IN THE NAME OF GOD

Oral hypoglycemic agents

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Agents Used for Treatment of Type 1 or Type 2 Diabetes

	MECHANISM OF ACTION	EXAMPLES	↓HBA1C (%)	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Biguanides	↓ Hepatic glucose production ↑ insulin sensitivity, influence gut function	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency	Renal insufficiency (for GFR <30 mL/min), CHF, radiographic contrast studies, hospitalized patients, acidosis

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Metformin
Dosing: Renal Impairment: Adult

- **eGFR >45 mL/minute/1.73 m^2:** No dosage adjustment necessary; monitor renal function at least annually.
- More frequent monitoring (every 3 to 6 months) and a maximum dose of 2 g/day has been recommended for patients with eGFR >45 to <60 mL/minute/1.73 m^2 .
- **eGFR 30 to 45 mL/minute/1.73 m^2:**
- *Preexisting impairment:* Use is not recommended for initiation of therapy by some experts
- *If eGFR falls between 30 and <45 mL/minute/1.73 m^2 during therapy*: Consider benefits/risks of continuing therapy. If continuing therapy, a dosage reduction of 50% (maximum: 1 g/day) and monitoring of renal function every 3 months is recommended.
- **eGFR <30 mL/minute/1.73 m^2:** Use is contraindicated.

Hepatic impairment prior to treatment initiation:

- In patients with concurrent kidney impairment, eGFR ≤45 mL/minute/1.73 m^2 and Child-Turcotte-Pugh A or B, defer to dosing in altered kidney function in adults.
- **Monitor kidney** function frequently (eg, every **1 to 3 months**) (expert opinion) during continuation of therapy

Hepatic impairment & Metformin

- **Child-Turcotte-Pugh class A *:*** No dosage adjustment necessary.
- **Child-Turcotte-Pugh class B :** 500 mg once daily; may increase by ≤500 mg/day increments every 30 days based on tolerability and response (expert opinion); consider slower titration (eg, every 60 days) in patients on concurrent agents that cause diarrhea (eg, lactulose) or fluid loss (eg, diuretics) (expert opinion); maximum dose: 1.5 g/day.
- **Note:** Do not initiate in patients at risk for lactic acid–producing events (eg, active alcohol consumption, dehydration, hypotension, sepsis, reduced cardiac function, reduced kidney function)
- **Child-Turcotte-Pugh class C**: Avoid use

Metformin
Pregnancy Implications

- Metformin crosses the placenta; concentrations may be comparable to those found in the maternal plasma.
- Agents other than metformin are currently recommended to treat diabetes mellitus in pregnancy

Breast-Feeding Considerations

- Metformin is present in breast milk.

Lactic acidosis

- Rare
- Symptoms of lactic acidosis are nonspecific and may include:
- anorexia
- nausea
- vomiting
- abdominal pain
- lethargy
- hyperventilation
- hypotension

Intravenous iodinated contrast

- Hold metformin in patients who are about to:
- receive intravenous iodinated contrast material (with potential for contrast-induced renal failure) or
- undergo a surgical procedure (with potential compromise of circulation),
- if they are at increased risk for lactic acidosis independent of metformin

Metformin

Efficacy	Hypoglycemia	Weight change	CV effects		Cost
			ASCVD	HF	
High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low

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Metformin

Oral/SQ	Renal effects		Additional considerations
	Progression of DKD	Dosing/use considerations*	
Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m²	▪ Gastrointestinal side effects commo (diarrhea, nausea) ▪ Potential for B12 deficiency

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Vitamin B12 deficiency

- Metformin reduces intestinal absorption of vitamin B12 in up to 30 percent of patients and lowers serum vitamin B12 concentrations in 5 to 10 percent, but it only rarely causes megaloblastic anemia (possibly due to folic acid supplementation of the United States food supply).
- In some patients, vitamin B12 deficiency may present as **peripheral neuropathy**.
- In one study, the reduction in serum vitamin B12 appeared to be due to poor absorption of B12 in the ileum and was corrected by administration of oral **calcium carbonate** (**1.2 g daily**). In another study, supplementation with a daily multivitamin was associated with a lower prevalence of vitamin B12 deficiency

Vitamin B12 deficiency

Parenteral or oral therapy (shared decision-making)

- **Dose:**
  - IM: 1000 mcg weekly for 4 weeks, followed by cyanocobalamin (monthly; available in the United States) or hydroxycobalamin (once every 2 months), administered by the clinician or the patient.

