

A person wearing a light blue t-shirt is shown from the chest up. They are holding a large, solid red heart against their chest with their right hand. The background is a soft-focus outdoor scene with greenery and a bright sky.

Navigating the Crossroads of Cardiometabolic Disease

**Contemporary Medication Management of Cardiovascular
Disease, Diabetes, and Chronic Kidney Disease**

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Learning Objectives



1 LIST

diabetes medications that have cardiovascular and/or renal benefits.



2 IDENTIFY

patients who may benefit from SGLT2 inhibitors or GLP1 receptor agonists.



3 GIVEN A CASE,

select monitoring parameters for SGLT2 inhibitors or GLP1 receptor agonists relevant to cardiac rehabilitation.

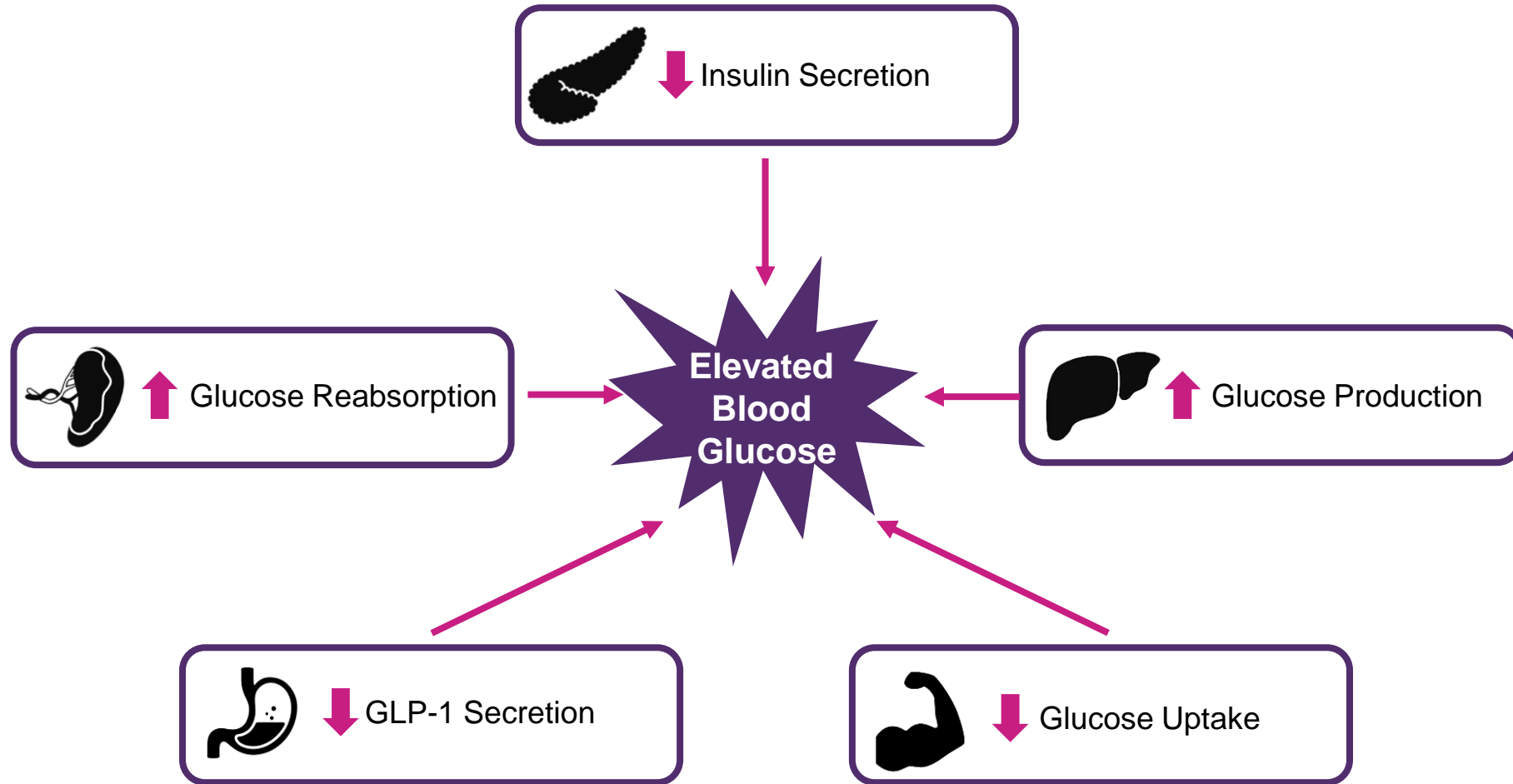
A 67-year-old female with a PMH of diabetes, hypertension, and hyperlipidemia was recently diagnosed with heart failure with reduced ejection fraction. Her current medications include insulin glargine, lisinopril, rosuvastatin, and PRN acetaminophen. Which medication may be beneficial to start in this patient?

