

Pharmacology Update for the Adult Patient - Newer Oral Medications for Diabetes

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Faculty Disclosure

- In accordance with policies of the Accreditation Council for Continuing Medical Education (ACCME) and the Accreditation Council for Pharmacy Education (ACPE), University of Kentucky UK HealthCare CECentral (UKHCCEC) have no relevant financial relationships during the past 12 months with commercial interests to disclose.

Need/Practice Gap & Supporting Resources

Annual revisions to American Diabetes Association Standards of Care and other diabetes management guidelines, specifically in the area of pharmacologic management of diabetes.

Emerging pharmacologic therapies for management of diabetes.

Objectives

- Summarize the 2017 revisions to the American Diabetes Association (ADA) Standards of Medical Care in Diabetes and other guidelines pertaining to oral pharmacologic management of diabetes
- Review oral pharmacologic approaches to patient-centered management of diabetes
- Discuss findings from recent clinical trials that may influence diabetes management and care
- Evaluate new and emerging oral pharmacologic therapies to improve diabetes control and complication management

Expected Outcome

- Understanding of the role of oral pharmacologic therapies for diabetes management and associated updates in recommendations.

What is the recommended first line pharmacologic agent for treatment of T2DM in *most* patients?

- **A. Metformin**
- B. Insulin
- C. Rosiglitazone
- D. Saxagliptin

Which medication recently gained an added indication of reduced risk of cardiovascular death in adults with T2DM and CAD?

- A. Glyburide
- B. Rosiglitazone
- C. Insulin Glargine
- D. Empagliflozin

Standards of Medical Care in Diabetes--2017

Cardiovascular Disease and Risk Management

- CV risk factors assessed at least annually
 - Hypertension
 - Dyslipidemia
 - Smoking
 - Family history of premature coronary disease
 - Albuminuria

Hypertension

- ADA Goal
 - <140/90 for most patients
 - <130/80 for patients at high risk of CVD if achievable
- AACE Goal
 - <130/80 for most patients
 - Less stringent goals in certain patients
 - <120/80 if able to be reached safely

Cardiovascular Disease and Risk Management

- HTN Alone (No Albuminuria)
 - ACEi
 - ARBs
 - Thiazide diuretics
 - CCBs
- HTN and Albuminuria
 - ACEi
 - ARBs

**Recommendation for Statin and
Combination Treatments in People
with Diabetes/ASCVD Risk Factor
Modifications—Stay Tuned**

Goals for Glycemic Control

	ADA	AACE
A1C (%)	<7*	≤6.5 For patients without concurrent illness and low risk for hypoglycemia
Fasting/preprandial glucose	80–130 mg/dL*	<110 mg/dL
Peak postprandial glucose	<180 mg/dL	<140 mg/dL**

