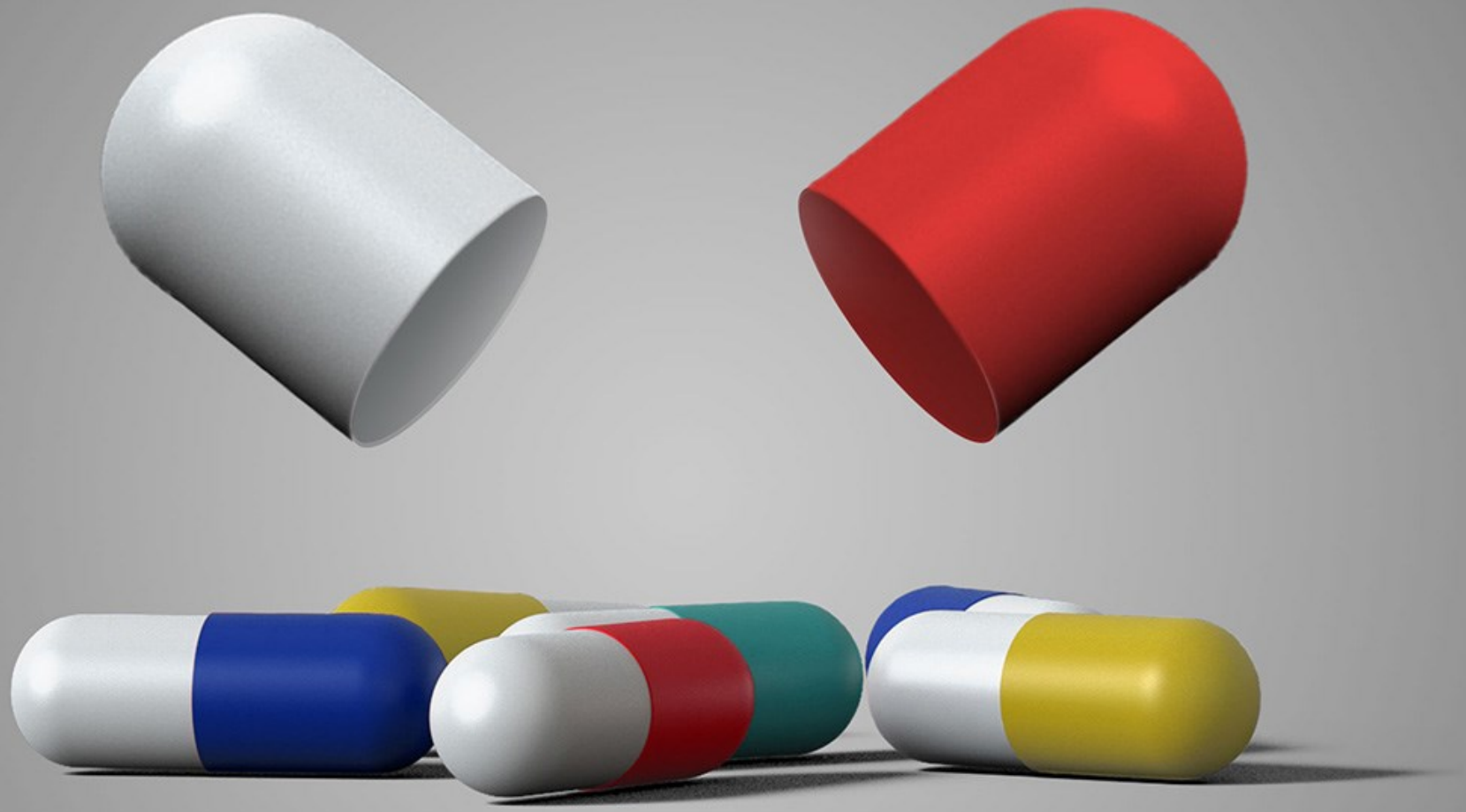


Oral Pharmacologic Therapy for DM2

Marjan Golshani

Endocrinologist; Assistant Professor of internal Medicine

DIABETES MANAGEMENT

01 A person-centered shared decisionmaking approach should guide the choice of glucose-lowering medications for adults with type 2 diabetes.

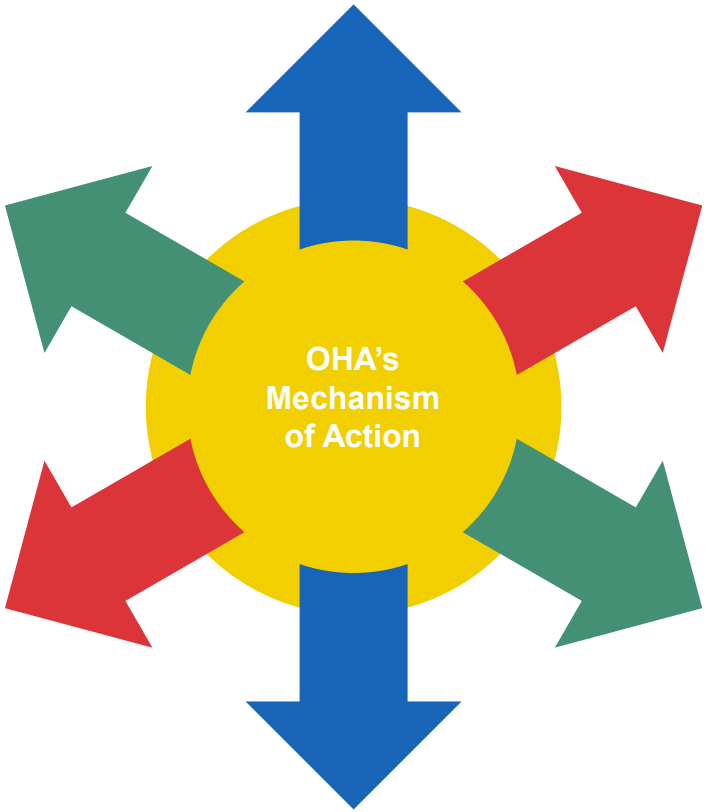
02 Use medications that provide sufficient effectiveness to achieve and maintain intended treatment goals with consideration of the effects on cardiovascular, kidney, weight, and other relevant comorbidities; hypoglycemia risk; cost and access.

03 Combination therapy can be considered in adults with type 2 diabetes at treatment initiation to shorten time to attainment of individualized treatment goals.

GLUCOSE LOWERING AGENTS

Reducing GI absorption

promote urinary excretion of glucose

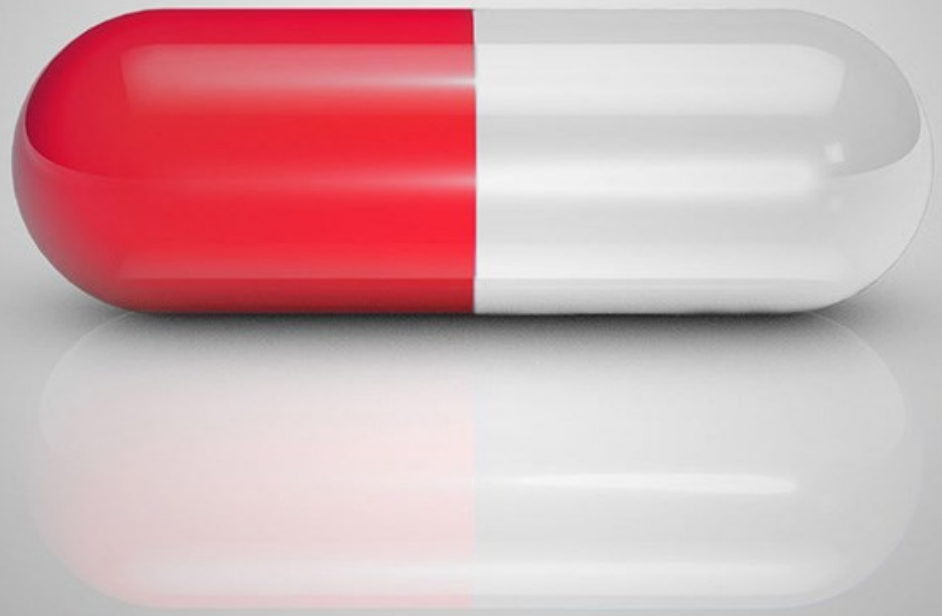


agents that increase insulin secretion

enhance GLP-1 action

reduce glucose production

increase insulin sensitivity



BIGUANIDES

Metformin

01 Reduces hepatic glucose production, and improves peripheral glucose utilization slightly

02 Metformin acts in multiple tissues, but its mechanism of action remains undefined.

03 Metformin reduces FBS and insulin levels, improves the lipid profile, and promotes modest weight loss.

04 Long-term use is associated with reduced micro- and macrovascular complications.

BIGUANIDES

Metformin's Mechanism of Action: Not Fully Understood

1. Metformin activates AMP-activated protein kinase (AMPK) in the liver.
   AMPK suppresses genes involved in gluconeogenesis, thereby **reducing hepatic glucose output**

2. Metformin enhances insulin action in peripheral tissues, **improving glucose uptake** and utilization.

3. Metformin slightly **reduces glucose absorption** from the gut, contributing to its glucose-lowering effect. And **mildly reduce appetite**.

4. Metformin **alters gut microbiota** and may **increase GLP-1 secretion**, indirectly aiding glycemic control.

HOW TO PRESCRIBE?

Initial: 500 mg twice daily, with the two largest meals

Administer with a meal to decrease GI upset

ER tablets: do not crush, cut or chew. Administer once daily doses with the evening meal.

The FBS begins to decrease within 3 to 5 days after therapy is started and reaches a nadir within 1 to 2 weeks

Adjustment: 500 mg/d every 1-2 weeks to Maximum dose of 2000 mg/d

80-85% of the maximal glucose-lowering effect is observed with a daily dose of 1500 mg

SIDE EFFECTS

Lactic acidosis

is very rare and can be prevented by careful patient selection

GI effects

- ✓ Include diarrhea, nausea, flatulence, dyspepsia, vomiting and abdominal pain.
- ✓ Dose related mechanism not fully understood
- ✓ Typically occurs at initiation of therapy.
- ✓ Generally subside after several weeks of therapy
- ✓ Risk factors: rapid dose escalation, IR formulations, H-pylori infection, Chronic asymptomatic gastritis

Vitamin B12 Deficiency

- ✓ Long term use of metformin is associated with reversible b12 deficiency and subsequent anemia and neuropathy.
- ✓ Risk factors: inadequate b12 store, poor nutrition, inadequate calcium intake or absorption

Discontinuation of therapy because of side effects occurs in less than 4% of patients.

CONTRAINDICATIONS

Metformin should not be used in:

- ✓ patients with moderate renal insufficiency (glomerular filtration rate [GFR] <30 mL/min)
- ✓ any form of acidosis
- ✓ unstable congestive heart failure (CHF)
- ✓ liver disease
- ✓ severe hypoxemia
- ✓ Excessive alcohol intake

Metformin should be discontinued in:

- ✓ hospitalized patients
- ✓ patients who can take nothing orally
- ✓ those receiving radiographic contrast material.

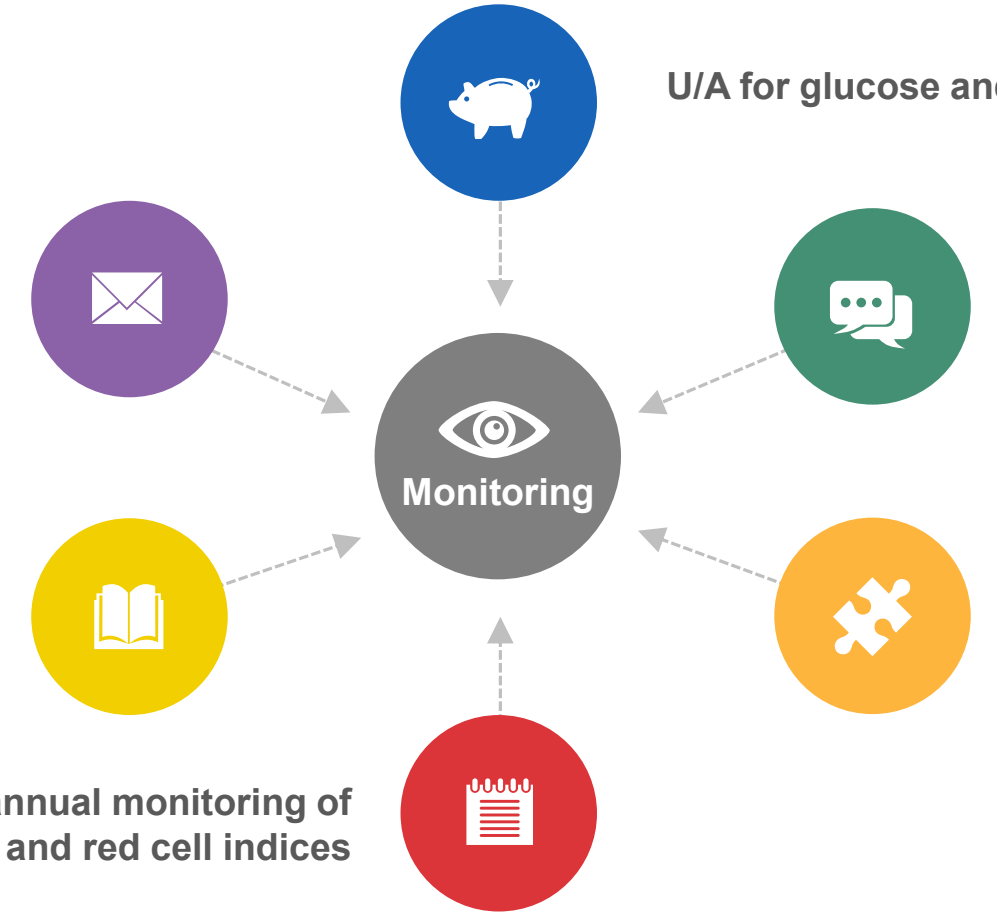
Pregnancy

Metformin crosses the placenta; concentration may be compatible to or higher than those found in the maternal plasma.

Breast feeding

Metformin is present in breast milk.
The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant and the benefits of treatment to the mother.

MONITORING



U/A for glucose and ketones

Folate level if megaloblastic anemia is suspected.