- A. Metformin
- B. Empagliflozin
- C. Glipizide
- D. Sitagliptin

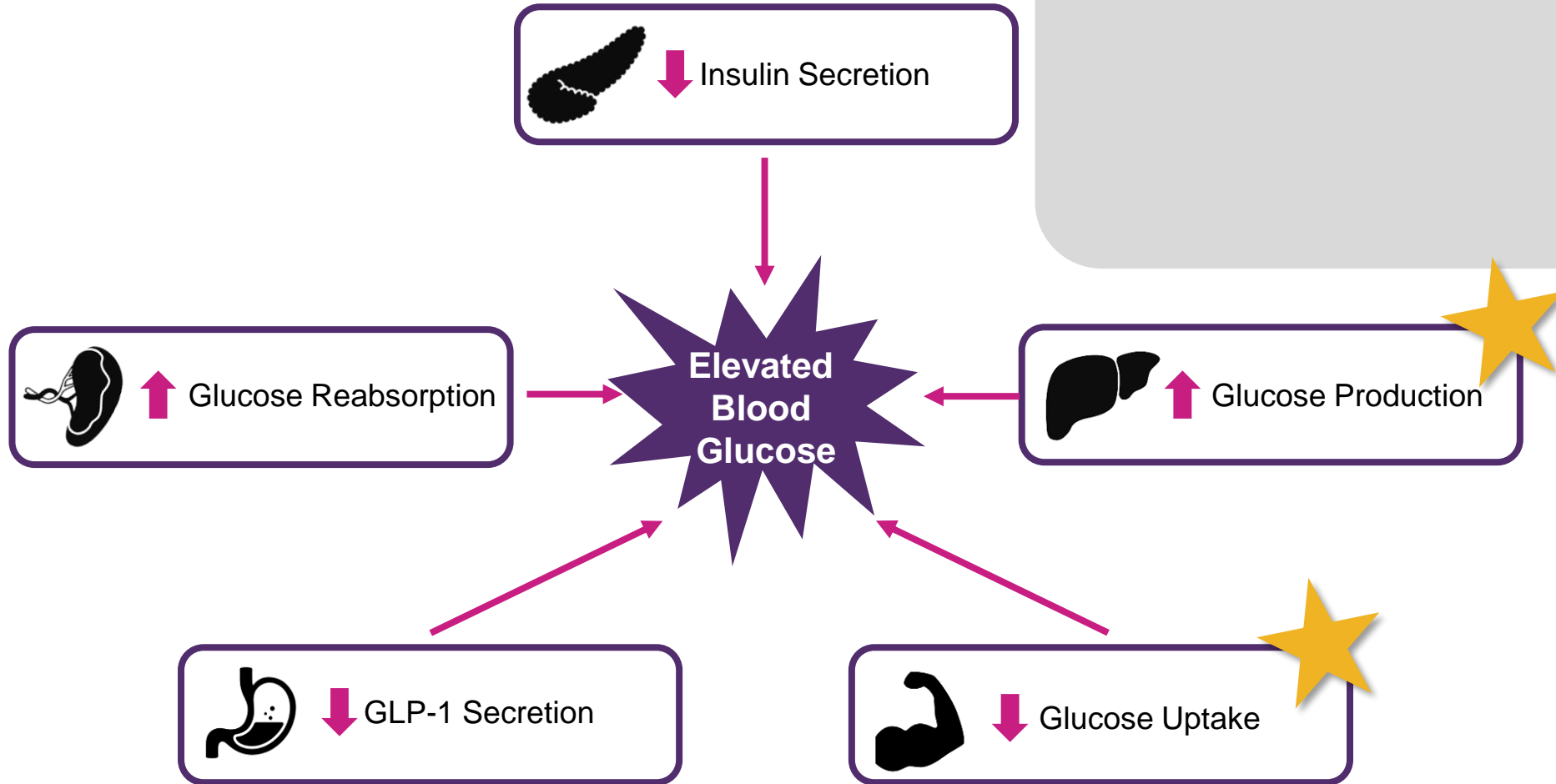
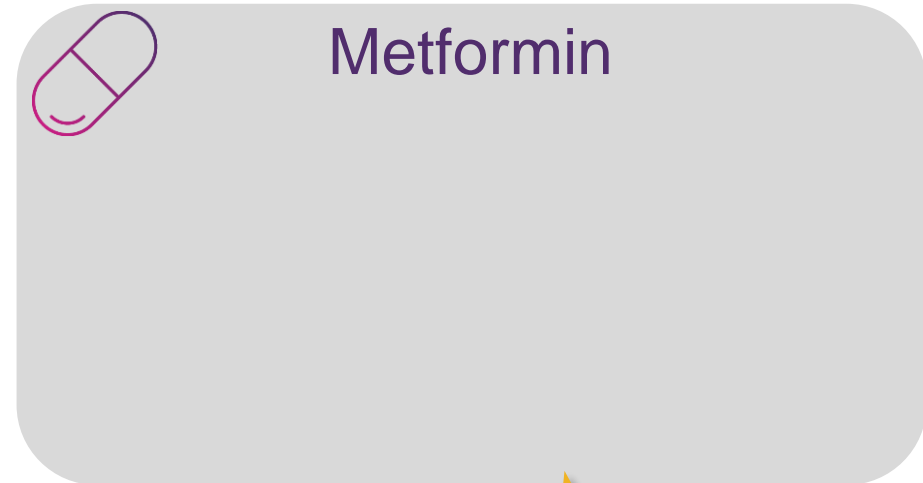
Review of Type 2 Diabetes