    - or -
  - Oral or SL: 1000 to 2000 mcg daily (available over-the-counter).
- **Monitor:** CBC and vitamin B12 level in 4 to 8 weeks, then in 6 months, then annually.

Vitamin B12 deficiency

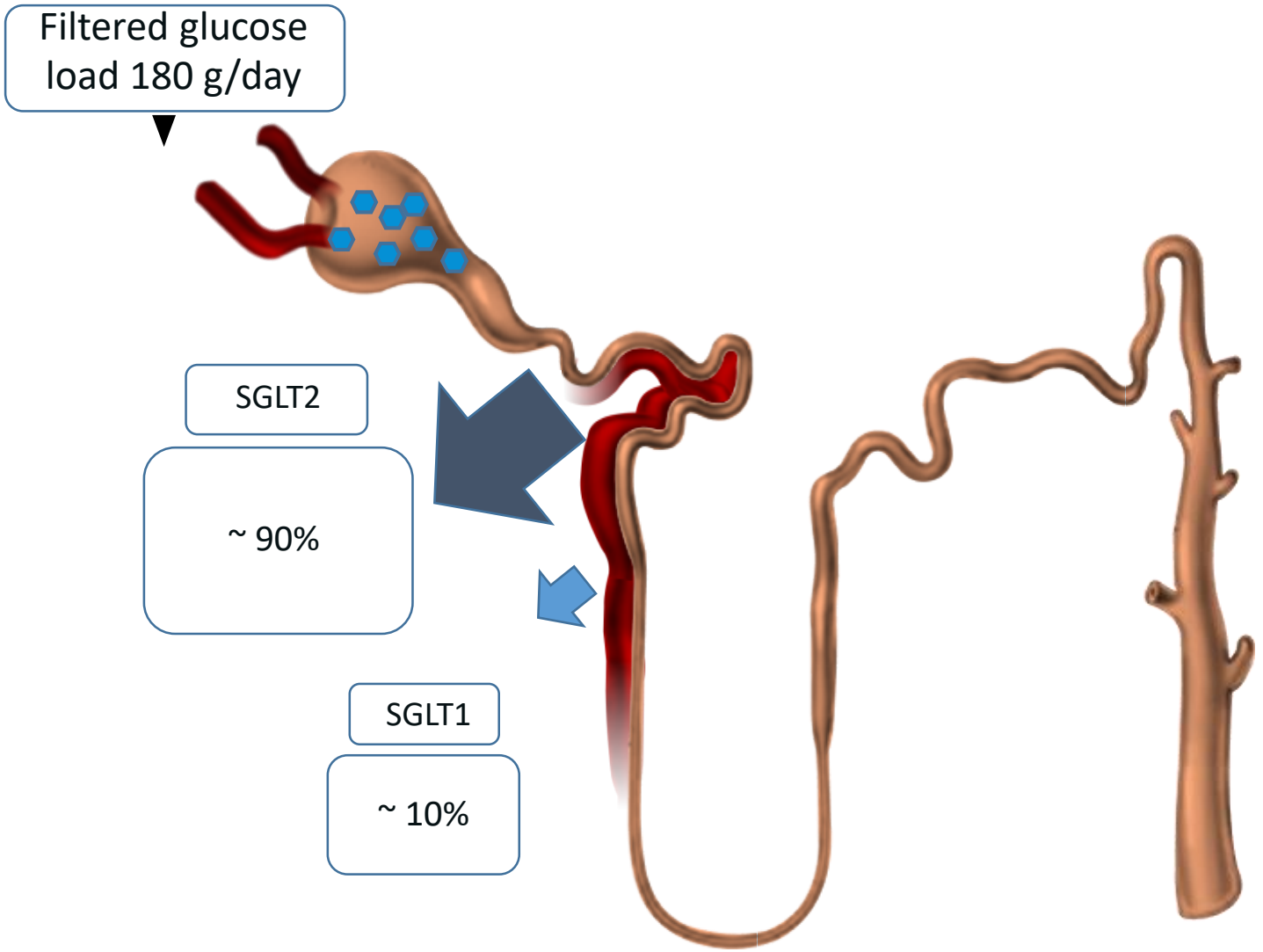
Maintenance therapy

- **Dose:** Continue same dose.
- **Duration:** Indefinite for individuals with an irreversible cause of deficiency. May be discontinued if a reversible cause of deficiency has been addressed (eg, if metformin is discontinued).
- **Monitor:** CBC every 6 months for the first year, then annually; more frequently if concerns or symptoms develop. Monitoring of the vitamin B12 level is not required but may be done on an individualized basis.