Blood glucose level

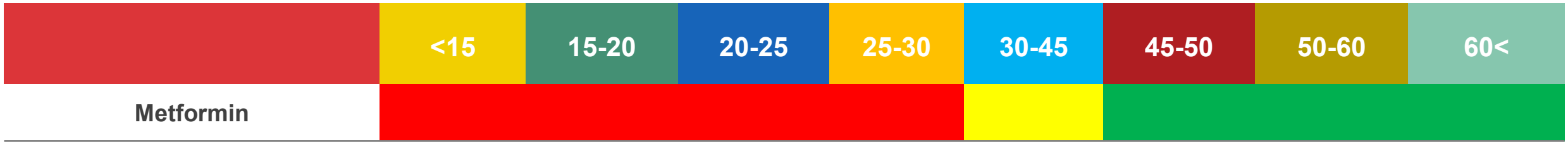
B12 level every 1-2 years specially in >4 years use of metformin

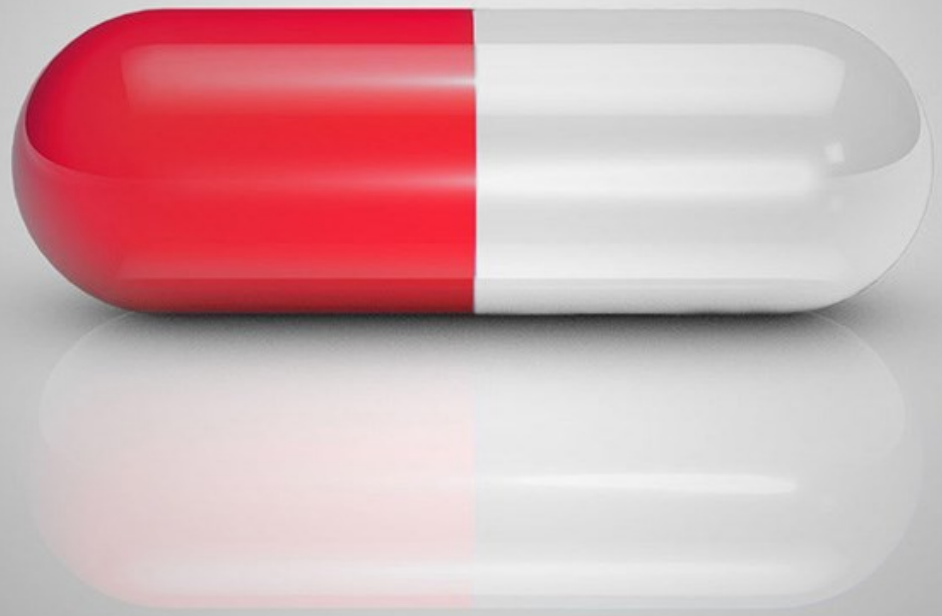
eGFR: prior to therapy and at least annually and
every 3-6 month if eGFR<60 and
every 1-3 month in patients with hepatic impairment

CBC: initial and annual monitoring of Hb/Hct and red cell indices

Text Here	EXAMPLES	HBA1C REDUCTION	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Biguanides	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency	eGFR <30, CHF, radiographic contrast studies, hospitalized patients, acidosis
Sulfonylureas	Glibenclamide, gliclazide	1–2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver insufficiency
Meglitinides	Repaglinide	0.5–1	Short onset of action, lower postprandial glucose	Hypoglycemia	liver insufficiency
Thiazolidinediones	Pioglitazone, rosiglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, renal/liver insufficiency
DPP4-i	Alogliptin, linagliptin, saxagliptin, sitagliptin, Vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia	Angioedema/urticarial and immune-mediated dermatologic effects	Reduced dose with renal insufficiency
α-Glucosidase inhibitors	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, elevated LFT	Renal/liver insufficiency
SGLT2-i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1.0	Do not cause hypoglycemia, ↓weight and BP, renal protective, ↓CV events	Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA	Severe renal insufficiency, insulin deficient DM

DOSE ADJUST IN CKD





INSULIN SECRETAGOGUES VIA ATP-SENSITIVE K+ CHANNEL:

SULFONYLUREAs

SULFONYLUREAs

01 stimulate insulin secretion by interacting with the ATP-sensitive potassium channel on the beta cell

02 These drugs are most effective in individuals with type2 DM of relatively recent onset (<5 years) who have residual endogenous insulin production.

03 First-generation sulfonylureas: chlorpropamide, tolazamide, tolbutamide; have a longer half-life, a greater incidence of hypoglycemia, and more frequent drug interactions, and are no longer used.

04 Second-generation sulfonylureas: more rapid onset of action; better coverage of the postprandial glucose rise, but the shorter half-life, some agents may require more than once-a-day dosing.

SULFONYLUREAs

05 reduce both fasting and postprandial glucose

06 sulfonylureas increase insulin acutely and thus should be taken shortly before a meal

07 Long-term use is associated with reduced micro- and macrovascular complications. But have no specific effect on plasma lipids or blood pressure

08 have the potential to cause hypoglycemia, especially in elderly individuals: delayed meals, increased physical activity, alcohol intake, or renal insufficiency

SULFONYLUREAs

09 Most sulfonylureas are metabolized in the liver to compounds that are cleared by the kidney.

10 their use in individuals with significant hepatic or renal dysfunction is not advisable.

11 Weight gain is a common side effect of sulfonylurea therapy.

12 Some sulfonylureas have significant drug interactions with alcohol and some medications including warfarin, aspirin, ketoconazole, α-glucosidase inhibitors, and fluconazole.

GLIBENCLAMIDE (GLYBURIDE): Tablet 5 mg

01 Has high affinity to a related isoform of ATP-sensitive potassium channels in the myocardium and the brain

03 Despite concerns that this agent might affect the myocardial response to ischemia, studies have not shown an increased cardiac mortality with it.

HOW TO PRESCRIBE?

Initial: 2.5-5 mg once daily, with breakfast or the first main meal

Maintenance: 1.25-20 mg/day given as single or divided doses

In patients who are more sensitive to hypoglycemic drugs, start at 1.25 mg/day

maximum: 20 mg/day

Adjustment: no more than 2.5 mg/day every 1-4 weeks based on the patient's blood glucose response

Doses >10 mg/day should be administered in divided doses

SIDE EFFECTS

Hypoglycemia

- ✓ occurs more frequently in patients who have type 2 diabetes with mild fasting hyperglycemia (140 mg/dL)
- ✓ typically occurring 2 to 3 hours after breakfast or during exercise.

Weight gain

- ✓ Because of increase in insulin level and
- ✓ Stimulation of appetite

Disulfiram like reaction

- ✓ Should not be used with alcohol

CONTRAINDICATIONS

Glibenclamide should not be used in:

- ✓ patients with renal insufficiency eGFR <60 mL/min
- ✓ liver disease or frank jaundice
- ✓ Excessive alcohol intake
- ✓ In G6PD deficiency may cause hemolytic anemia
- ✓ Hypersensitivity to sulfonamide

Pregnancy

- ✓ Gibenclamide crosses the placenta;
- ✓ may cause severe hypoglycemia lasting 4-10 days in infants
- ✓ Not recommended as an initial therapy

Breast feeding

Gibenclamide is present in breast milk.

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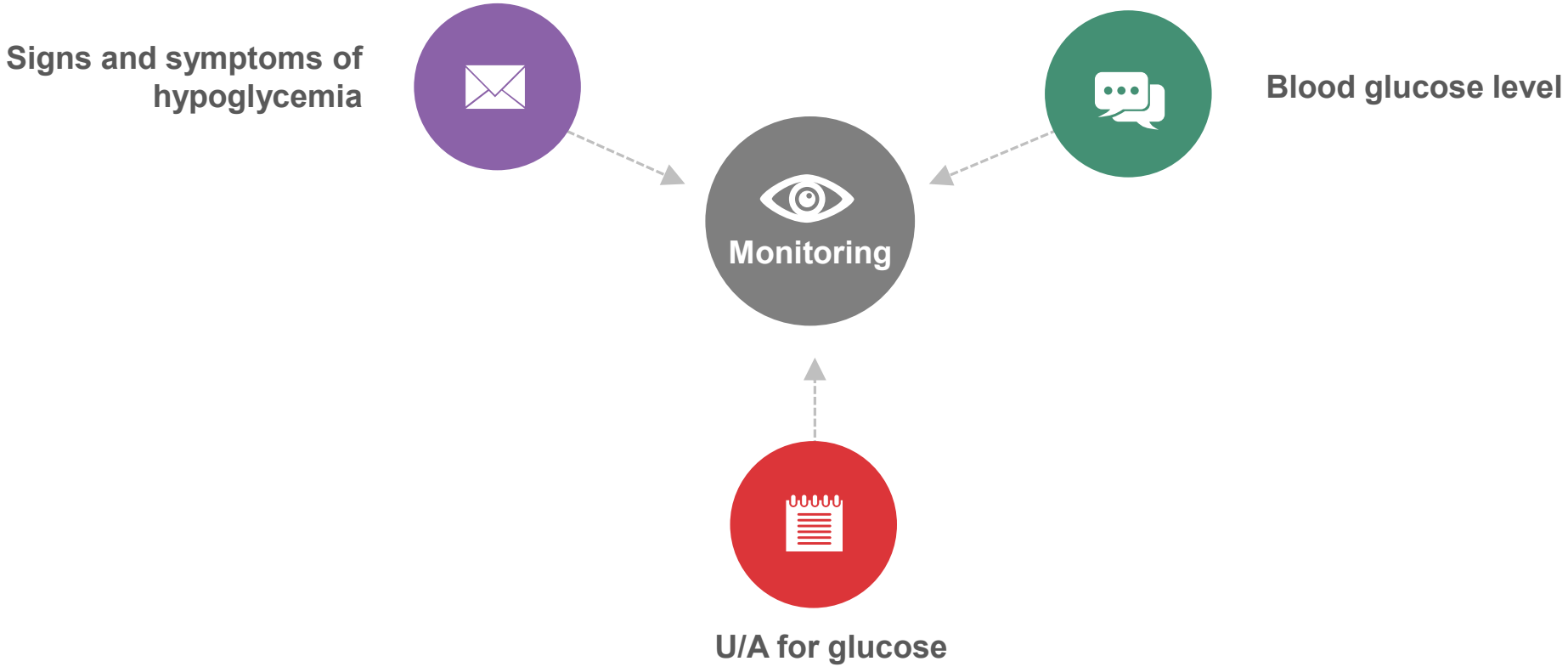
MONITORING


Signs and symptoms of hypoglycemia
Blood glucose level
Monitoring
U/A for glucose

GLICLAZIDE: 30mg MR, 60mg MR, 80mg IR

01 Patients who are NPO may need doses held to avoid hypoglycemia.

02 Administer with meal, MR tablets should be administered with breakfast.

03 May split 60mg MR tablets in half; however the 30mg MR tablet must be swallowed whole.

04 MR tablets should not be crushed or chewed

HOW TO PRESCRIBE?

Tablet IR initial: 40-80mg once daily with first main meal

Tablet MR initial: 30mg once daily with first main meal

Adjustment IR tablets: 40-80 mg increments every 1-4 weeks based on the patient's blood glucose response

Adjustment MR tablets: 30 mg increments every 1-4 weeks based on the patient's blood glucose response

maximum: 320 mg/day
Doses ≥ 160 mg/day should be divided in 2 doses

maximum: 120 mg/day

SIDE EFFECTS

Hypoglycemia

- ✓ occurs more frequently in patients who have type 2 diabetes with mild fasting hyperglycemia (140 mg/dL)
- ✓ typically occurring 2 to 3 hours after breakfast or during exercise.

Weight gain

- ✓ Because of increase in insulin level and
- ✓ Stimulation of appetite

Disulfiram like reaction

- ✓ Should not be used with alcohol

CONTRAINDICATIONS

Gliclazide should not be used in:

- ✓ In patients with eGFR <60 mL/min use with caution, and in eGFR< 15 mL/min avoid use if possible.
- ✓ liver disease: Use conservative initial and maintenance doses and avoid use in severe disease.
- ✓ In G6PD deficiency may cause hemolytic anemia
- ✓ Hypersensitivity to sulfonamide

Pregnancy

- ✓ Gliclazide is contraindicated in pregnancy.

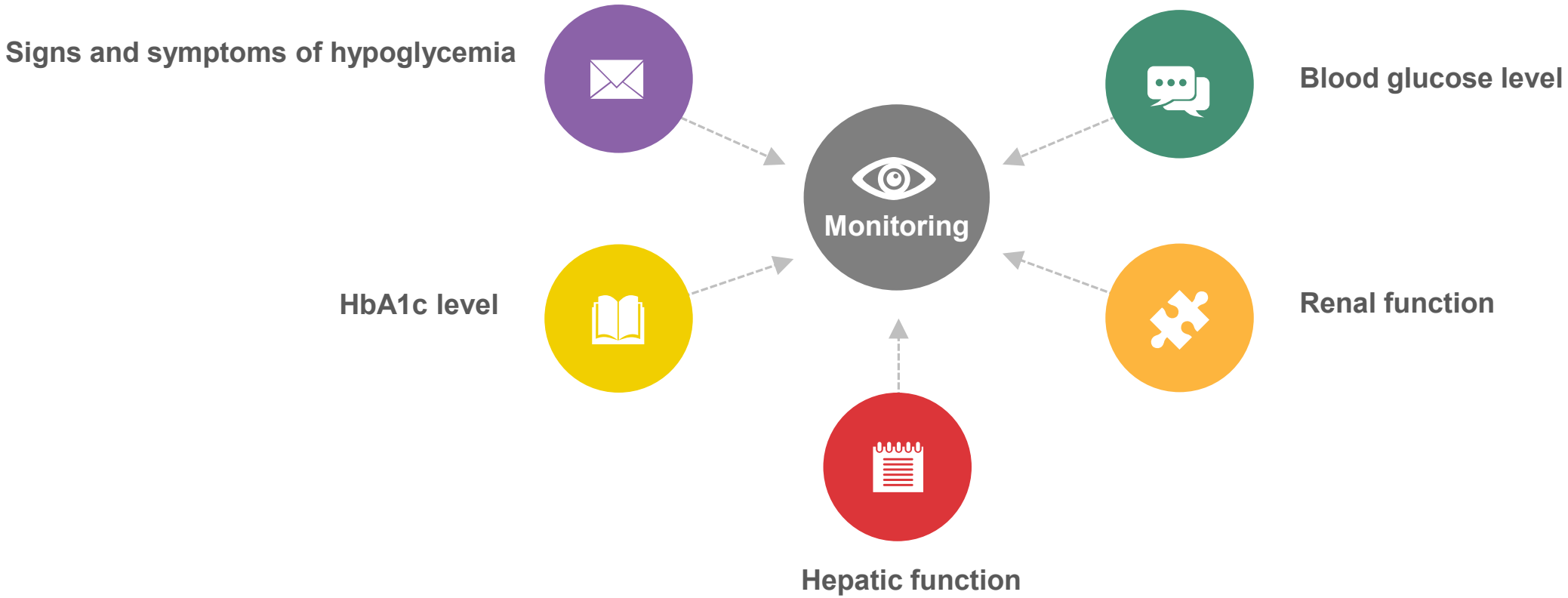
Breast feeding

Gliclazide is contraindicated in breastfeeding mothers.