Physiology of Type 2 Diabetes



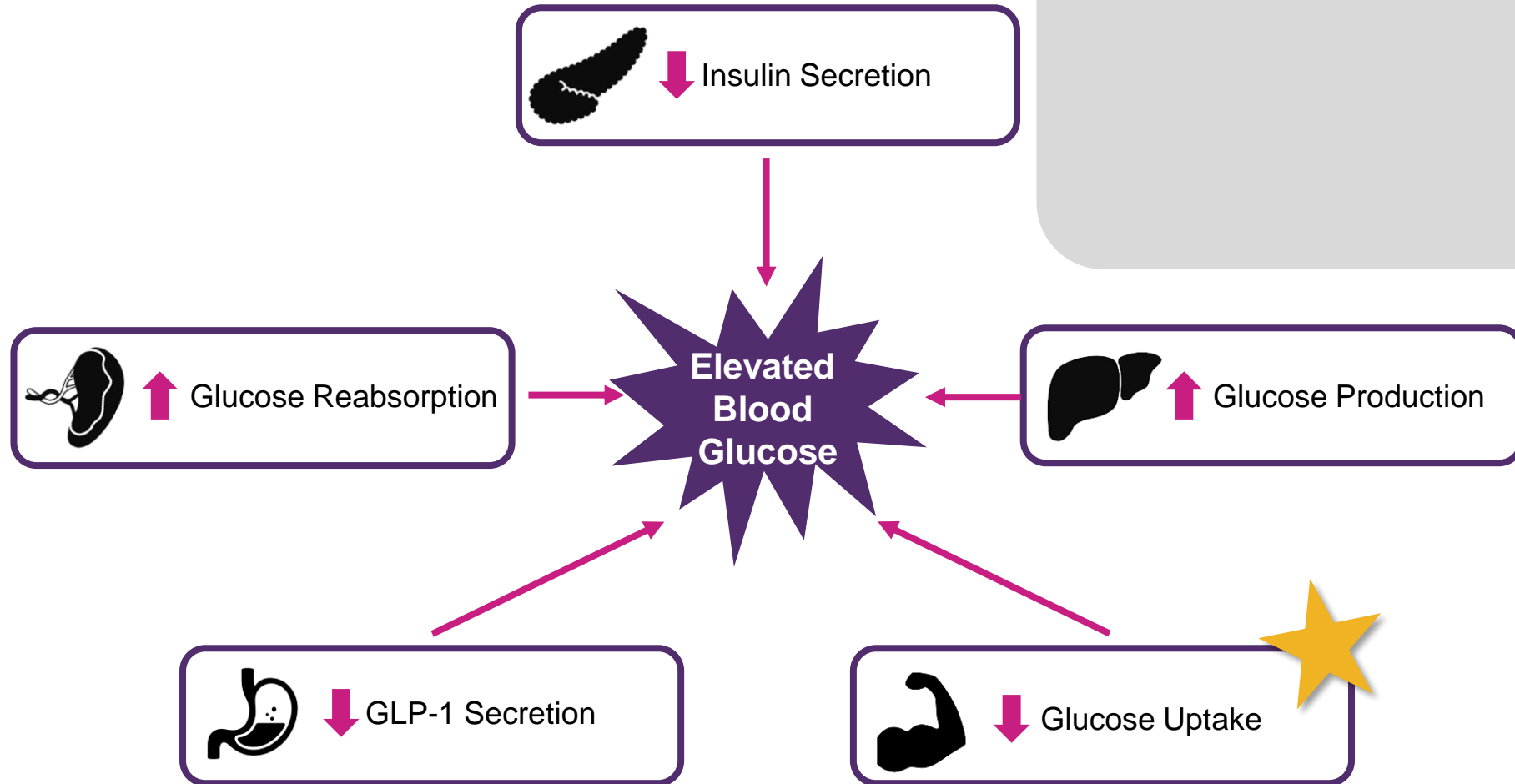
Medications for Treatment of Diabetes



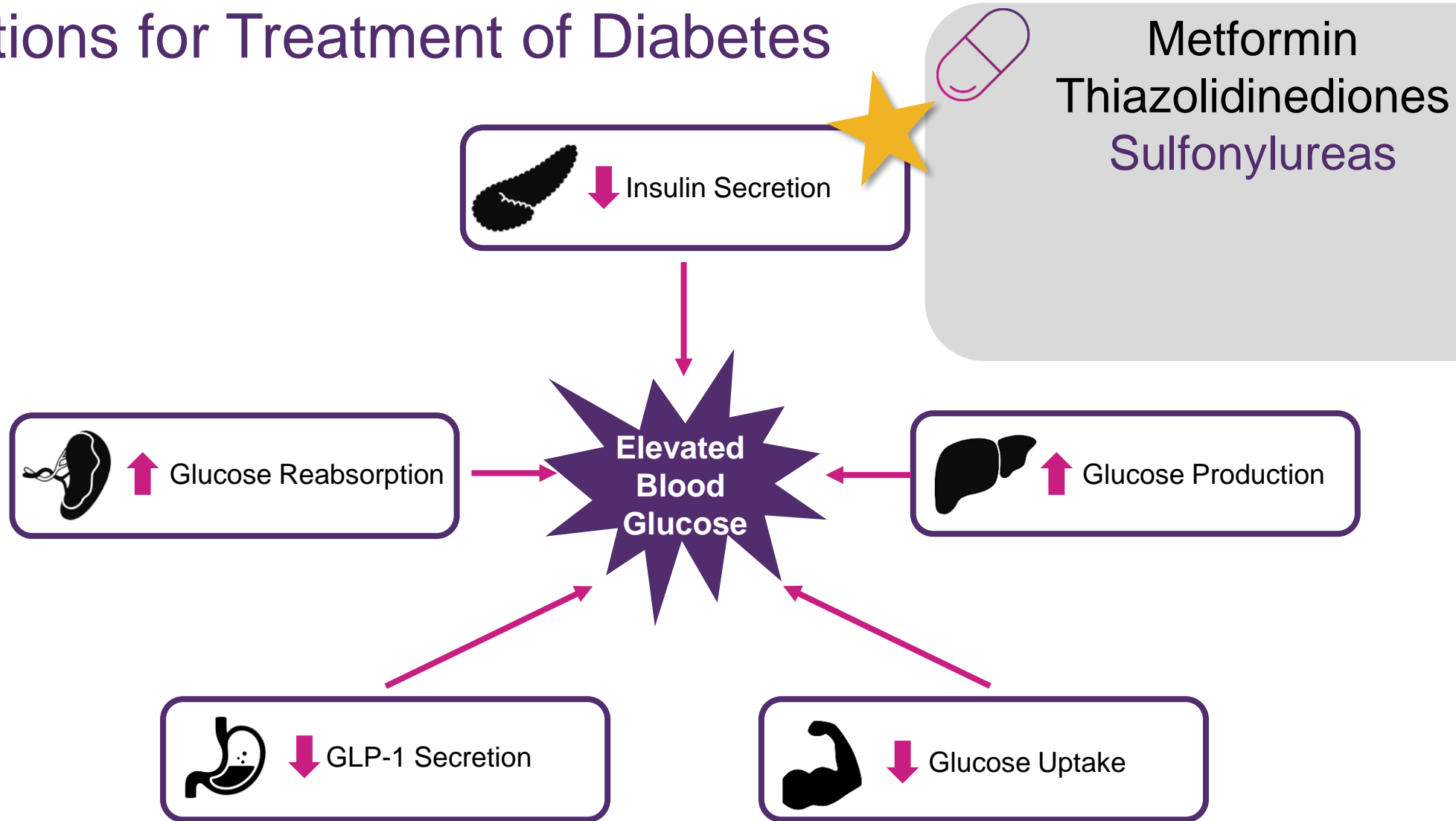
Medications for Treatment of Diabetes



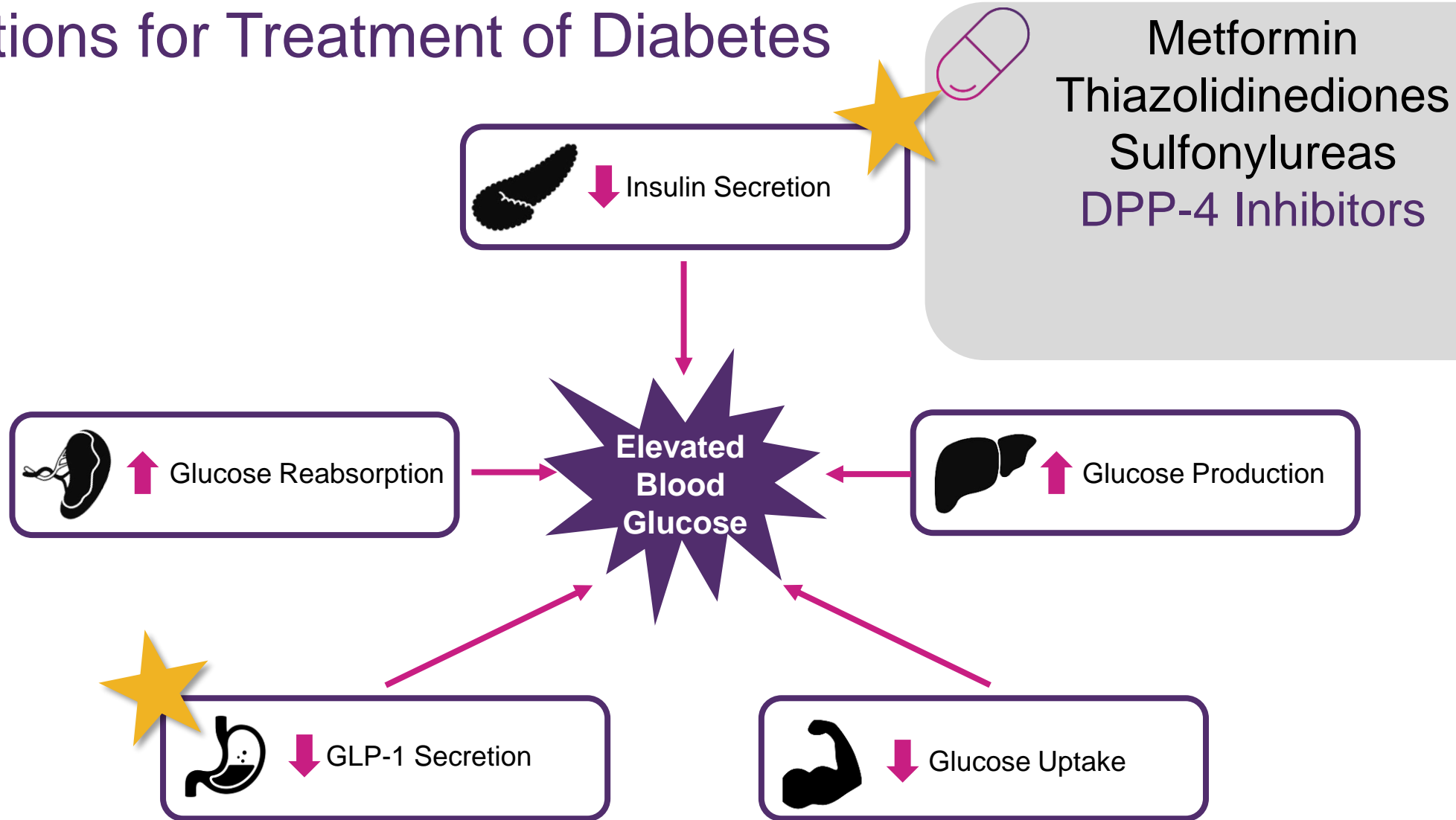
Metformin
Thiazolidinediones



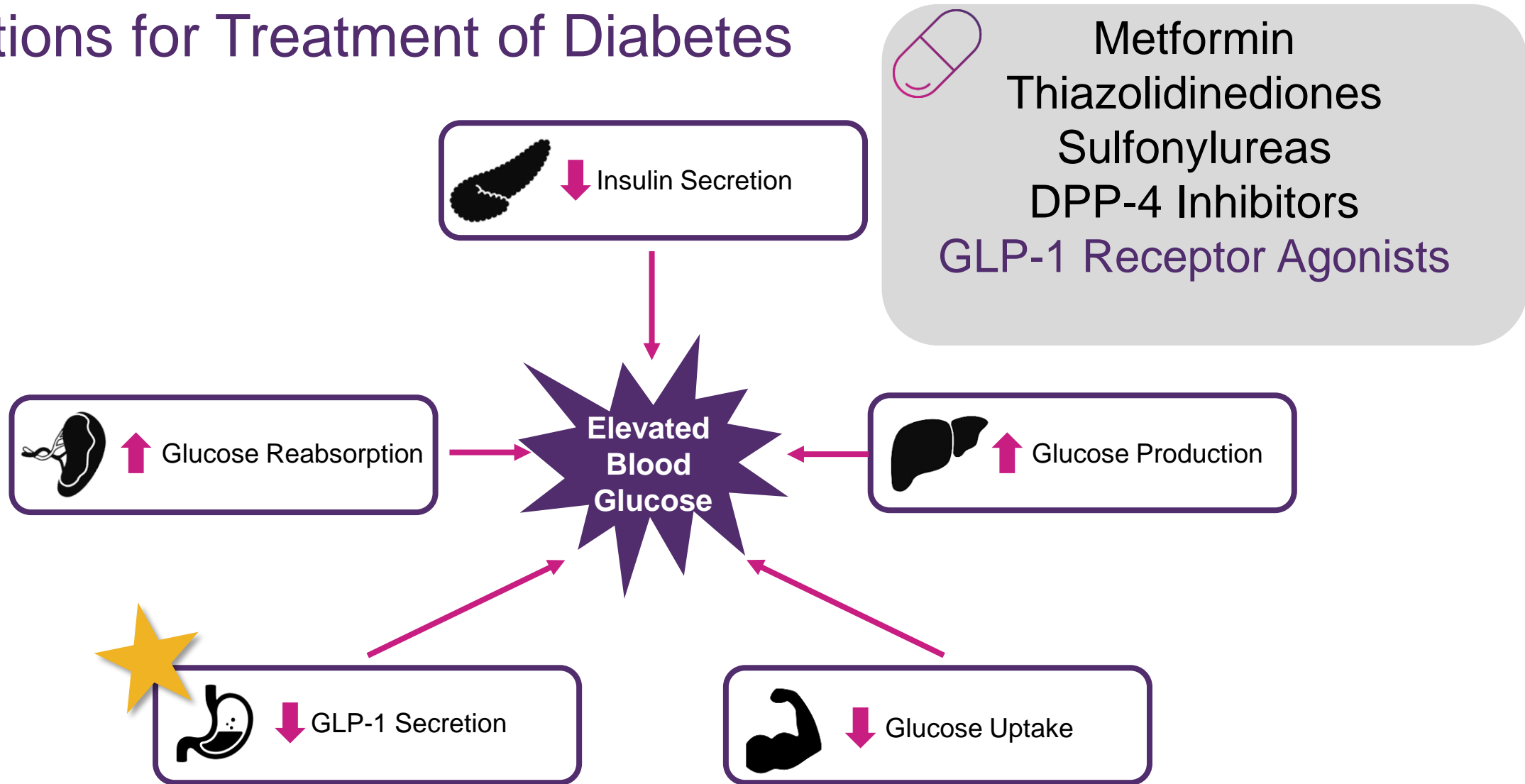
Medications for Treatment of Diabetes



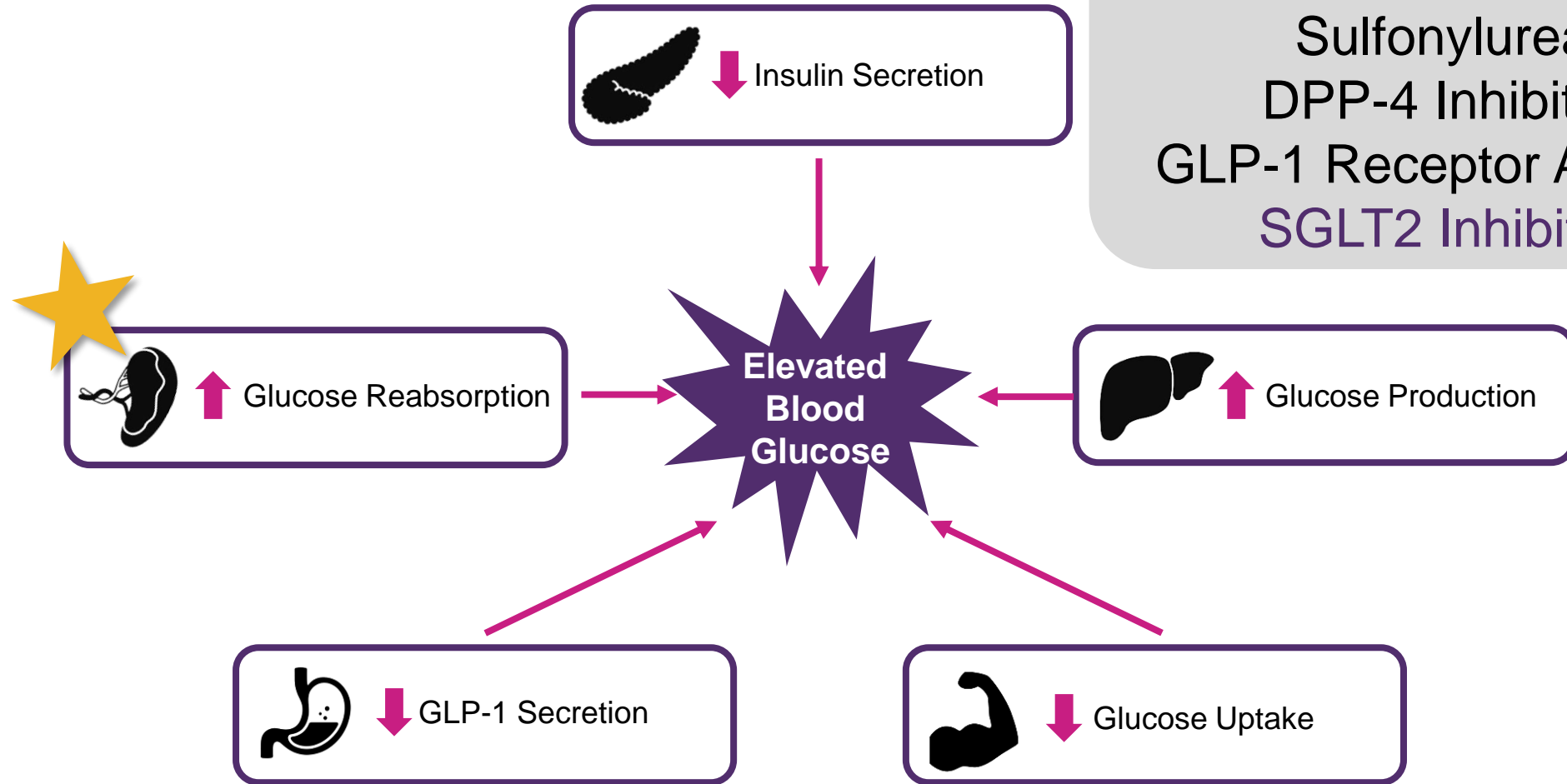
Medications for Treatment of Diabetes




Medications for Treatment of Diabetes



Medications for Treatment of Diabetes

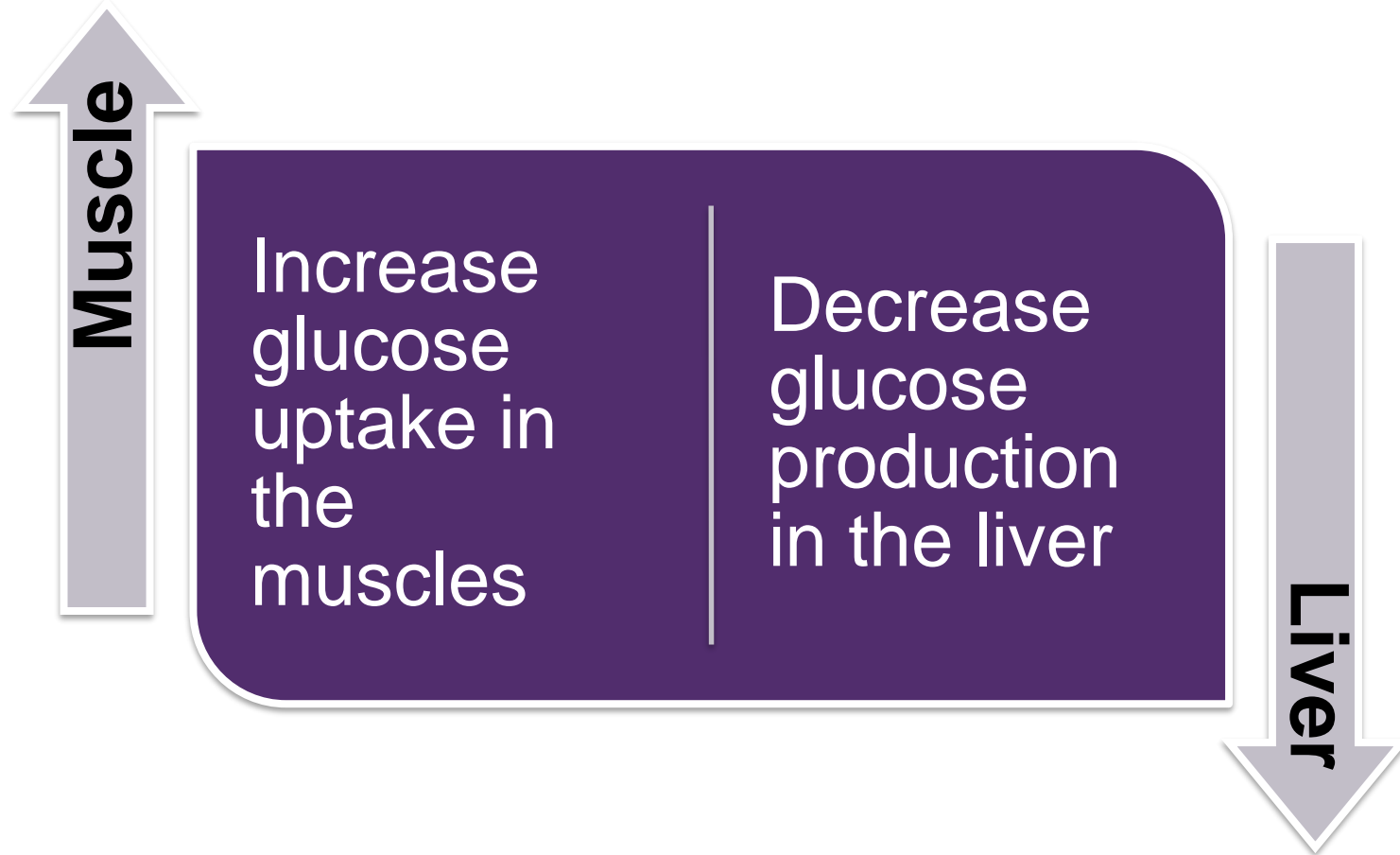


- 
- Metformin
 - Thiazolidinediones
 - Sulfonylureas
 - DPP-4 Inhibitors
 - GLP-1 Receptor Agonists
 - SGLT2 Inhibitors

Medications Used to Treat Type 2 Diabetes



Metformin



Mainstay of therapy for patients with diabetes

- **Low** risk of hypoglycemia
- Common side effects
 - GI upset including nausea and vomiting

Thiazolidinediones (TZDs)

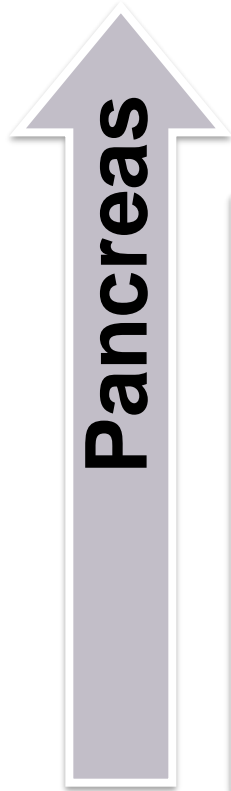
Pioglitazone
Rosiglitazone