*More or less stringent goals may be appropriate for individual patients

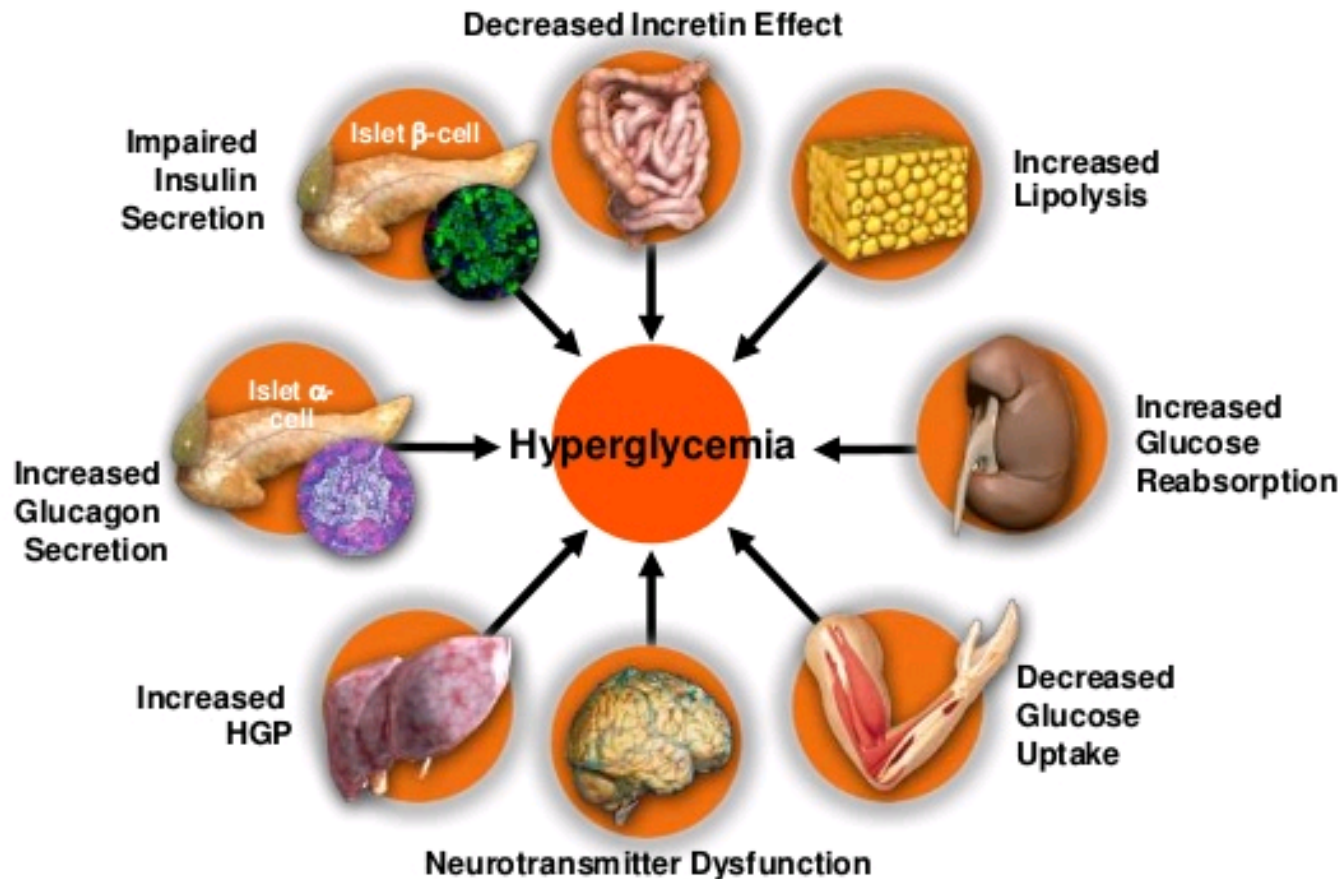
**2-hour postprandial.

Pharmacologic Treatment 2017

Revisions

- Vitamin B12 deficiency
 - Long-term metformin use
 - Periodic measurement of B12 levels
 - Supplementation as needed
- Cardiovascular benefits and SGLT-2 and GLP-1
- Combination injectable therapy
- Insulin considerations
 - Costs
 - Biosimilar
 - Use in hospital setting

Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet



A1C $\geq 9\%$

A1C $\geq 10\%$, BG ≥ 300 mg/dL, or symptomatic

Lifestyle Management

Monotherapy

Metformin

If A1C target not achieved after ~3 months, move to dual therapy

Dual Therapy

Metformin +

Sulfonylurea

Thiazolidinedione

DPP-4 inhibitor

SGLT2 inhibitor

GLP-1 receptor agonist

Insulin (basal)