Reproductive Consideration

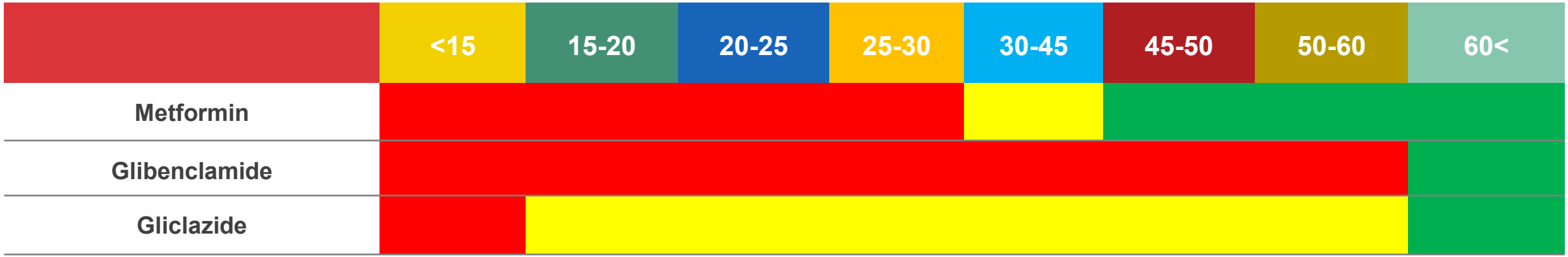
Not recommended for whom planning to become pregnant.

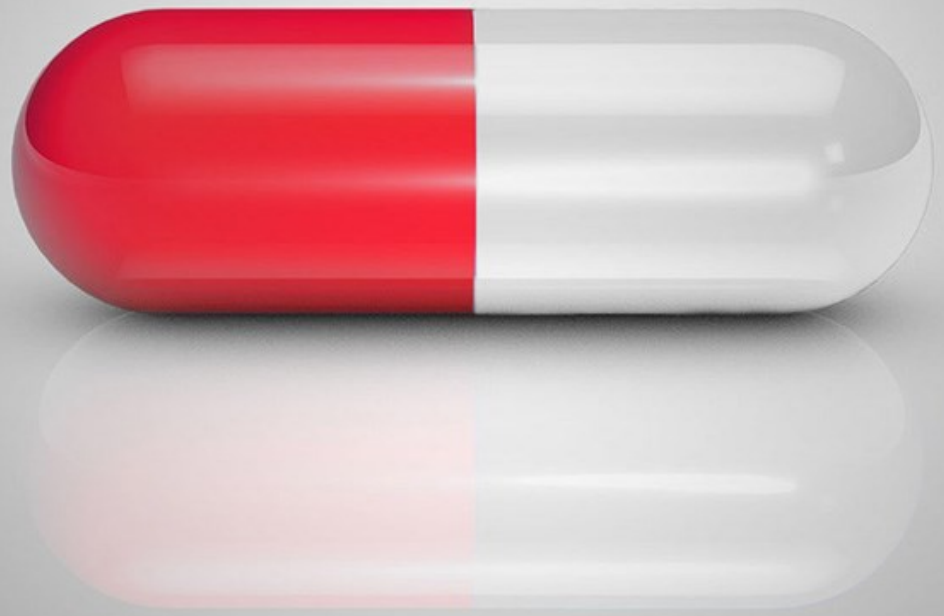
MONITORING


Signs and symptoms of hypoglycemia
Blood glucose level
Monitoring
HbA1c level
Renal function
Hepatic function

Text Here	EXAMPLES	HBA1C REDUCTION	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Biguanides	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency	eGFR <30, CHF, radiographic contrast studies, hospitalized patients, acidosis
Sulfonylureas	**Glibenclamide, gliclazide**	**1–2**	**Short onset of action, lower postprandial glucose, inexpensive**	**Hypoglycemia, weight gain**	**Renal/liver insufficiency**
Meglitinides	Repaglinide	0.5–1	Short onset of action, lower postprandial glucose	Hypoglycemia	liver insufficiency
Thiazolidinediones	Pioglitazone, rosiglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, renal/liver insufficiency
DPP4-i	Alogliptin, linagliptin, saxagliptin, sitagliptin, Vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia	Angioedema/urticarial and immune-mediated dermatologic effects	Reduced dose with renal insufficiency
α-Glucosidase inhibitors	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, elevated LFT	Renal/liver insufficiency
SGLT2-i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1.0	Do not cause hypoglycemia, ↓weight and BP, renal protective, ↓CV events	Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA	Severe renal insufficiency, insulin deficient DM

DOSE ADJUST IN CKD





NONSULFONYLUREA INSULIN SECRETAGOGUES:

MEGLITINIDEs

MEGLITINIDEs

01 Increase endogenous insulin secretion by binding to the sulfonylurea receptor at a different site.

02 The onset of action is faster and the half-life is shorter in comparison to sulfonylureas.

03 These compounds are metabolized in the liver through the cytochrome p450 system into inactive biliary products. So are safe in renal failure.

04
- ✓ They target post-meal glucose levels.
- ✓ are particularly useful for people who often miss meals and would otherwise have a high risk of hypoglycemia.

REPAGLINIDE: TABLET 0.5, 1, 2 mg

01 Repaglinide is rapidly absorbed (0.5 to 1 hours) and displays rapid plasma elimination (half-life , 1 hour).

02 Duration of action is about 4-5 hours.
We can call them oral rapid acting insulin!

03 These medicines may be useful for older adults.

04 They may be taken 3 or even 4 times daily.

HOW TO PRESCRIBE?

Initial: 0.5 mg three times daily, given 30 minutes before each meal

1mg three times daily produces 90% of the maximal glucose-lowering effect .

Adjustment: weekly

If a meal is missed, do not administer next scheduled dose.

Maximum : 16 mg

If hypoglycemia occurs, reduce dose.

CONTRAINDICATIONS

Repaglinide should not be used in:

- ✓ Severe hepatic impairment
- ✓ Concurrent use with clopidogrel

Pregnancy

- ✓ Low potential to cross placenta
- ✓ Information limited so other agents are preferred.

Breast feeding

- ✓ It is not known if repaglinide is present in breast milk
- ✓ It is not recommended

.

Text Here	EXAMPLES	HBA1C REDUCTION	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Biguanides	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency	eGFR <30, CHF, radiographic contrast studies, hospitalized patients, acidosis
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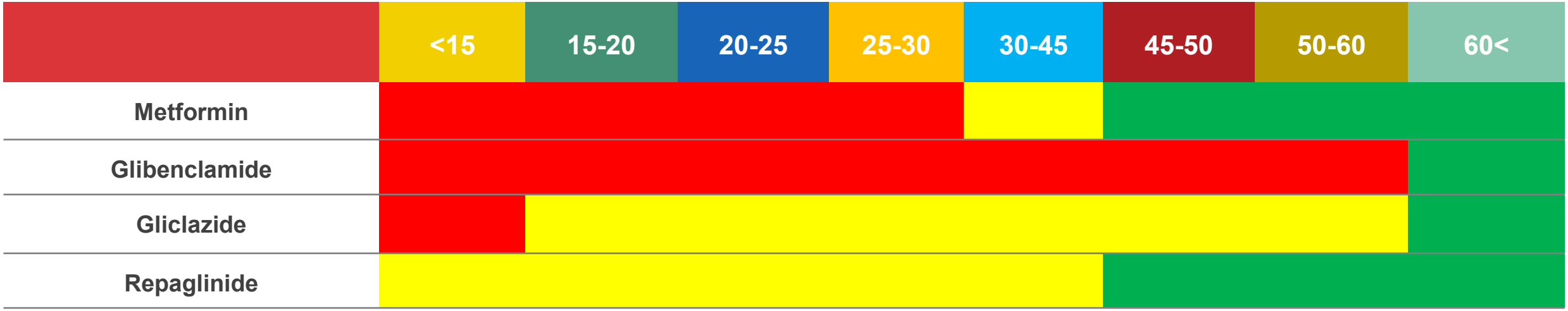
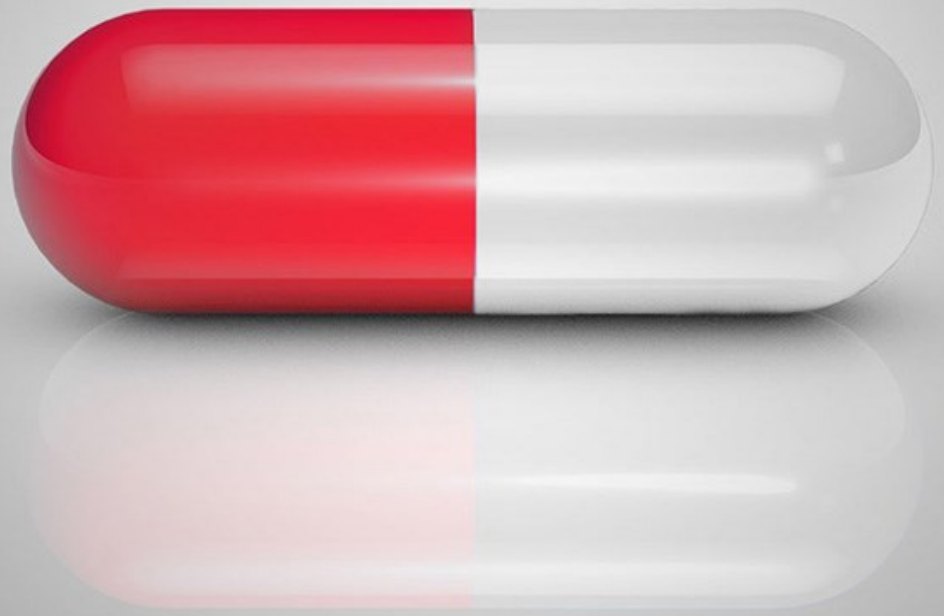
Meglitinides	**Repaglinide**	**0.5–1**	**Short onset of action, lower postprandial glucose**	**Hypoglycemia**	**liver insufficiency**
Thiazolidinediones	Pioglitazone, rosiglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, renal/liver insufficiency
DPP4-i	Alogliptin, linagliptin, saxagliptin, sitagliptin, Vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia	Angioedema/urticarial and immune-mediated dermatologic effects	Reduced dose with renal insufficiency
α-Glucosidase inhibitors	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, elevated LFT	Renal/liver insufficiency
SGLT2-i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1.0	Do not cause hypoglycemia, ↓weight and BP, renal protective, ↓CV events	Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA	Severe renal insufficiency, insulin deficient DM

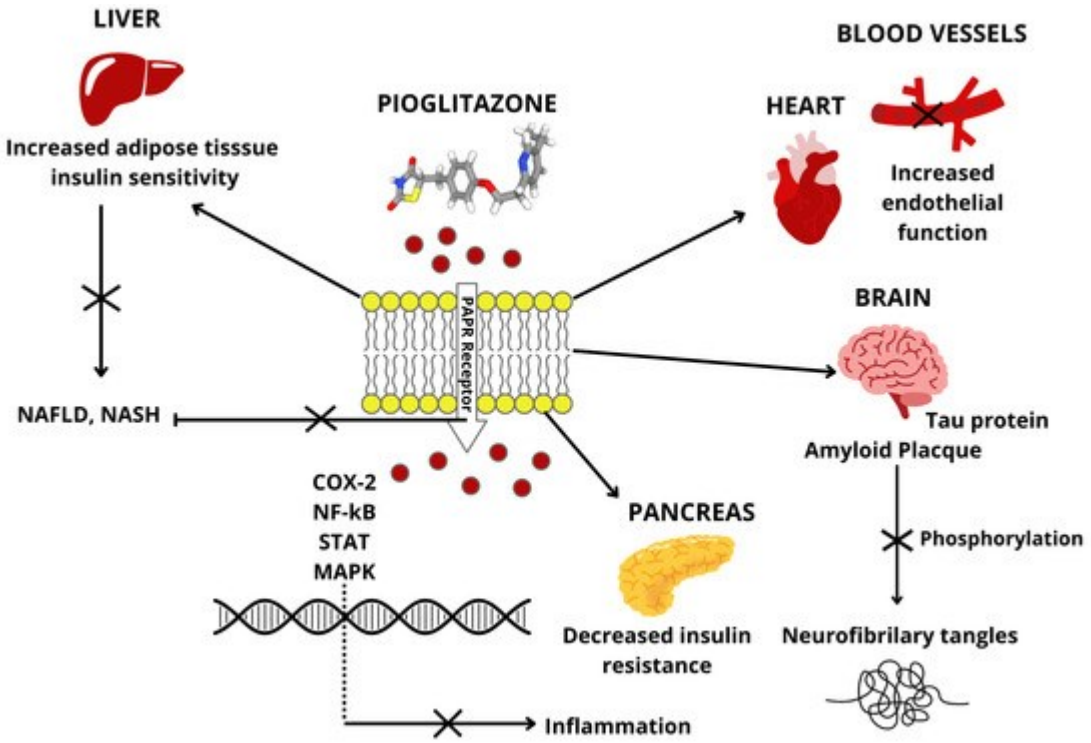
DOSE ADJUST IN CKD





THIAZOLIDINEDIONEs

THIAZOLIDINEDIONEs



Mechanism of Action:

Activation of PPAR-γ receptor

1. pioglitazone activates the PPAR-γ receptor, increasing insulin sensitivity, without inducing insulin release from pancreatic cells
2. The PPAR-γ receptor is found at highest levels in adipocytes but is expressed at lower levels in many other tissues.
3. PPAR-γ receptor Agonists regulate a large number of genes, promote adipocyte differentiation, reduce hepatic fat accumulation, and promote fatty acid storage.
4. They promote a redistribution of fat from central to peripheral locations.