Sodium-glucose cotransporter 2 inhibitors

SGL2I

Renal glucose re-absorption in healthy individuals



Gerich JE. *Diabet Med*. 2010;27:136–142.

Agents Used for Treatment of Type 1 or Type 2 Diabetes

	MECHANISM OF ACTION	EXAMPLES	↓HBA1C (%)	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Sodium-glucose cotransporter 2 inhibitors	↑ renal glucose excretion	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;	Moderate renal insufficiency, insulin-deficient DM

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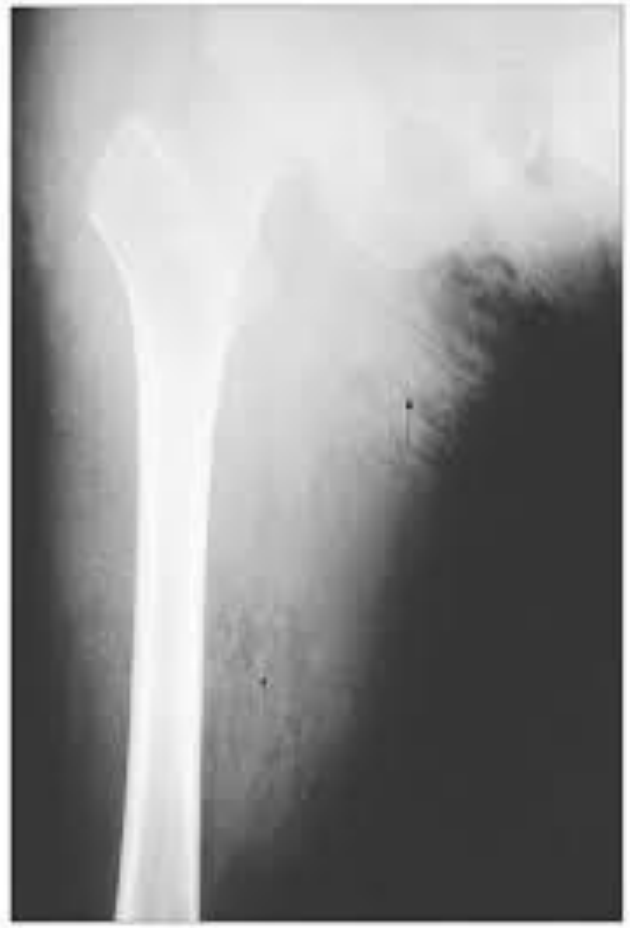
	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m^2
SGLT2 inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR

SGL2I

Oral/SQ	Cost	Clinical considerations
Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable

GANGRENE FOURNIER



Clinical presentation

Fournier’s gangrene should be considered in anyone with painful swelling of the scrotum or perineum with features of sepsis. The most common presenting feature, in over 75% of patients, is perianal/scrotal pain and swelling. Systemic features such as pyrexia and tachycardia are frequently present and may be associated with end organ dysfunction and increased mortality

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The diagnosis and management of Fournier's gangrene

Andrew Brown, CT2 Urology; **Nadine Coull,** Consultant Urologist, Kingston Hospital NHS Foundation Trust, London

Fournier's gangrene is a life-threatening condition and, although rare, should be considered in anyone with painful swelling of the scrotum or perineum with features of sepsis. In this article the author discusses risk factors, diagnosis and management of Fournier's gangrene and the importance of early diagnosis and treatment.