If A1C target not achieved after ~3 months, move to triple therapy

Triple Therapy

Metformin +

Sulfonylurea +

TZD +

DPP-4 i +

SGLT2 i +

GLP-1 RA +

Insulin (basal) +

TZD or

SU or

SU or

SU or

SU or

TZD or

DPP-4-i or

DPP-4-i or

TZD or

TZD or

TZD or

DPP-4-i or

SGLT2-i or

SGLT2-i or

SGLT2-i or

DPP-4 i or

SGLT2-i or

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GLP-1-RA or

GLP-1-RA or

Insulin

GLP-1-RA or

Insulin

GLP-1-RA

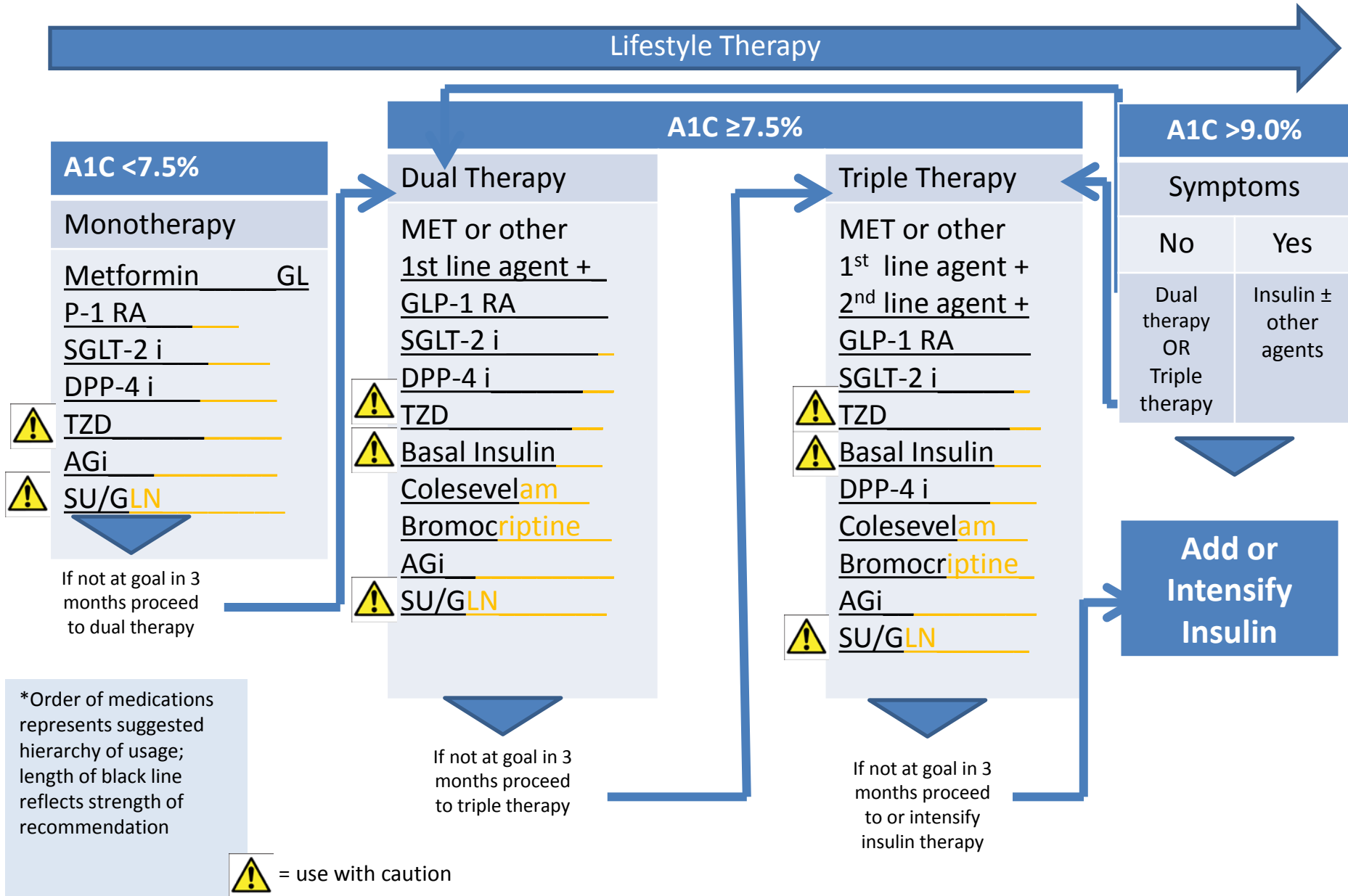
Insulin

Insulin

Insulin

Combination Injectable Therapy

AACE Glycemic Control Algorithm



*Order of medications represents suggested hierarchy of usage; length of black line reflects strength of recommendation

= use with caution

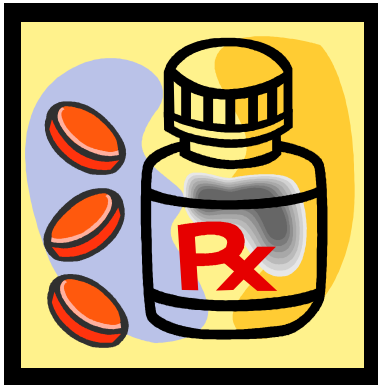
Profiles of Antidiabetic Medications

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (mod. Dose)	SU/GLN	COLSVL	BCR-QR	INSULIN	PRAML
Hypo	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate to severe/ Mild	Neutral	Neutral	Moderate to Severe	Neutral
Weight	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
Renal/GU	Contra- indicated if eGFR <30 mL/min/ 1.73 m2	*Exenatide not in CRCL<30 *Possible benefit Liraglutide	Not indicated eGFR <45 mL/min/ 1.73m2 *Possible benefit of Empagliflozin	Dose adjust in all except linagliptin Effective reducing albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF		Possible benefit of Liraglutide	Possible benefit of Empagliflozin	Possible Risk for Saxagliptin & Alogliptin		Moderate	More CHF Risk	Neutral	Neutral	More CHF risk	
ASCVD	Neutral	Possible CV benefit	Possible CV benefit	Neutral	Neutral	May Reduce Stroke Risk	?	Benefit	Safe	Neutral	Neutral