Thiazolidinediones

01 Thiazolidinediones reduce insulin resistance

02 Because of reduction in insulin resistance, they reduce circulating insulin levels.

03 They are metabolized by the cytochrome P450 hepatic enzymes with a half-life of approximately 9 h, and excreted in the urine.

04 When used as monotherapy or with metformin, they do not cause hypoglycemia.

PIOGLITAZONE: TABLET 15, 30, 45 mg

01 Women who previously were not menstruating due to PCOS may ovulate. Therefore, birth control should be discussed with these women prior to starting treatment.

02 No adjustment is necessary in CKD

03 PROactive study: Pioglitazone added to current therapy for T2DM patients with vascular disease reduced CV events (secondary endpoint).

04 raises HDL to a greater degree and LDL a lesser degree but lowers triglycerides.

HOW TO PRESCRIBE?

Initial: 15-30 mg once daily

Administer without regard to meal

Adjustment: may increase in 15mg/day increments every 4-12 weeks.

Although some effect can be seen in 2-3 weeks, it may take 6-12 weeks to observe the full BS lowering effect.

Maximum: 45 mg/day

Therapy should not be initiated if the patient exhibits active liver disease or increased transaminases (>2.5 times ULN) at baseline.

SIDE EFFECTS

Weight Gain

About 2–3 kg weight gain, is dose related. Mechanism: unknown but may be due to fluid retention and fat accumulation. However, the distribution of fat appears to be improved from a metabolic point of view — there is less visceral fat and more peripheral fat

Edema

See in 3-27% of patients, specially when used with insulin

Anemia

It may decrease Hb/Hct; may be related to increased plasma volume

Macular Edema

- ✓ May be new onset or worsening.
- ✓ Most have peripheral edema at time of diagnosis

CHF

Should not be prescribed in CHF.

Fracture in post menopausal women?

Bladder cancer: do not use in individuals with active bladder cancer, and use caution in those with prior history of bladder cancer.

CONTRAINDICATIONS

Pioglitazone should not be used in:

- ✓ Heart failure
- ✓ Serious hepatic impairment
- ✓ Active bladder cancer
- ✓ History of bladder cancer
- ✓ Uninvestigated macroscopic hematuria
- ✓ pregnancy

Remember:

- ✓ It is not contraindicated in renal insufficiency

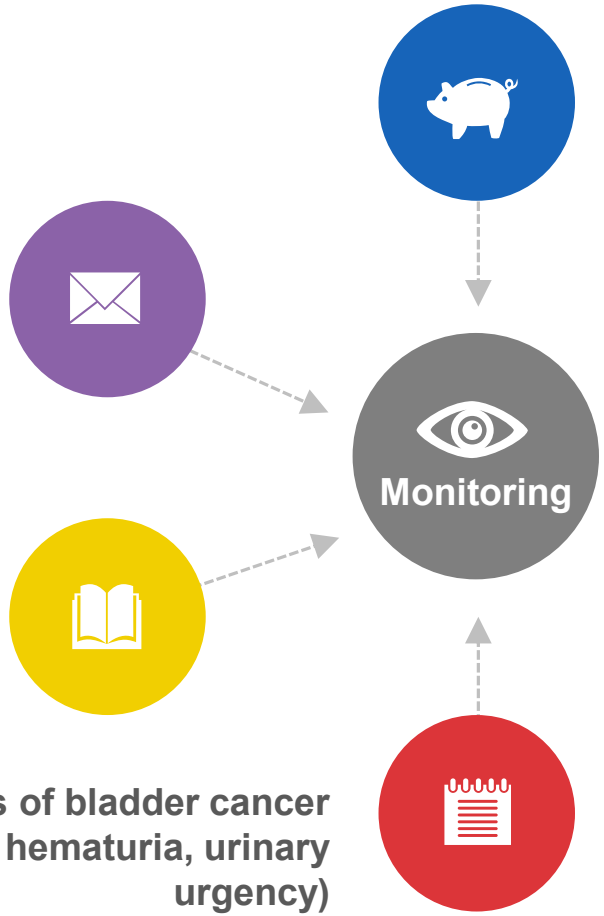
Pregnancy

Not recommended

Breast feeding

It is not known if pioglitazone is present in breast milk.
The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant and the benefits of treatment to the mother.

MONITORING



Signs and symptoms of heart failure (rapid weight gain, dyspnea, edema)

Patient's weight

Blood glucose level

Ophthalmologic examination

Signs and symptoms of bladder cancer (dysuria, macroscopic hematuria, urinary urgency)

- ✓ Liver enzymes (ALT, AST, Alkp, Bili) prior to initiation, continue periodic monitoring
- ✓ During treatment if ALT levels elevate >3 times ULN, the test should be repeated as soon as possible. If ALT levels remain >3 times ULN or if the patient is jaundiced, therapy should be discontinued.

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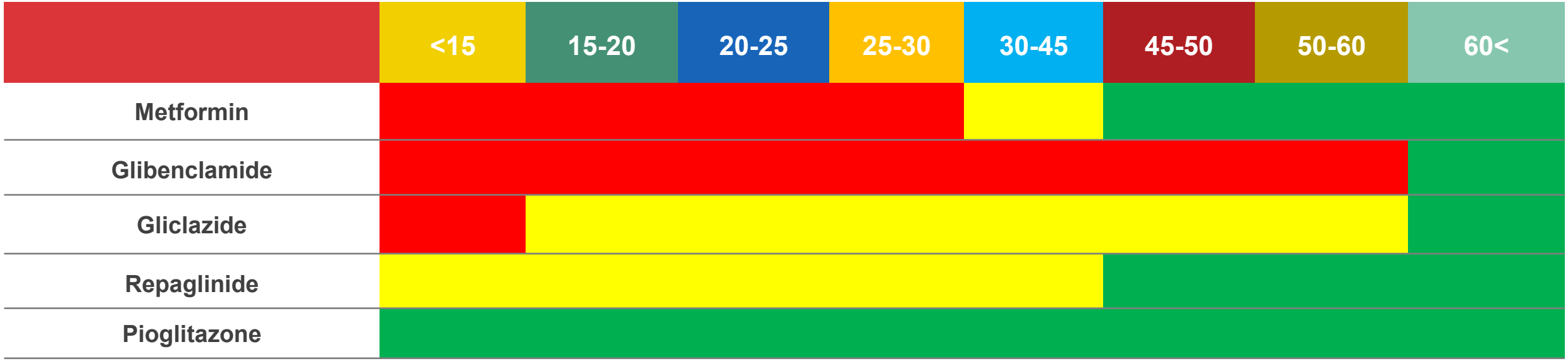
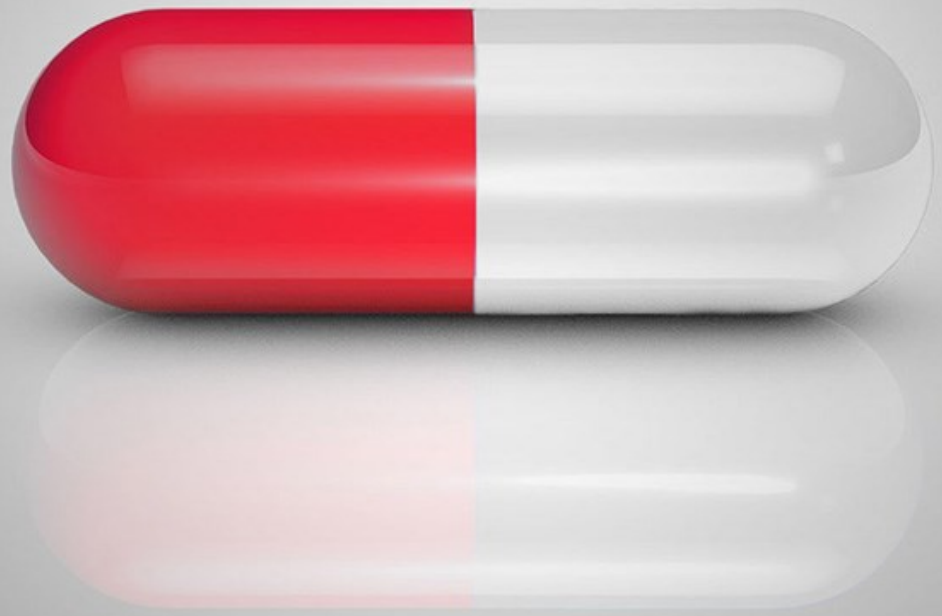
SGLT2-i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1.0	Do not cause hypoglycemia, ↓weight and BP, renal protective, ↓CV events	Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA	Severe renal insufficiency, insulin deficient DMf

DOSE ADJUST IN CKD

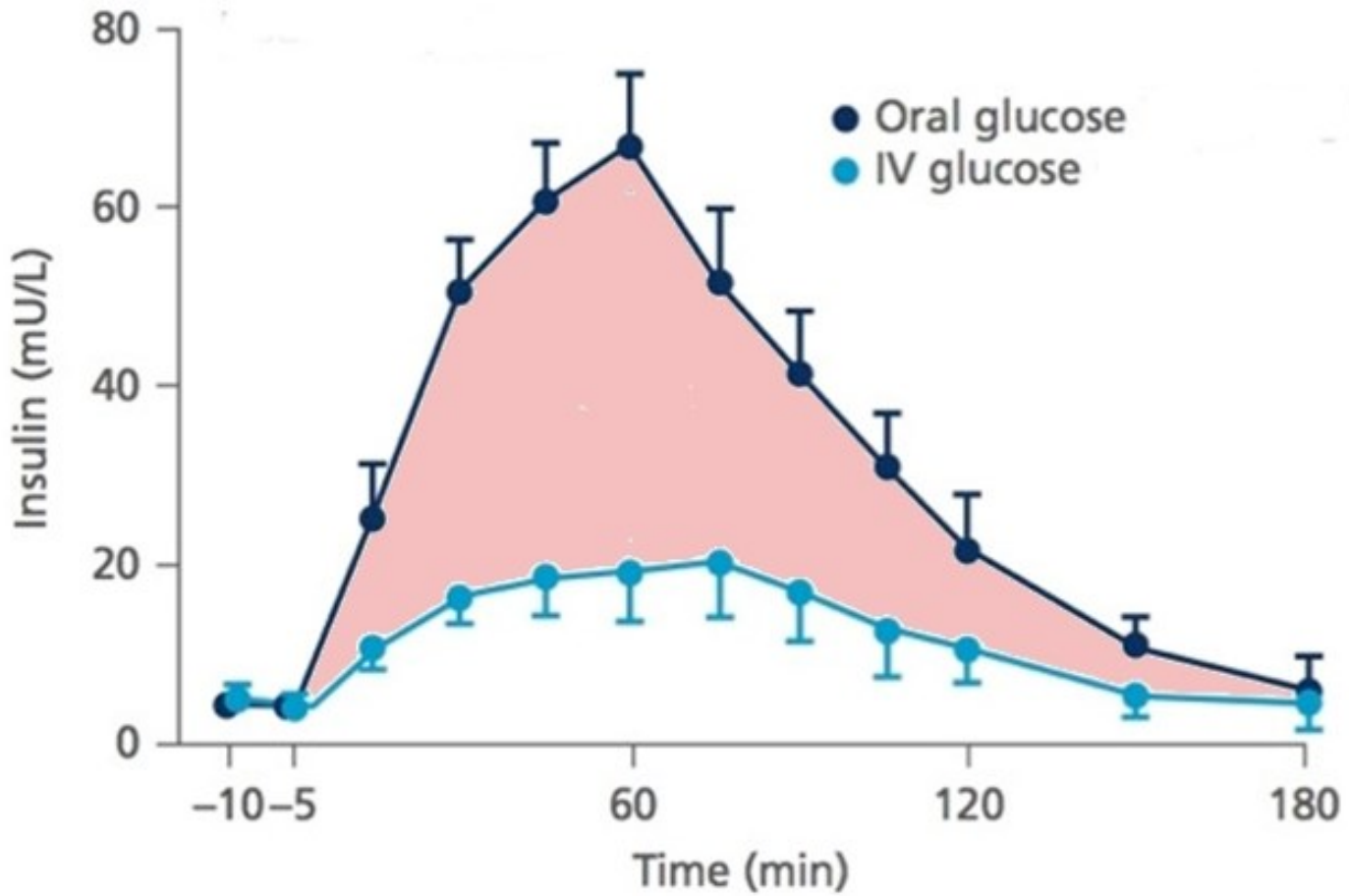


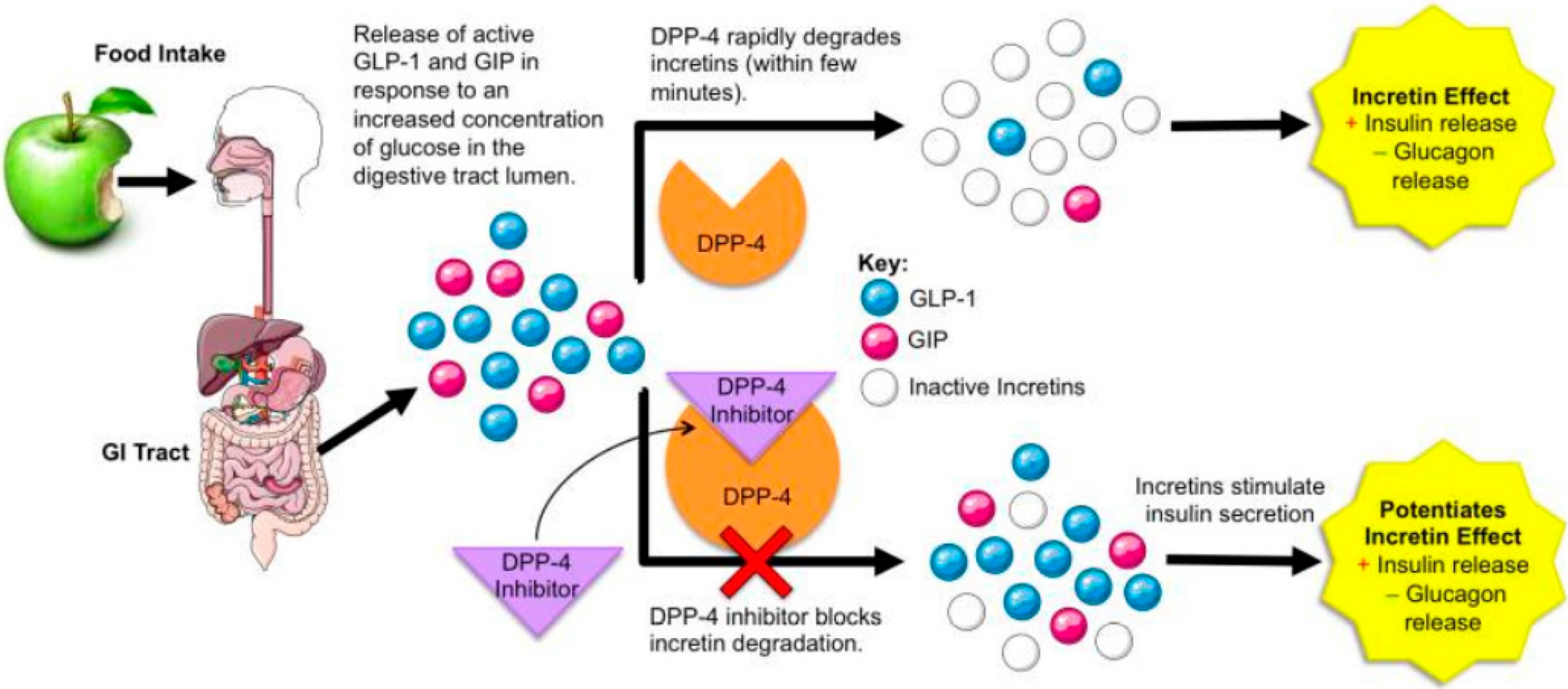


INSULIN SECRETAGOGUES VIA ENHANCING GLP-1 RECEPTOR SIGNALING:

DPP4 INHIBITORS

Incretin effect: glucose




Food Intake
Release of active GLP-1 and GIP in response to an increased concentration of glucose in the digestive tract lumen.
DPP-4 rapidly degrades incretins (within few minutes).
Incretin Effect
+ Insulin release
– Glucagon release
DPP-4
Key:
GLP-1
GIP
Inactive Incretins
GI Tract
DPP-4 Inhibitor
DPP-4
DPP-4 Inhibitor
DPP-4 inhibitor blocks incretin degradation.
Incretins stimulate insulin secretion
Potentiates Incretin Effect
+ Insulin release
– Glucagon release

DPP4 INHIBITORS

01 inhibit degradation of native GLP-1 and thus enhance the incretin effect.

02
- ✓ Do not cause hypoglycemia because of the glucose-dependent nature of incretin-stimulated insulin secretion.
- ✓ Do not cause weight gain

03 appear to have a preferential effect on postprandial blood glucose.

04 Allergy, including rash, hypersensitivity reactions (including anaphylaxis, angioedema, and Stevens-Johnson syndrome), and severe joint pain have been reported in association with DPP-IV inhibitors.

SITAGLIPTIN: TABLET 25, 50, 100 mg

01 It is absorbed quickly, with a half life of 12.4 hours

02 Time to peak: 1-4 hours

03
- ✓ Do not cause hypoglycemia or weight gain.
- ✓ Is not associated with improvement in cardiovascular or renal outcome.

04 Excretion: 87% from urine, 13% from feces

HOW TO PRESCRIBE?

Initial: 100 mg once daily,

Administer without regard to meal.

May require a dose reduction of insulin and/or insulin secretagogues to avoid hypoglycemia.

Avoid use with GLP1-RA

Adjustment: not needed

SIDE EFFECTS

GI adverse events

Minimal

Pancreatitis

- ✓ Pancreatitis has been reported, although no causal relationship has been established
- ✓ Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents.

There is concern about increased risk for acute pancreatitis with DPP-IV inhibitors.
It is reasonable to avoid these agents in patients with pancreatic disease or with other significant risk factors for acute pancreatitis (e.g., heavy alcohol use, severely elevated serum triglycerides, hypercalcemia).

Arthralgia

- ✓ Mechanism is not well established.
- ✓ Onset: may occur within 1 day to years after treatment initiation. (mostly within first 3m)
- ✓ Symptoms may resolve with discontinuation (mostly within a month).
- ✓ Symptoms may recur after therapy resumes.

CONTRAINDICATIONS

Sitagliptin should not be used in:

✓ Serious hypersensitivity to drug

Sitagliptin should be prescribe with catious in:

✓ Renal impairment

Pregnancy

Not recommended

Breast feeding

The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant and the benefits of treatment to the mother.

Reproductive

Not recommended for patients with DM2 planning to become pregnant

LINAGLIPTIN: TABLET 5 mg

01 It is not extensively metabolized

02 Time to peak: 1.5 hours

03
- ✓ Do not cause hypoglycemia or weight gain.
- ✓ Is not associated with improvement in cardiovascular or renal outcome.

04 Excretion: 80% from feces, 5% from urine unchanged

HOW TO PRESCRIBE?

Initial: 5 mg once daily,

Administer without regard to meal.

May require a dose reduction of insulin and/or insulin secretagogues to avoid hypoglycemia.

Avoid use with GLP1-RA

Adjustment: not needed

SIDE EFFECTS

Metabolic adverse events

Increased uric acid

GI adverse effects

- ✓ Increased serum lipase up to 3 times
- ✓ Oral mucosa ulcer
- ✓ Cholecystitis
- ✓ pancreatitis

Neuromuscular and skeletal adverse events

- ✓ Myalgia
- ✓ arthralgia

There is concern about increased risk for acute pancreatitis with DPP-IV inhibitors.
It is reasonable to avoid these agents in patients with pancreatic disease or with other significant risk factors for acute pancreatitis (e.g., heavy alcohol use, severely elevated serum triglycerides, hypercalcemia).

CONTRAINDICATIONS

linagliptin should not be used in:

✓ Serious hypersensitivity to drug (anaphylaxis, angioedema, exfoliative skin conditions, urticaria, bronchial hyperreactivity)

linagliptin:

✓ Should not be used with GLP1-RAs

Pregnancy

✓ Not recommended

Breast feeding

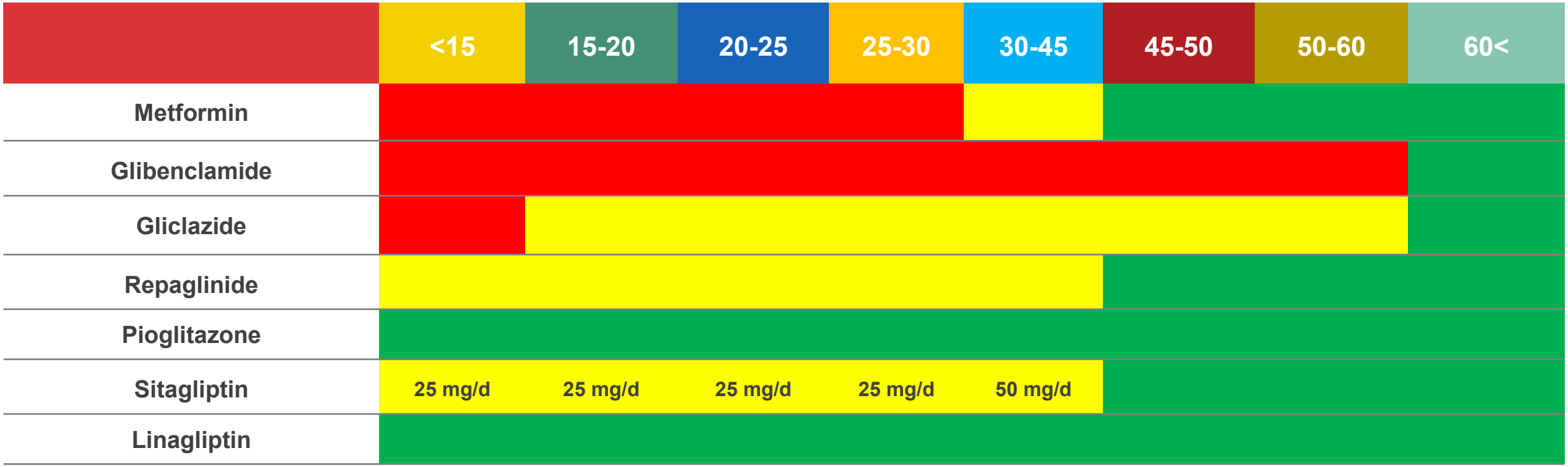
The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant and the benefits of treatment to the mother.

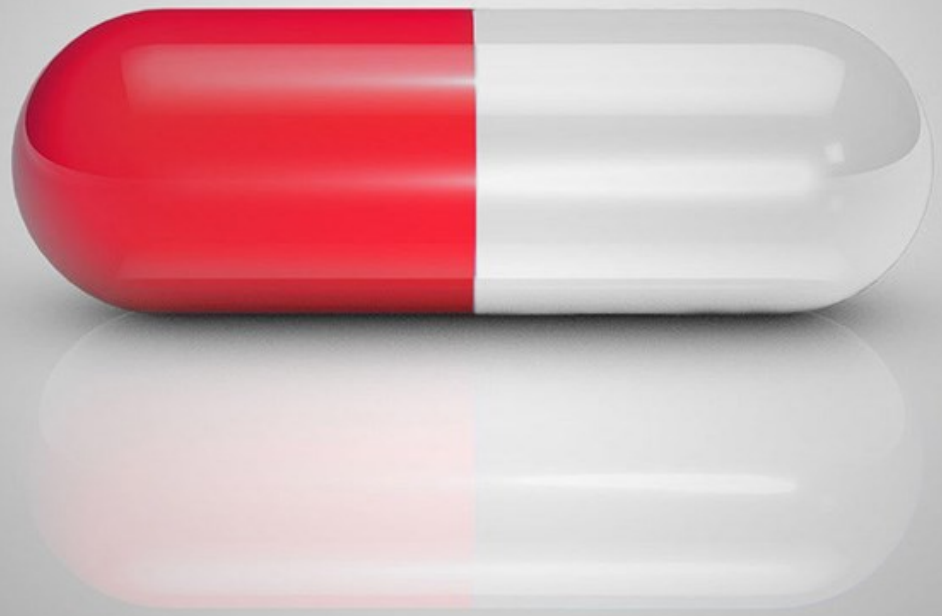
Reproductive

Not recommended for patients with DM2 planning to become pregnant

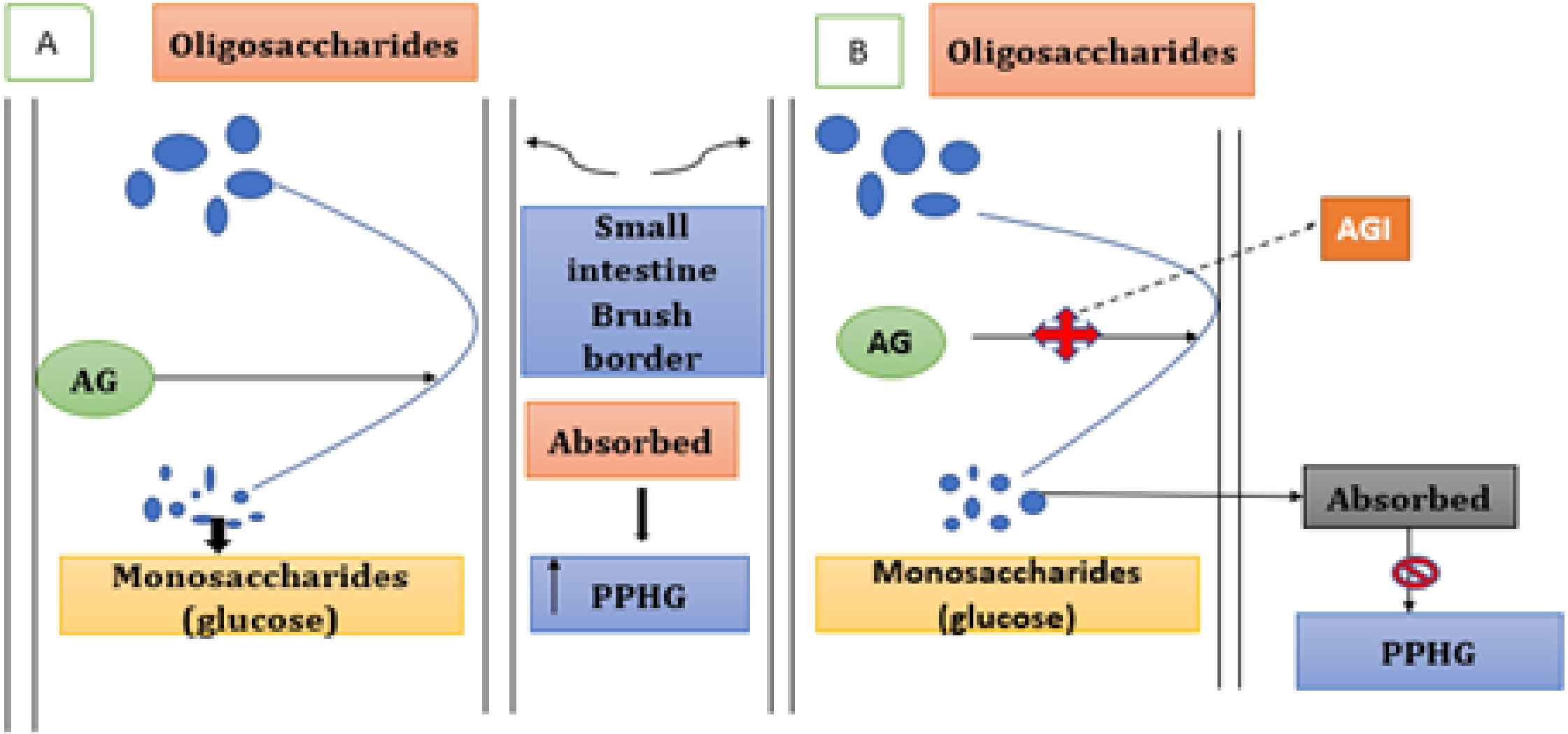
Text Here	EXAMPLES	HBA1C REDUCTION	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Biguanides	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency	eGFR <30, CHF, radiographic contrast studies, hospitalized patients, acidosis
Sulfonylureas	Glibenclamide, gliclazide	1–2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver insufficiency
Meglitinides	Repaglinide	0.5–1	Short onset of action, lower postprandial glucose	Hypoglycemia	liver insufficiency
Thiazolidinediones	Pioglitazone, rosiglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, renal/liver insufficiency
DPP4-i	**Alogliptin, linagliptin, saxagliptin, sitagliptin, Vildagliptin**	**0.5–0.8**	**Well tolerated, do not cause hypoglycemia**	**Angioedema/urticarial and immune-mediated dermatologic effects**	**Reduced dose with renal insufficiency**
α-Glucosidase inhibitors	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, elevated LFT	Renal/liver insufficiency
SGLT2-i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1.0	Do not cause hypoglycemia, ↓weight and BP, renal protective, ↓CV events	Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA	Severe renal insufficiency, insulin deficient DM