Muscle

Increase
glucose
uptake in
the
muscles

- Relatively low risk of hypoglycemia
 - Risk increases when taken in combination with insulin
- Can cause weight gain
- Can lead to edema
 - Should be AVOIDED in patients with heart failure

Sulfonylureas



Increase release of insulin from the pancreas

On Beers List –
Should be avoided
in older adults

- Glipizide
- Glimepiride
- Glyburide

- High risk of hypoglycemia
 - Should not be used in combination with insulin
- Can cause weight gain
- Loss of efficacy over time
 - Beta cell function declines

DPP4

Stomach

Increase amount of GLP-1 in circulation

Glucose dependent secretion of insulin

Pancreas

Sitagliptin
Linagliptin
Saxagliptin
Alogliptin

- **Relatively low** risk of hypoglycemia
 - Does not cause hypoglycemia when used alone
 - Increased risk of hypoglycemia if used in combination with insulin
- Because insulin release is glucose dependent, administration of glucose can cause further hypoglycemia
- Should not be used in combination with GLP-1 receptor agonists

GLP1

Semaglutide
Dulaglutide
Liraglutide
Exenatide

Stomach

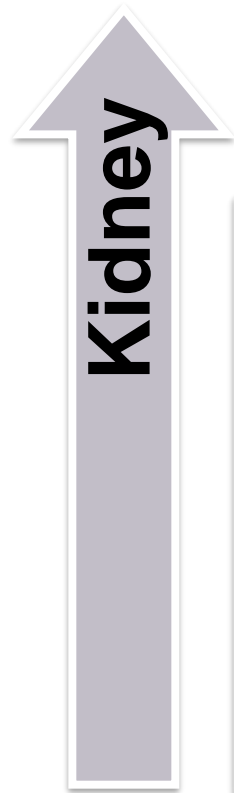
Increase
satiety

Delay
gastric
emptying

Stomach

- Relatively low risk of hypoglycemia
 - Risk increases when taken in combination with insulin
- Can lead to significant weight loss
- Patient's dietary habits may change after starting this medication

SGLT2 Inhibitors



Increased excretion of glucose through kidneys

Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

- Low risk of hypoglycemia
- Common side effects
 - Urinary tract infections
 - Genital yeast infections

The Impact of Exercise on Blood Glucose



Exercise and Blood Glucose – Patients withOUT Diabetes



During exercise, the body uses glucose in the muscles to provide energy.



Glucose in the muscle is unable to move into the body to prevent hypoglycemia.



Exercising muscles are also able to pull glucose from circulation for an additional energy source



Body is able to recognize lowering glucose levels and stops releasing insulin to prevent hypoglycemia

Exercise and Blood Glucose – Patients WITH Diabetes*



During exercise, the body uses glucose in the muscles to provide energy.



Glucose in the muscle is unable to move into the body to prevent hypoglycemia.



Exercising muscles are also able to pull glucose from circulation for an additional energy source



Be able to
manage lowering
glucose levels and
preventing hypoglycemia



Exercise and Blood Glucose – Patients WITH Diabetes*



Patients with diabetes who are on exogenous insulin or secretagogues are unable to compensate for lowering blood glucose due to the medication that has been administered.

Glucose in the muscle is unable to get into the body to prevent hypoglycemia.


Evidence for Cardiometabolic Effect of Diabetes Medications



Why are we using diabetes medicines in patients without diabetes?