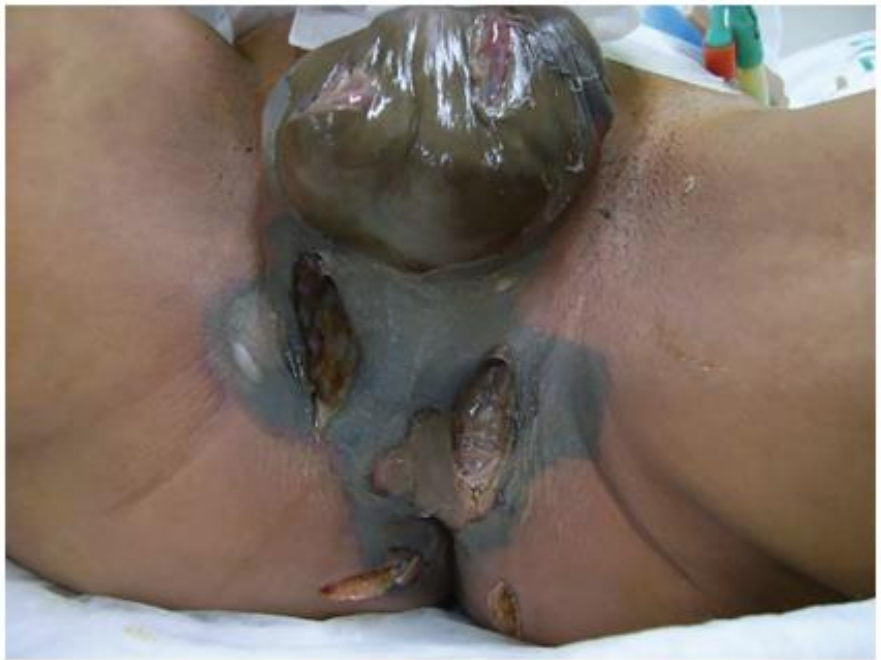

Figure 1. Skin ischaemia and necrosis in late presentation of Fournier's gangrene[a] (© 2017 Medicalhelplines.com Inc. and John Wiley & Sons Ltd.)

Fournier's gangrene is a fulminating, polymicrobial, necrotising fasciitis of the anogenital region, which spreads rapidly along the deep fascial planes. This eponymous syndrome was first mentioned by venereologist Jean Alfred Fournier in 1883 when he described an idiopathic, rapidly spreading genital gangrene occurring in five healthy young males.[1]

administration of broad-spectrum antibiotics and timely surgical debridement are the basic principles

to presentation being five to seven days - hence patients may present with late features such as skin

SGLT-2 inhibitors

Additional considerations

- **FDA Black Box:** Risk of amputation (**canagliflozin**)
- Risk of bone fractures (canagliflozin)
- DKA risk (all agents, rare in T2DM)
- Genitourinary infections
- Risk of volume depletion, hypotension
- ↑LDL cholesterol
- Risk of Fournier's gangrene

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Empaglifluzin

- **Dosing: Adult**
- 10 mg once daily; may increase to 25 mg once daily as tolerated

Dosing: Renal Impairment: Adult
Empagliflozin

- **eGFR ≥30 mL/minute/1.73 m^2:** No dosage adjustment necessary.
- **eGFR <30 mL/minute/1.73 m^2:**
- **Diabetes mellitus, type 2, treatment:**
- The US manufacturer does not recommend use for glycemic control; however, in patients previously established on empagliflozin, some experts continue use off label at a dose of 10 mg once daily as a treatment for diabetic kidney disease; renal and heart failure benefits have been shown in patients with an eGFR ≥20 mL/minute/1.73 m^2 (Ref).
- **Heart failure:** Benefits of 10 mg once daily have been shown in patients with an eGFR ≥20 mL/minute/1.73 m^2 (Ref).
- **Hemodialysis, intermittent (thrice weekly):** Use is contraindicated.
- **Peritoneal dialysis:** Use is contraindicated .

Dosing: Hepatic Impairment: Adult

- **Empaglifluzin**
- No dosage adjustment necessary.

Contraindications

- **Empaglifluzin**
- History of serious hypersensitivity to empagliflozin or any component of the formulation
- Severe renal impairment (eGFR <20 mL/minute/1.73 m^2), end-stage renal disease (ESRD), or dialysis