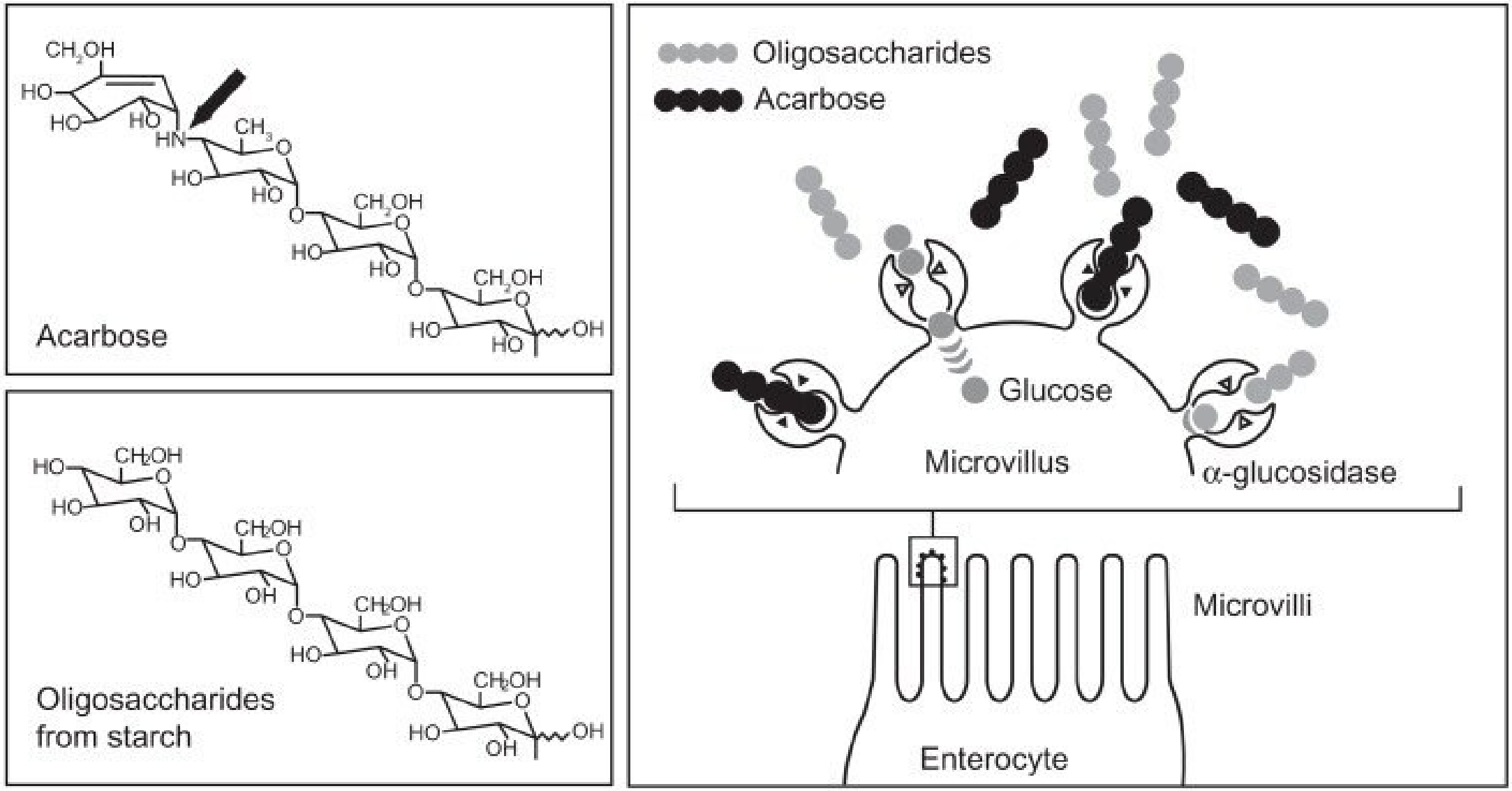
DOSE ADJUST IN CKD





α-GLUCOSIDASE INHIBITORs


A
Oligosaccharides
AG
Monosaccharides
(glucose)
Small
intestine
Brush
border
Absorbed
PPHG
B
Oligosaccharides
AGI
AG
Absorbed
Monosaccharides
(glucose)
PPHG


Acarbose
Oligosaccharides
from starch
Oligosaccharides
Acarbose
Glucose
Microvillus
α-glucosidase
Microvilli
Enterocyte

α-GLUCOSIDASE INHIBITORs

01 Carbohydrate convert to oligosacarides by amylase and then by alpha glucosidase to glucose.

02 Acarbose inhibit amylase and alpha glucosidase, but does not inhibit beta glucosidase. so dose not interfere with lactose absorption

03 May increase levels of sulfonylureas and increase the incidence of hypoglycemia.

04 reduce postprandial hyperglycemia by delaying glucose absorption.

ACARBOSE: TABLET 25, 50, 100 mg

01 Competitive inhibitor of pancreatic alpha amylase and intestinal brush border α-glucosidase

02 Delay absorption of glucose. Dose dependent reduction in postprandial serum insulin and glucose peak

03 Inhibits metabolism of sucrose to glucose and fructose.

04 Simultaneous treatment with bile acid resins and antacids should be avoided

HOW TO PRESCRIBE?

Initial: 25 mg once daily with gradual titration to 25 mg three times daily

Administer with the first bite of each main meal.

Adjustment: increase dose at 4-8 weeks interval based on 1h postprandial BS and tolerance

Some experts state the drug is best initiated with the smallest meals

Maximum:
- ✓ 50 mg TDS for <60 Kg
- ✓ 100 mg TDS for >60 Kg

Its effectiveness is diminished with low carbohydrate intake.

SIDE EFFECTS

GI side effects

- ✓ Flatulence: tend to abate with time
- ✓ diarrhea
- ✓ Abdominal pain: tend to return to pretreatment levels over time
- ✓ Frequently GI side effects limit the tolerated dose to 50 mg.

Hepatic side effects

May increase serum transaminases specially in females and thin people

Be careful !!!!

Although hypoglycemia does not occur when a drug in this class is used alone, hypoglycemia must be treated with glucose itself (e.g., dextrose tablets or milk) instead of complex carbohydrates, since absorption of the latter is delayed.

Side effects can be very pronounced. Therefore warn people.

CONTRAINDICATIONS

Acarbose should not be used in:

- ✓ DKA
- ✓ Cirrhosis
- ✓ IBD
- ✓ Colonic ulceration
- ✓ Partial intestinal obstruction
- ✓ Autonomic neuropathy affecting the GI tract

Acarbose is not recommended in:

- ✓ Cr> 2 mg/dL or eGFR< 25

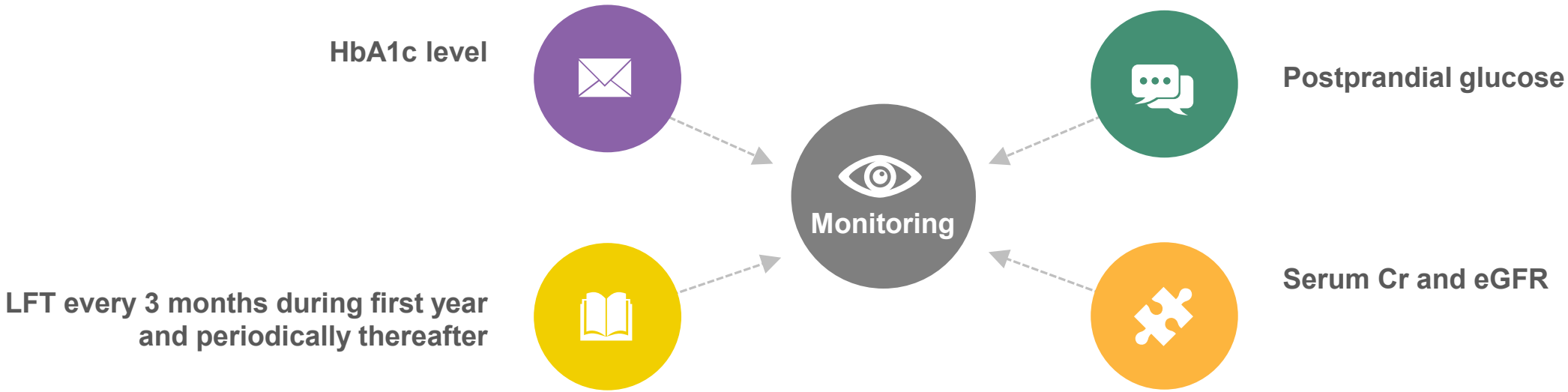
Pregnancy

Agents other than acarbose are recommended in pregnancy.

Breast feeding

Is not recommended by the manufacturer but , 2% is absorbed

MONITORING


HbA1c level
Postprandial glucose
Monitoring
LFT every 3 months during first year and periodically thereafter
Serum Cr and eGFR

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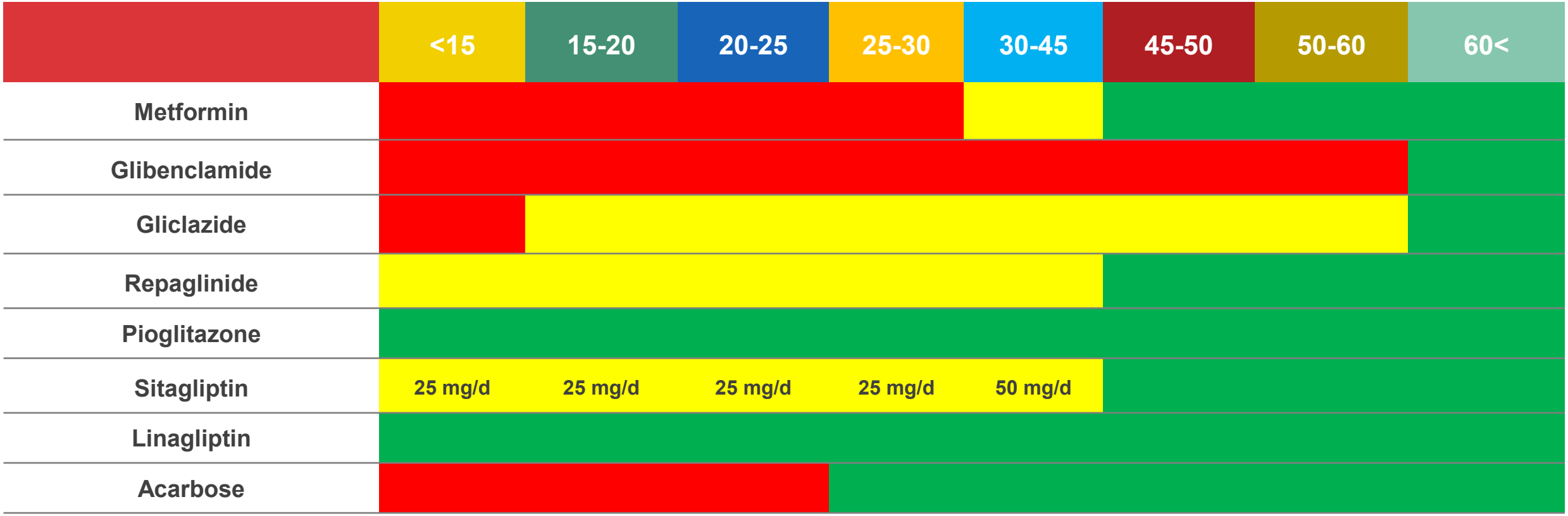
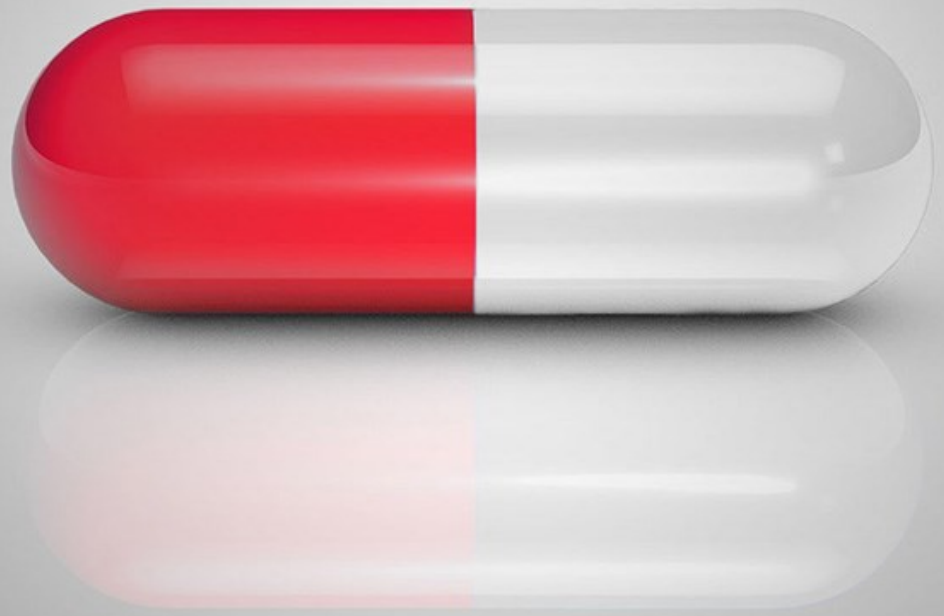
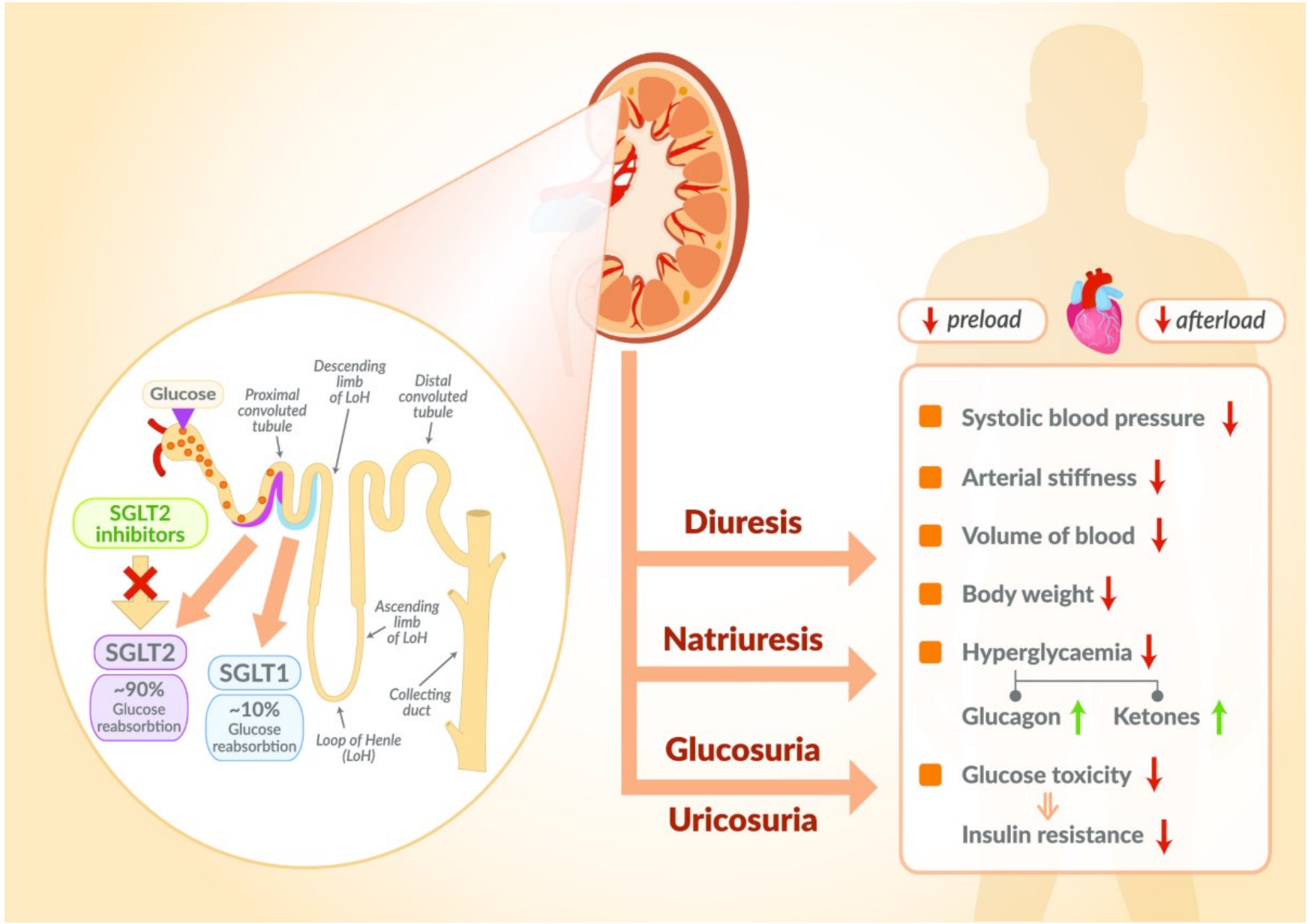
SGLT2-i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1.0	Do not cause hypoglycemia, ↓weight and BP, renal protective, ↓CV events	Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA	Severe renal insufficiency, insulin deficient DM