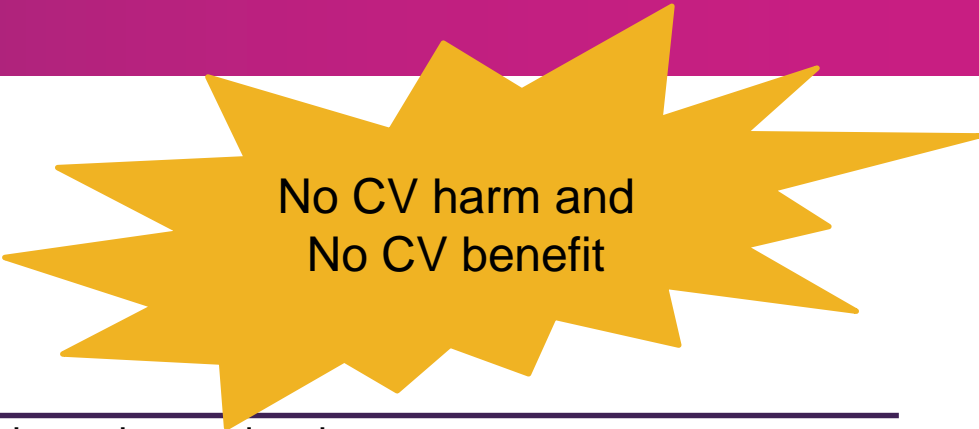
2007 Meta-Analysis
studying cardiovascular
effects of Avandia
suggested increased risk
of MI and CV death

DPP4 inhibitors, SGLT2
inhibitors, GLP1 agonists
approved by FDA



FDA requires new
diabetes drugs to
exclude excess
cardiovascular risk prior
to approval

DPP4 trials in patients with DM



2013

Saxagliptin (Onglyza)

- No difference in composite of cardiovascular death, myocardial infarction, or ischemic stroke vs placebo
- More hospitalizations for heart failure in saxagliptin group vs placebo

2013

Alogliptin (Nesina)

- No difference in composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke vs placebo
- Posthoc analysis did not find significant difference in hospitalizations for heart failure between groups

2015

Sitagliptin (Januvia)

- No difference in first confirmed event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina vs placebo
- No difference in hospitalizations for heart failure between groups

2019

Linagliptin (Tradjenta)

- No difference in time to first occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke vs placebo

GLP1 trials in patients with DM

Liraglutide (Victoza)

- Reduced time to first occurrence of composite death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

Semaglutide (Ozempic)

- Reduced major adverse cardiovascular outcomes (driven by a reduction in nonfatal stroke)

Dulaglutide (Trulicity)

- Reduced time to first occurrence composite death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

GLP1 trials in patients with DM



ASCVD &
renal benefit

Liraglutide (Victoza)

- Reduced time to first occurrence of composite death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
- Fewer renal events vs placebo, driven by lower incidence of new, persistent macroalbuminuria

Semaglutide (Ozempic)

- Reduced major adverse cardiovascular outcomes (driven by a reduction in nonfatal stroke)
- Lower incidence of new or worsening nephropathy, driven by lower incidence of persistent macroalbuminuria

Dulaglutide (Trulicity)

- Reduced time to first occurrence composite death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
- Lower incidence of clinical microvascular outcomes, driven by fewer renal outcomes (significant reduction in development of macroalbuminuria)

GLP1 trials in patients with DM

ASCVD & renal benefit

Liraglutide (Victoza)

- Reduced time to first occurrence of composite death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
- Fewer renal events than placebo, driven by lower incidence of new-onset persistent macroalbuminuria

Semaglutide (Ozempic)

Additional analyses led to studies showing significant weight loss in patients receiving GLP1 agonists

Dulaglutide (Trulicity)

Reduced time to first occurrence composite death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

Lower incidence of clinical cardiovascular outcomes, driven by fewer renal outcomes (significant reduction in development of macroalbuminuria)

GLP1 trials in patients WITHOUT DM

Liraglutide (Saxenda)

- Mean weight loss of 8 kg
- 33% of patients lost over 10% of their body weight

Semaglutide (Wegovy)