Bone	Neutral	Neutral	Canagliflozin Warning	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
Ketoacidosis	Neutral	Neutral	DKA in T2D in various settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Therapy Selection Considerations

- Efficacy
- Cost
- Comorbidities
- Side effects
- Effects on weight
- Risk of hypoglycemia
- Goals of therapy
- Patient Preferences

Medication Management of Type 2 DM



Classes

1. Biguanides
2. Sulfonylureas
3. Thiazolidinediones (glitazones)
4. Alpha-glucosidase inhibitors
5. Meglitinides
6. Non-insulin injectables (amylin & incretin mimetics)
7. DPP-IV inhibitors
8. SGLT-2 inhibitors
9. Dopamine Agonists
10. Bile Acid Sequestrants
11. Insulins

Biguanides

- MOA
 - Primary: decreases gluconeogenesis (reduces hepatic glucose production)
 - Improves peripheral sensitivity to insulin
 - Decreases intestinal glucose absorption
 - Does NOT stimulate release of insulin
- Medication
 - Metformin (Glucophage)
 - Metformin extended-release (Glucophage XR, Fortamet)
- Contraindications and Precautions
 - Renal impairment, hepatic disease, hypoxia, or h/o lactic acidosis are contraindicated
 - eGFR < 30 mL/min/1.73 m² contraindication
 - Iodinated parenteral contrast dye—hold 48 hrs before and 48 hrs after procedure
- Pearls
 - Lowers A1C 1-2%
 - Not associated with weight gain (may be associated with weight loss)
 - GI side effects
 - Favorable effects on LDL
 - Reduction in cardiovascular events and mortality (UKPDS f/u)
 - B12 deficiency
 - Caution in elderly until renal function verified
 - Cost: low

