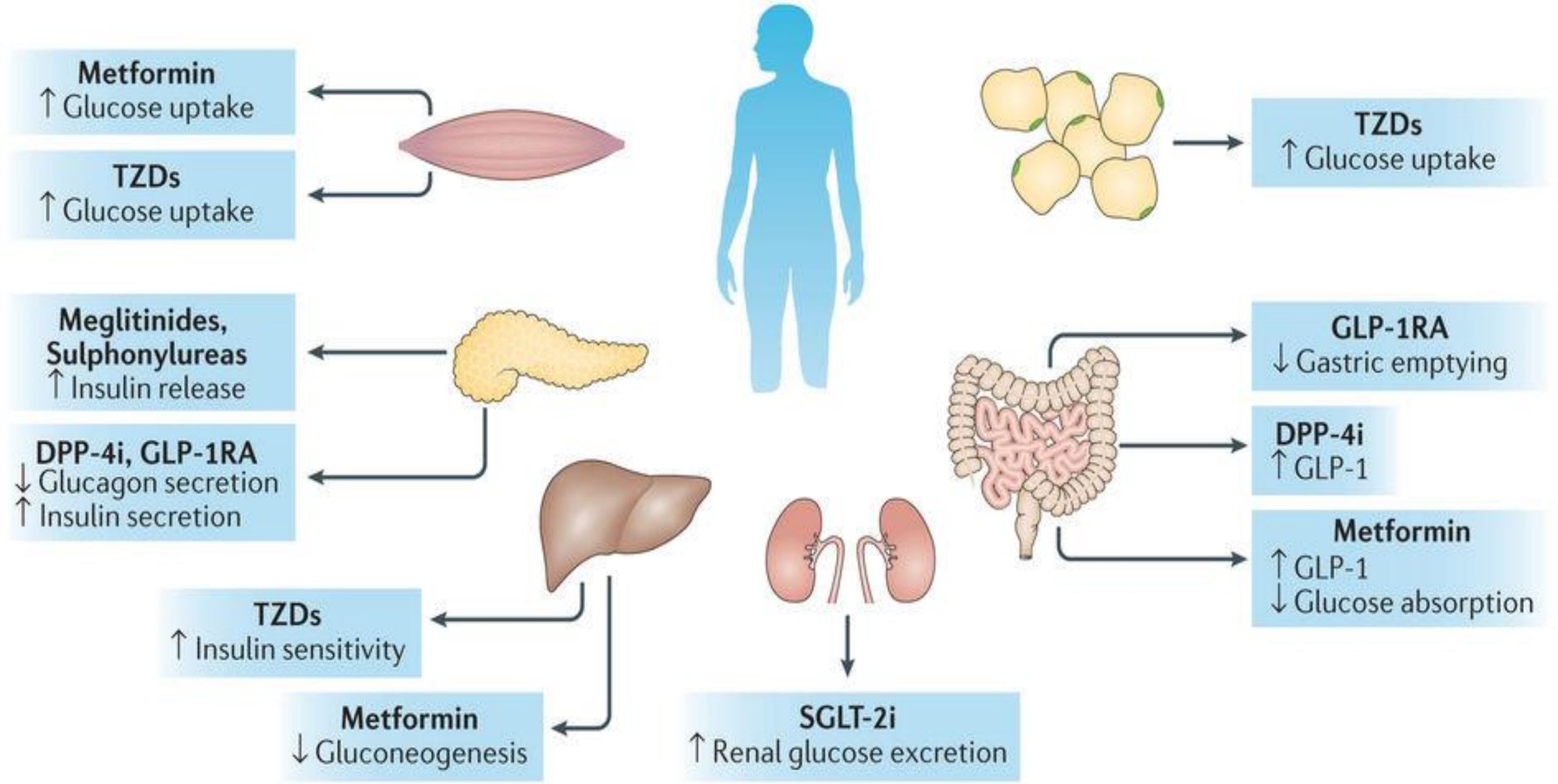
- Bromocriptine quick-release (Cycloset)
- Approved indications: Parkinson's disease, hyperprolactinemia, acromegaly, and T2DM
- Possible mechanism of action in T2DM?
  - ↓ hypothalamic adrenergic tone
  - ↑ morning dopaminergic activity → improves postprandial insulin sensitivity
- Possible CV benefit based on ↓ adrenergic tone


"Heart
disease
is a
SUGAR
disease."
-dietitian cassie


Metformin
↑ Glucose uptake
TZDs
↑ Glucose uptake
Meglitinides, Sulphonylureas
↑ Insulin release
DPP-4i, GLP-1RA
↓ Glucagon secretion
↑ Insulin secretion
TZDs
↑ Insulin sensitivity
Metformin
↓ Gluconeogenesis
SGLT-2i
↑ Renal glucose excretion
TZDs
↑ Glucose uptake
GLP-1RA
↓ Gastric emptying
DPP-4i
↑ GLP-1
Metformin
↑ GLP-1
↓ Glucose absorption