- Mean weight loss of 15% of baseline body weight
- Mean weight loss of 15 kg

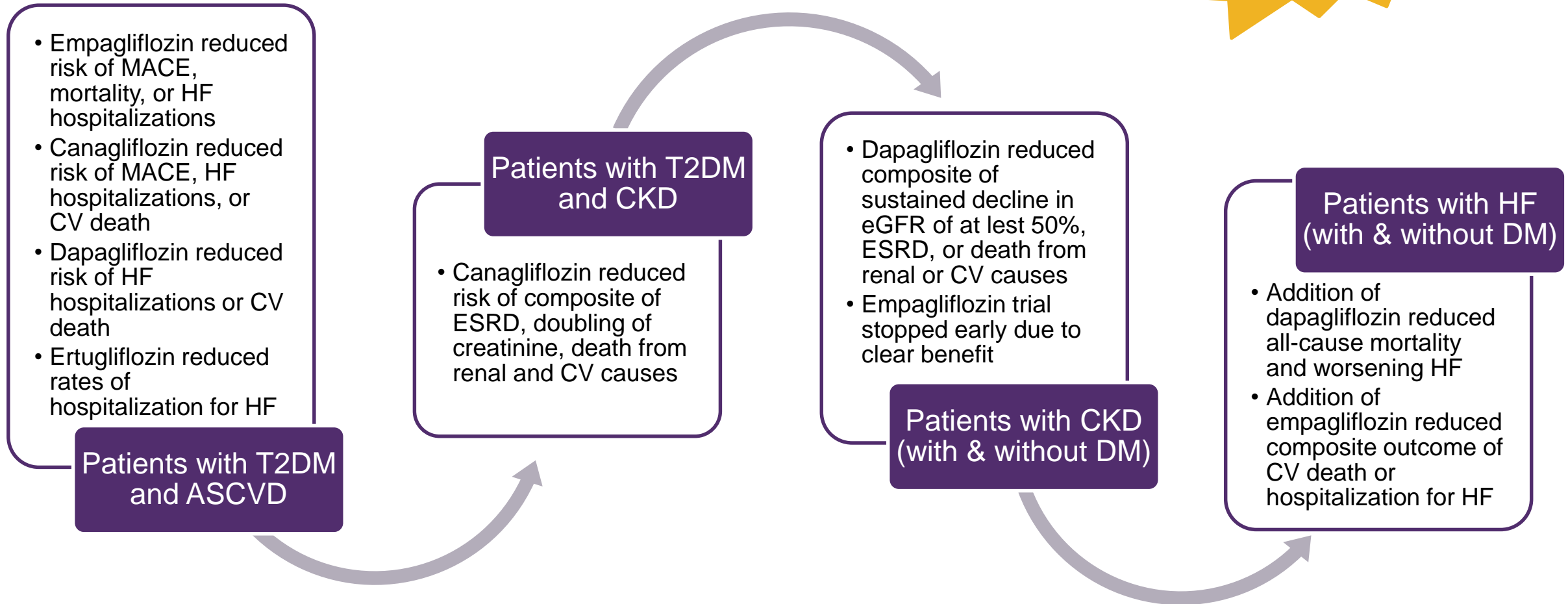
Obesity
management

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graph TD; L["Liraglutide (Saxenda)"] --> O((Obesity management)); S["Semaglutide (Wegovy)"] --> O;
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SGLT2 trials



HF & renal benefit



Patient Cases



Case 1



SP is a 65-year-old female with a PMH of HFrEF and Type 2 DM

Patient was started on Jardiance 10 mg daily 2 weeks ago during her visit with the cardiologist.

Today she presents for initial visit with cardiac rehab. You discover she does not have a blood glucose meter and has not been checking her blood sugars.

Current Medications

Aspirin 81 mg daily
Entresto 24-26 mg twice daily
Furosemide 20 mg daily
Metformin 500 mg twice daily
Metoprolol succinate 50 mg daily

Recent Labs and Vitals

Weight	65 kg
BP	139/89
HR	67
K	4.1
SCr	1.1
BUN	26
A1c	7.0%
EF	32%

#1 What things would you want to monitor for in this patient?

#2 What education could you provide this patient regarding her new medication?

Case 2



RL is a 58-year-old male with a PMH of HFrEF and Afib

Patient was started on Farxiga 10 mg daily 1 week ago.

Today he presents to cardiac rehab. He mentions that he does not understand why his heart doctor started him on Farxiga since his brother takes Farxiga for his diabetes. He is wondering if he needs to start checking his blood sugar at home.

#1 What education could you provide the patient about his new medication?

#2 Would you recommend the patient start checking his blood sugar?

Current Medications

Amiodarone 200 mg daily

Eliquis 5 mg twice daily

Furosemide 40 mg daily

Lisinopril 10 mg daily

Metoprolol succinate 50 mg daily

Recent Labs and Vitals

Weight	92.5 kg
BP	146/87
HR	68
K	4.1
SCr	0.8
BUN	17
EF	27%

Case 3



MJ is a 77-year-old female with a PMH of CAD s/p CABG, T2DM, CKD and obesity

The patient was started on Ozempic 0.25 mg weekly injections to help with weight loss and blood glucose control.

#1 What other disease states could the patient see benefit in when starting Ozempic?

#2 During rehab sessions, what should the patient be monitored for as she starts this new medication?

Current Medications

Aspirin 81 mg daily

Lasix 20 mg daily

Humalog sliding scale

Invokana 300 mg daily

Metoprolol succinate 50 mg daily

Nitroglycerin 0.4 mg PRN chest pain

Rosuvastatin 20 mg daily

Tresiba 16 units nightly

Recent Labs and Vitals

Weight	95 kg
BMI	33 kg/m ²
BP	128/50
HR	72
SCr	1.2
A1c	7.8% (previously 9.0%)

A 67-year-old female with a PMH of diabetes, hypertension, and hyperlipidemia was recently diagnosed with heart failure with reduced ejection fraction. Her current medications include insulin glargine, lisinopril, rosuvastatin, and PRN acetaminophen. Which medication may be beneficial to start in this patient?

A. Metformin

B. Empagliflozin

C. Glipizide

D. Sitagliptin

References

Kelsey MD, Nelson AJ, Green JB, et al. Guidelines for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes: JACC Guideline Comparison. *J Am Coll Cardiol.* 2022;79(18):1849-1857. doi:10.1016/j.jacc.2022.02.046

Winnick JJ, Sherman WM, Habash DL, et al. Short-term aerobic exercise training in obese humans with type 2 diabetes mellitus improves whole-body insulin sensitivity through gains in peripheral, not hepatic insulin sensitivity. *J Clin Endocrinol Metab.* 2008;93(3):771-778. doi:10.1210/jc.2007-1524

Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular cause. *N Engl J Med.* 2007;356:2457-2471. doi: 10.1056/NEJMoa072761

Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial [published correction appears in *Circulation.* 2015 Oct 13;132(15):e198]. *Circulation.* 2014;130(18):1579-1588. doi:10.1161/CIRCULATIONAHA.114.010389

Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet.* 2015;385(9982):2067-2076. doi:10.1016/S0140-6736(14)62225-X

Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes [published correction appears in *N Engl J Med.* 2015 Aug 6;373(6):586]. *N Engl J Med.* 2015;373(3):232-242. doi:10.1056/NEJMoa1501352

References

McGuire DK, Alexander JH, Johansen OE, et al. Linagliptin Effects on Heart Failure and Related Outcomes in Individuals With Type 2 Diabetes Mellitus at High Cardiovascular and Renal Risk in CARMELINA. *Circulation*. 2019;139(3):351-361. doi:10.1161/CIRCULATIONAHA.118.038352

Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827

Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141

Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121-130. doi:10.1016/S0140-6736(19)31149-3

Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. *N Engl J Med*. 2017;377(9):839-848. doi:10.1056/NEJMoa1616011

Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet*. 2019;394(10193):131-138. doi:10.1016/S0140-6736(19)31150

Davies MJ, Bergenstal R, Bode B, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial [published correction appears in *JAMA*. 2016 Jan 5;315(1):90]. *JAMA*. 2015;314(7):687-699. doi:10.1001/jama.2015.9676

References

Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med.* 2015;373(1):11-22. doi:10.1056/NEJMoa1411892

Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med.* 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med.* 2017;377(7):644-657. doi:10.1056/NEJMoa1611925

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2019;380(4):347-357. doi:10.1056/NEJMoa1812389

Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med.* 2020;383(15):1425-1435. doi:10.1056/NEJMoa2004967

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med.* 2017;377(7):644-657. doi:10.1056/NEJMoa1611925

References

Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med.* 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303

Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med.* 2020;383(15):1413-1424. doi:10.1056/NEJMoa2022190