Sulfonylureas

- MOA: stimulate insulin secretion from the pancreas
- Medications
 - Glyburide
 - Glipizide
 - Glimepiride
- Pearls
 - Lower A1C 1-2%
 - Hypoglycemia-most common ADR
 - Elderly are most susceptible to hypoglycemia
 - Weight gain due to insulin release
 - Reduction in microvascular events (UKPDS)
 - Cost: low

Thiazolidinediones (TZDs)

- MOA
 - “Insulin sensitizer”
 - Decrease insulin resistance in muscle and liver, which enhances glucose utilization and decreases hepatic glucose output
- Medications
 - Pioglitazone
 - Rosiglitazone
- Adverse Effects
 - Weight gain-mild to mod
 - Edema
 - Increased fracture risk (distal upper or lower limb)
 - Increased LDL-C (rosiglitazone)
- Pioglitazone and bladder cancer
 - Do not use with active bladder cancer
 - Caution with bladder cancer history
 - Counsel on signs/symptoms of bladder cancer
- Pearls
 - Lowers A1C 0.5-1.4%
 - Pioglitazone has favorable effects on HDL and triglycerides
 - ? ↓ CVD events (PROactive, pioglitazone)
 - ↓ Risk of stroke and MI in patients without diabetes and with insulin resistance and history of recent stroke or TIA (IRIS study, pioglitazone)
 - Monitor for signs/sx of CHF
 - Cost: low

Alpha-glucosidase Inhibitors

- MOA
 - Inhibition of enzymes (glucosidases) present in brush-border cells of the mucosa of the small intestine responsible for breakdown of complex polysaccharides and sucrose into absorbable monosaccharides
 - Delay CHO absorption
 - Results in a reduction of postprandial hyperglycemia
- Medications
 - Acarbose
 - Miglitol
- Pearls
 - Lowers A1C 0.5-0.8%
 - ? ↓ CVD events in prediabetes (STOP-NIDDM)
 - If hypoglycemia occurs in patients on these drugs (rare), administer oral glucose vs. sucrose since absorption of sucrose will be blunted by these drug
 - Many patients will find GI side effects intolerable
 - Frequent dosing schedule not desirable
 - Cost: low to moderate

Meglitinides (Glinides)

- MOA
 - Similar to sulfonylureas in action
 - Stimulate the release of insulin
 - Rapid onset and short duration of action require dosing with meals to enhance postprandial glucose utilization
- Medications
 - Repaglinide
 - Nateglinide
- Pearls
 - Lowers A1C 1-1.5%
 - Can cause hypoglycemia
 - Skip dose if meal is skipped-offers some flexibility
 - Best for postprandial hyperglycemia
 - More expensive than sulfonylureas (cost: moderate)

Incretin-Based Therapies

- GLP-1 Receptor Agonists
- DPP-IV Inhibitors







Incretins Overview

- Intestinal hormones released after meal ingestion
 - Glucagon-like peptide 1 (GLP-1)
 - Glucose-dependent insulintropic polypeptide (GIP)
- Released from the intestine in response to food ingestion
 - Produced by the L-cells of the small intestine and binds to the GLP-1 receptor on the pancreatic B-cells
 - GLP-1 and GIP cause release of insulin in response to glucose levels
 - GLP-1 also suppresses glucagon secretion from alpha cells in response to glucose levels, slows gastric emptying, reduces food intake

Incretins Overview

- GLP-1 and GIP are rapidly degraded by DPP-IV (dipeptidyl-peptidase 4) enzyme
 - Enzyme present on many cells & tissues
 - Half-life of GLP-1 < 2 minutes
 - Therapeutic use of human GLP-1 limited
- The incretin effect is diminished in type 2 diabetes

Role of Incretin System

-  Glucose-dependent insulin secretion
-  Glucagon secretion;  hepatic glucose output
- Regulates gastric emptying;  rate of nutrient absorption
-  Food intake
-  Plasma glucose acutely