DOSE ADJUST IN CKD

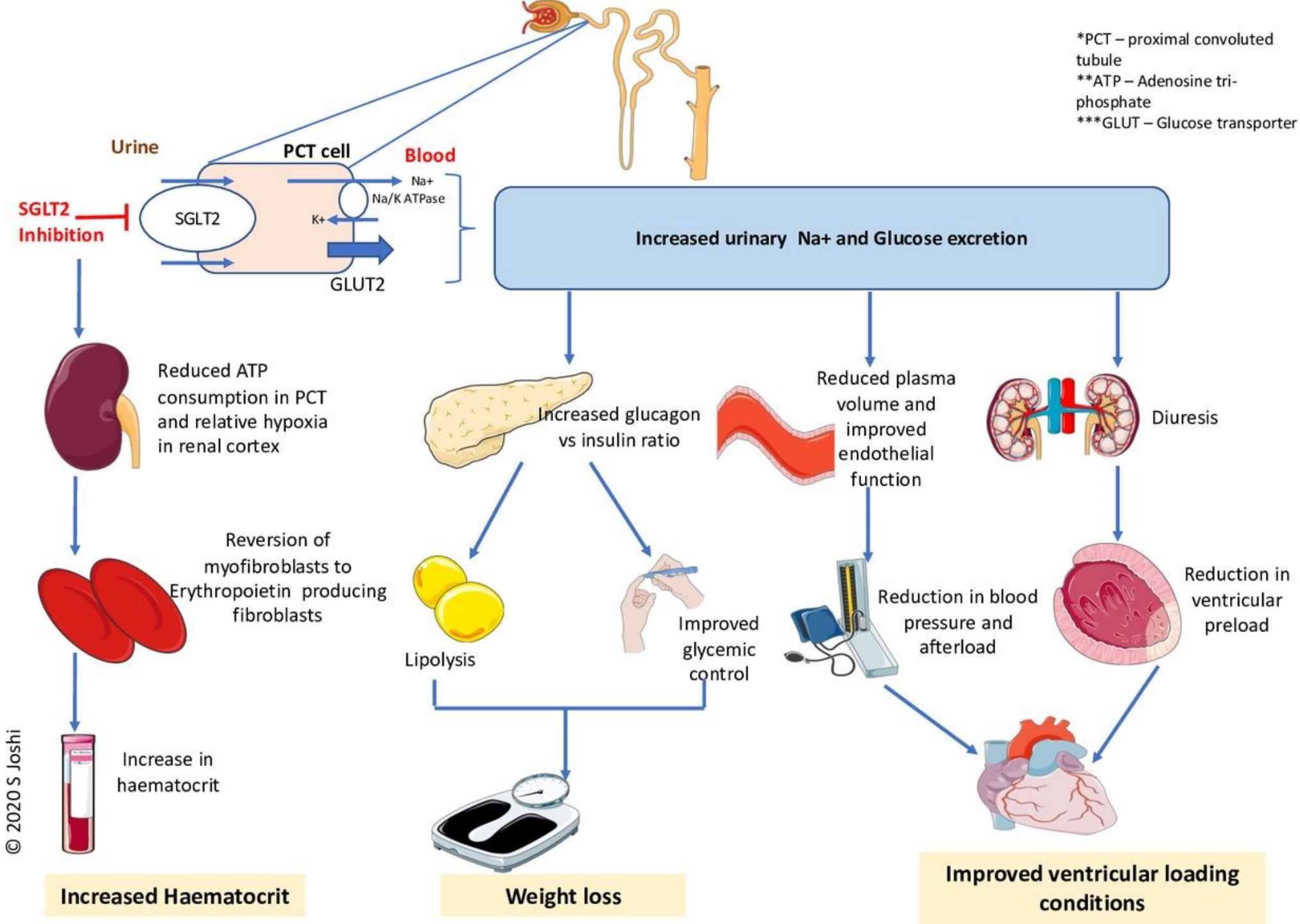




SGLT2 INHIBITORs


Glucose
Proximal convoluted tubule
Descending limb of LoH
Distal convoluted tubule
SGLT2 inhibitors
SGLT2
~90% Glucose reabsorbtion
SGLT1
~10% Glucose reabsorbtion
Ascending limb of LoH
Collecting duct
Loop of Henle (LoH)
Diuresis
Natriuresis
Glucosuria
Uricosuria
preload
afterload
Systolic blood pressure
Arterial stiffness
Volume of blood
Body weight
Hyperglycaemia
Glucagon
Ketones
Glucose toxicity
Insulin resistance


1
2
3
4


*PCT – proximal convoluted tubule
**ATP – Adenosine tri-phosphate
***GLUT – Glucose transporter
Urine
PCT cell
Blood
Na+
Na/K ATPase
K+
SGLT2
SGLT2 Inhibition
GLUT2
Increased urinary Na+ and Glucose excretion
Reduced ATP consumption in PCT and relative hypoxia in renal cortex
Increased glucagon vs insulin ratio
Reduced plasma volume and improved endothelial function
Diuresis
Reversion of myofibroblasts to Erythropoietin producing fibroblasts
Lipolysis
Improved glycemic control
Reduction in blood pressure and afterload
Reduction in ventricular preload
Increase in haematocrit
Increased Haematocrit
Weight loss
Improved ventricular loading conditions
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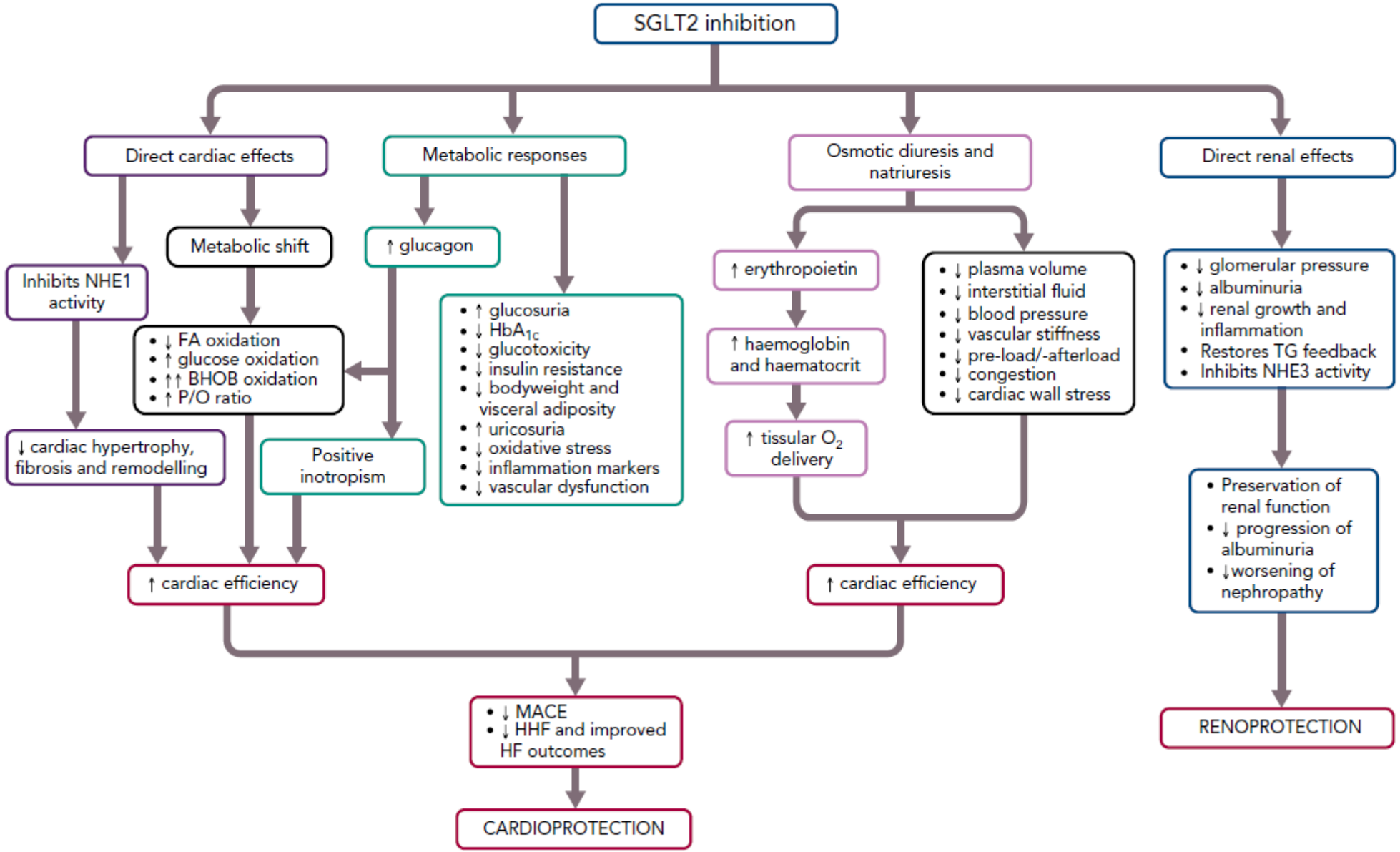

SGLT2 inhibition
Direct cardiac effects
Metabolic responses
Osmotic diuresis and natriuresis
Direct renal effects
Inhibits NHE1 activity
Metabolic shift
↑ glucagon
↑ erythropoietin
• ↓ plasma volume
• ↓ interstitial fluid
• ↓ blood pressure
• ↓ vascular stiffness
• ↓ pre-load/-afterload
• ↓ congestion
• ↓ cardiac wall stress
• ↓ glomerular pressure
• ↓ albuminuria
• ↓ renal growth and inflammation
• Restores TG feedback
• Inhibits NHE3 activity
• ↓ FA oxidation
• ↑ glucose oxidation
• ↑↑ BHOB oxidation
• ↑ P/O ratio
• ↑ glucosuria
• ↓ HbA1c
• ↓ glucotoxicity
• ↓ insulin resistance
• ↓ bodyweight and visceral adiposity
• ↑ uricosuria
• ↓ oxidative stress
• ↓ inflammation markers
• ↓ vascular dysfunction
↑ haemoglobin and haematocrit
↑ tissular O2 delivery
↓ cardiac hypertrophy, fibrosis and remodelling
Positive inotropism
• Preservation of renal function
• ↓ progression of albuminuria
• ↓worsening of nephropathy
↑ cardiac efficiency
↑ cardiac efficiency
• ↓ MACE
• ↓ HHF and improved HF outcomes
RENOPROTECTION
CARDIOPROTECTION

SGLT2 Inhibitors

01 These agents lower the blood glucose by selectively inhibiting this co-transporter, which is expressed almost exclusively in the proximal, convoluted tubule in the kidney.

02 the glucose-lowering effect is insulin independent and not related to changes in insulin sensitivity or secretion.

03 The loss of urinary glucose may promote modest weight reduction

04 their use is associated with a diuretic effect and 3–6 mmHg reduction in systolic blood pressure.

SGLT2 Inhibitors

05 urinary and genital mycotic infections are more common in both men and women

06 the diuretic effect can lead to reduced intravascular volume and acutely impaired kidney function.

07 Euglycemic DKA may occur during illness

08 These agents should not be prescribed for patients with type 1 DM or pancreatogenic forms of DM associated with insulin deficiency.