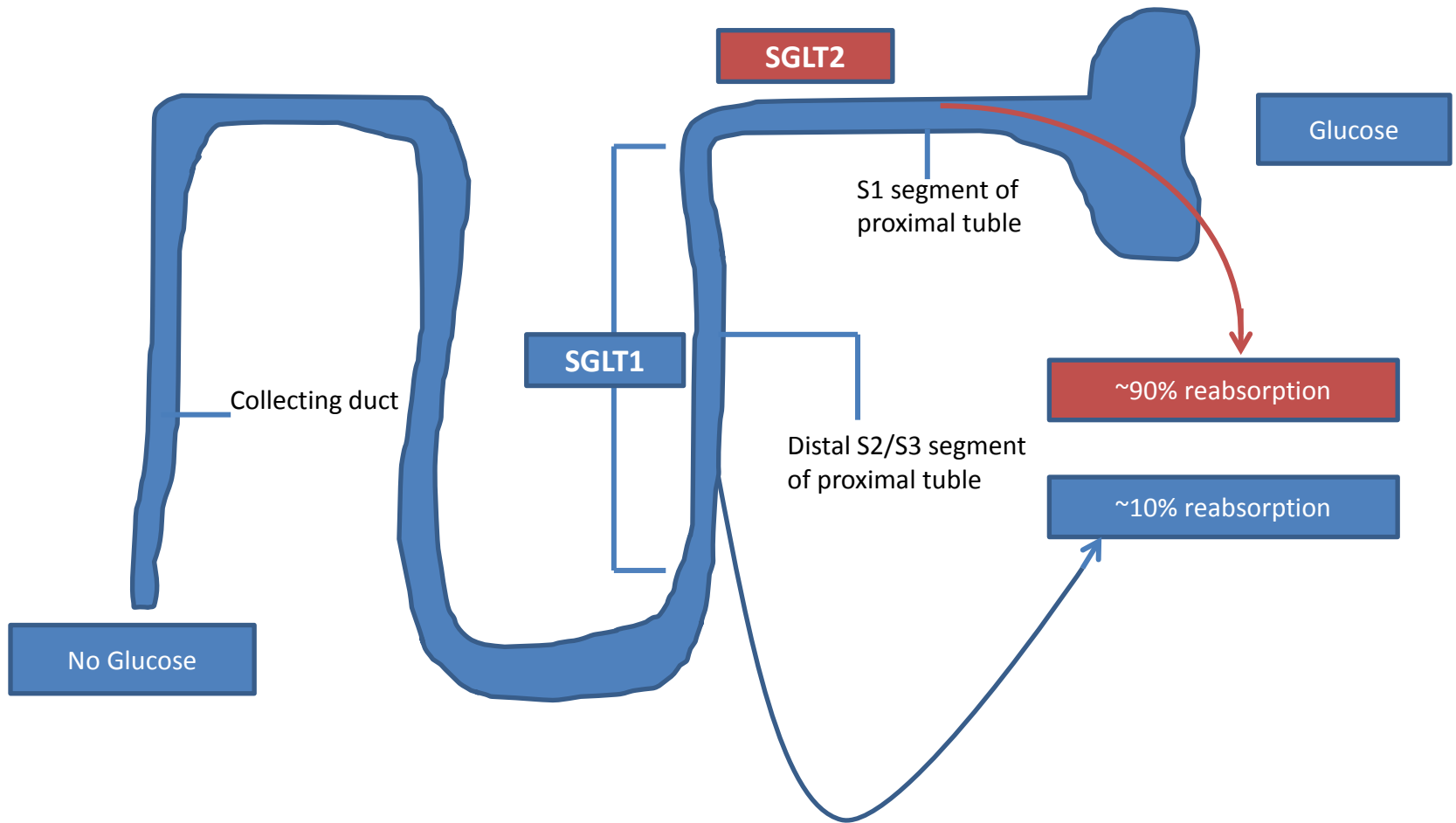
DPP-4 Inhibitors

- MOA
 - Lengthens the activity time of GLP-1 and GIP
- Medications:
 - Sitagliptin
 - Saxagliptin
 - Linagliptin
 - Alogliptin
- Pearls
 - Lower A1C levels 0.5-0.8%
 - Hypoglycemia (Sulfonylureas)
 - Weight neutral
 - Cases of pancreatitis observed
 - Cost: high

DPP-4 Inhibitors Cardiovascular Safety

- EXAMINE (N=5380; 1.5 years median follow-up)
 - Alogliptin
 - No increased risk of major CV events
 - In patients with no history of HF: increase in HF admissions (2.2% vs. 1.3%, HR 1.76; 95% CI 1.07-2.90)
- SAVOR-TIMI 53 (N=16492; 2 years median follow-up)
 - Saxagliptin
 - No increased risk of major CV events
 - Increased risk in HF admissions (3.5% vs. 2.8%, HR 1.27; 95% CI 1.07-1.51)
- TECOS (N=14735; ~3 years median follow-up)
 - Sitagliptin
 - No increased risk of major CV events
 - No difference in HF admissions (3.1% vs. 3.1%, HR 1.00; CI 0.83-1.20)
- FDA advisory committee recommended revision of labels of medications containing alogliptin and saxagliptin to inform of potential increased HF risk
- Linagliptin long-term CV trials in progress

SGLT2 Inhibitors



SGLT2 Inhibitors

- MOA
 - Blocks glucose reabsorption by the kidney, increasing glucosuria
- Medications
 - Canagliflozin
 - Dapagliflozin
 - Empagliflozin
- Pearls
 - Increased risk for genital mycotic infections
 - Increased risk of hypotension, renal insufficiency, and dehydration
 - DKA
 - Weight loss
 - Efficacy dependent upon kidney function
 - Lowers blood pressure
 - Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin EMPA-REG OUTCOME)
 - Cost: high

CANVAS and CANVAS-R

- CANVAS (N=4330) and CANVAS-R (N=5812)
 - Patients with type 2 diabetes and established cardiovascular disease or at high risk for cardiovascular events
- Canagliflozin reduced the overall risk of cardiovascular disease by 14% and reduced the risk of heart failure hospitalization by 33%
- FDA concluded that canagliflozin causes an increased risk of leg and foot amputations based on CANVAS and CANVAS-R trials
- New results suggest canagliflozin reduces cardiovascular stress in older patients with type 2 diabetes; consistent with previous findings suggesting cardioprotective effects of SGLT-2 inhibitors

EMPA-REG

- Empagliflozin (SGLT-2 inhibitor)
 - Randomized, double blind trial
 - Compared to placebo
 - CV outcomes (MI, Stroke, or CV death)
 - T2DM and existing CVD
 - Results
 - 14% reduction of composite outcome (P=0.04)
 - 38% reduction of cardiovascular death (P=0.08)
 - Added indication: reduced risk of cardiovascular death in adults with T2DM and CAD

Dopamine-2 Agonists

- MOA: dopamine agonist
 - Modulates hypothalamic regulation of metabolism
 - ↑ Insulin sensitivity
- Medication
 - Bromocriptine Mesylate (Cycloset)
- Pearls
 - Lowers A1c 0.5-1%
 - Best in pre-diabetes or early disease
 - Adverse effects
 - **Nausea/vomiting**
 - **Hypotension**
 - Headache
 - Fatigue
 - Decreased triglycerides
 - Cost: high

Bile Acid Sequestrants

- MOA: bile acid sequestrant
 - May reduce hepatic insulin resistance and reduce intestinal glucose absorption
- Medication
 - Colesevelam
- Pearls
 - Adverse effects: constipation, nausea, indigestion
 - Lowers A1C 0.5%
 - No hypoglycemia
 - Lowers LDL up to 20%
 - Increases TG
 - Monitor for drug interactions
 - Cost: high