EMPAGLIFLOZIN: TABLET 10, 25 mg

01 reduces CVD events and all cause cardiovascular mortality in patients with DM2 and established CVD

02 reduce hospitalization for CHF

03 reduce progression of diabetic kidney disease

04 Should prescribe in diabetic patients with HF, established ASCVD, high risk for ASCVD or renal failure irrespective of the HbA1c level.

HOW TO PRESCRIBE?

Initial: 10 mg once daily

Administer with or without food.

Adjustment: may increase to 25 mg once daily after 4-12 weeks if needed.

10 mg daily dose produces 80% of 25 mg effect

It is prescribed in the morning.

Correct hypovolemia prior to initiating treatment

SIDE EFFECTS

Acute Kidney Injury

- ✓ Early decrease in eGFRoccurs
- ✓ It tends to stabilized after about 4 weeks
- ✓ Overall reduction in adverse kidney outcomes

Bone Fracture

- ✓ Meta-analysis of trial data for empagliflozin have not demonstrated increased risk of fracture.

Hypotension/ Volume Depletion

- ✓ Reduction of about 4-6 mmHg in SBP
- ✓ Reduction of about 1-2 mmHg in DBP

Infection

- ✓ Increased risk of genitourinary fungal infection
- ✓ Increased risk of UTI
- ✓ May be apparent within the first month and remain elevated throughout the course of therapy (Fournier gangrene may have an average onset of 9 months)
- ✓ These are often mild, respond to treatment, and do not lead to discontinuation

Euglycemic DKA

- ✓ Risk factors: insulin deficiency, metabolically stressful event, history of pancreatitis or pancreatic surgery

Lower limb Amputation

Mostly seen with canagliflozin

CONTRAINDICATIONS

Empagliflozin should not be used in:

✓ eGFR< 20

Empagliflozin should be discontinued in:

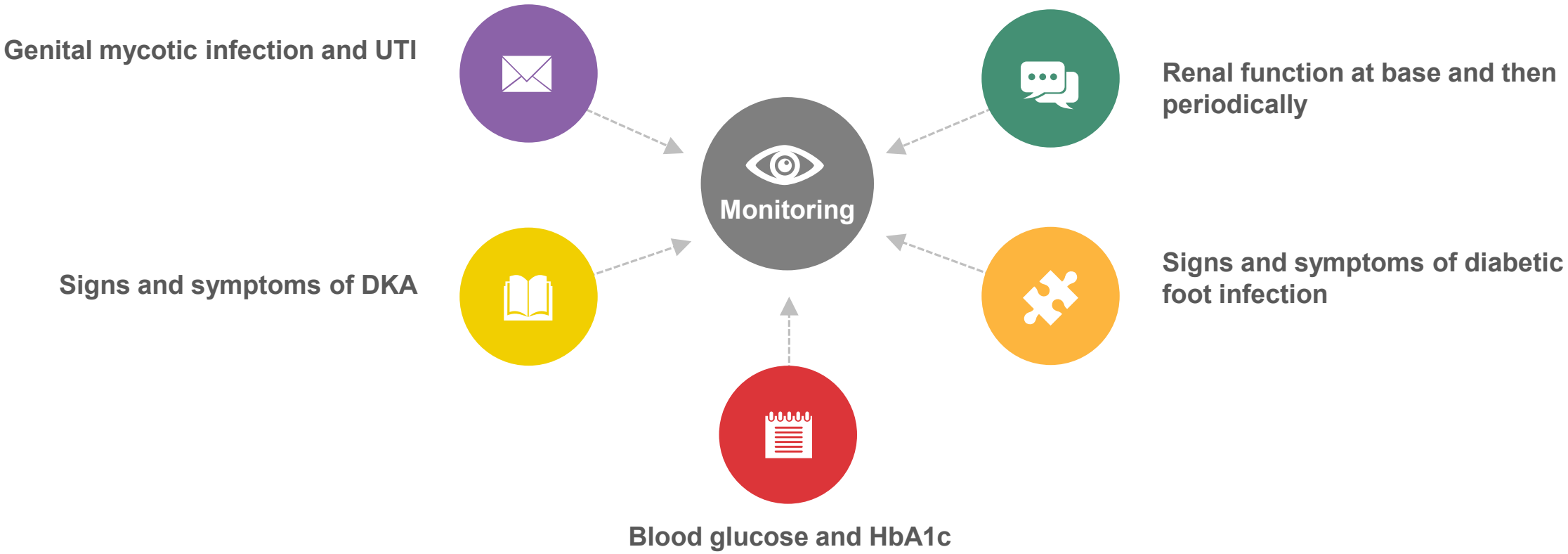
✓ 3-4 days before surgery
✓ Risk of intravascular volume depletion may be increased in patients > 75 years of age
✓ Hospitalized patients for glycemic control

Pregnancy
Not recommended

Breast feeding
Is not recommended

Reproductive
Not recommended for patients with DM2 planning to become pregnant

MONITORING


Genital mycotic infection and UTI
Signs and symptoms of DKA
Monitoring
Renal function at base and then periodically
Signs and symptoms of diabetic foot infection
Blood glucose and HbA1c

DAPAGLIFLOZIN: TABLET 5, 10 mg

01 reduces CVD events and all cause cardiovascular mortality in patients with DM2 and established CVD

02 reduce hospitalization for CHF

03 reduce progression of diabetic kidney disease

04 A possible increased risk of bladder cancer has been seen with dapagliflozin.

HOW TO PRESCRIBE?

Initial: 5 mg once daily

Administer with or without food.

Adjustment: may increase to 10 mg once daily after 4-12 weeks if needed.

Correct hypovolemia prior to initiating treatment

It is prescribed in the morning.

SIDE EFFECTS

Acute Kidney Injury

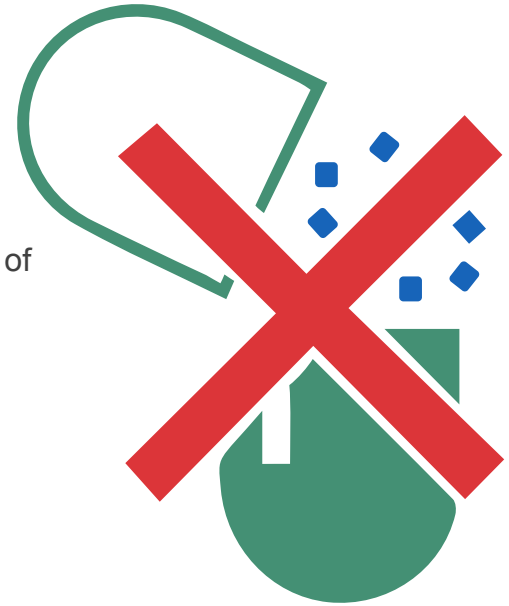
- ✓ May cause decrease in eGFR in first 2 weeks
- ✓ Overall reduction in adverse kidney outcomes
- ✓ An acute reduction in eGFR after 2 weeks of dapagliflozin is not associated with higher rates of CKD progression.

Bone Fracture

- ✓ Conflicting data
- ✓ It appears not to increase risk

Hypotension/ Volume Depletion

- ✓ Reduction of about 4-6 mmHg in SBP
- ✓ Reduction of about 1-2 mmHg in DBP



Infection

- ✓ Increased risk of genitourinary fungal infection
- ✓ Increased risk of UTI
- ✓ May be apparent within the first month and remain elevated throughout the course of therapy (Fournier gangrene may have an average onset of 9 months)
- ✓ These are often mild, respond to treatment, and do not lead to discontinuation

Euglycemic DKA

- ✓ Risk factors: insulin deficiency, metabolically stressful event, history of pancreatitis or pancreatic surgery

Lower limb Amputation

Mostly seen with canagliflozin

CONTRAINDICATIONS

Dapagliflozin should not be used in:

✓ eGFR< 25

Dapagliflozin should be discontinued in:

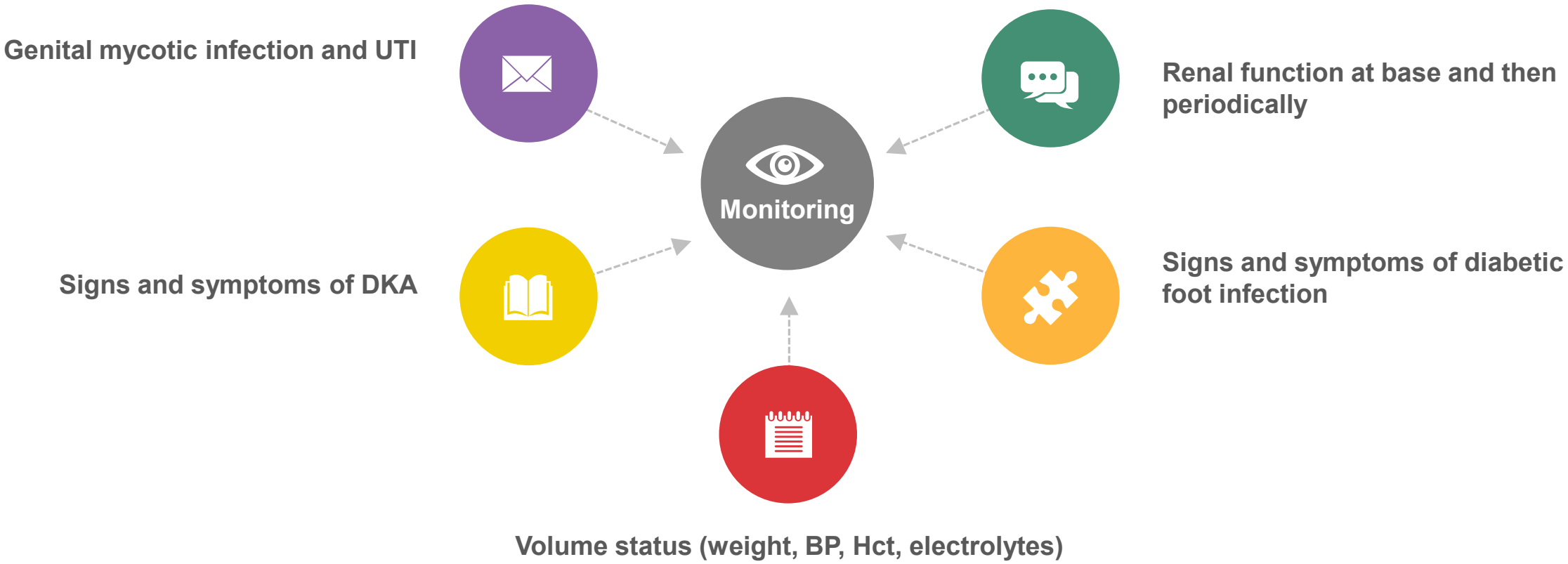
✓ 3-5 days before surgery
✓ Risk of intravascular volume depletion may be increased in patients > 75 years of age
✓ Hospitalized patients for glycemic control

Pregnancy
Not recommended

Breast feeding
Is not recommended

Reproductive
Not recommended for patients with DM2 planning to become pregnant

MONITORING


Genital mycotic infection and UTI
Renal function at base and then periodically
Monitoring
Signs and symptoms of DKA
Signs and symptoms of diabetic foot infection
Volume status (weight, BP, Hct, electrolytes)

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DPP4-i	Alogliptin, linagliptin, saxagliptin, sitagliptin, Vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia	Angioedema/urticarial and immune-mediated dermatologic effects	Reduced dose with renal insufficiency
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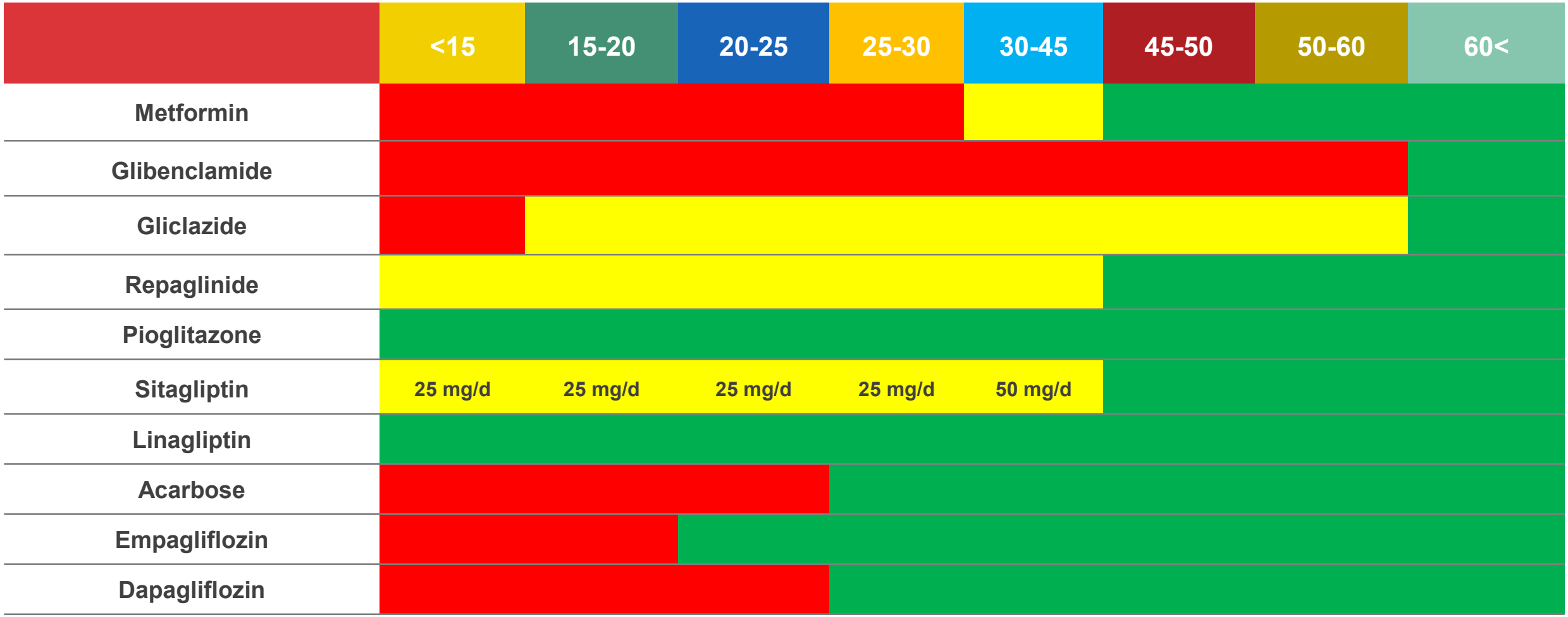
DOSE ADJUST IN CKD



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THANK YOU