UPTODATE
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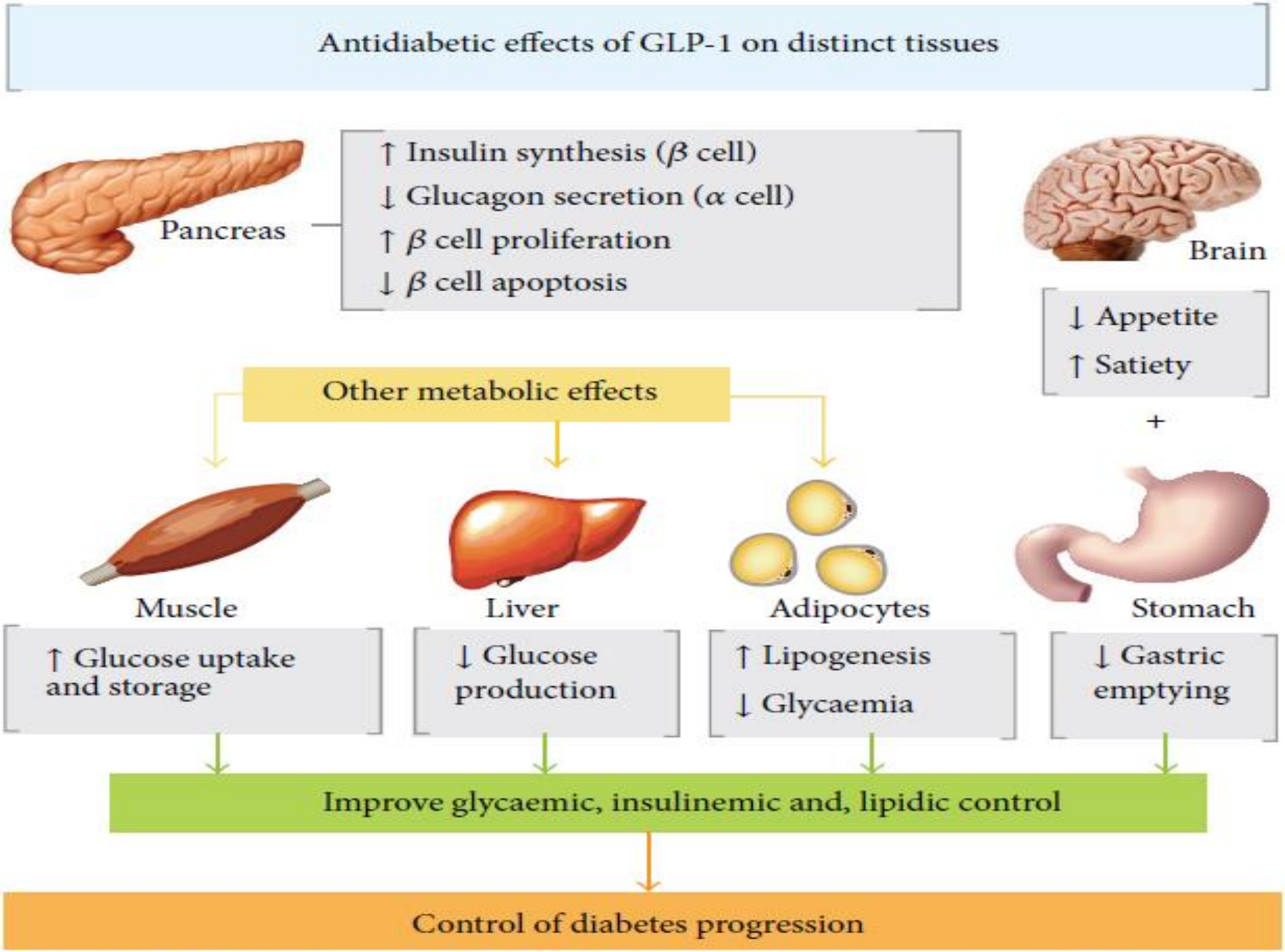
Empaglifluzin

- **Administration** Oral:
- Administer once daily in the morning, with or without food.

DPP4I


Antidiabetic effects of GLP-1 on distinct tissues
Pancreas
↑ Insulin synthesis (β cell)
↓ Glucagon secretion (α cell)
↑ β cell proliferation
↓ β cell apoptosis
Brain
↓ Appetite
↑ Satiety
+
Other metabolic effects
Muscle
↑ Glucose uptake and storage
Liver
↓ Glucose production
Adipocytes
↑ Lipogenesis
↓ Glycaemia
Stomach
↓ Gastric emptying
Improve glycaemic, insulinemic and, lipidic control
Control of diabetes progression

	Efficacy	Hypoglycemia	Weight change
DPP-4 inhibitors	Intermediate	No	Neutral

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	CV effects		Cost
	ASCVD	HF	
DPP-4 inhibitors	Neutral	Potential risk: saxagliptin	High

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	Oral/SQ	Renal effects	
		Progression of DKD	Dosing/use considerations*
DPP-4 inhibitors	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin

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	Additional considerations
DPP-4 inhibitors	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected

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Agents Used for Treatment of Type 1 or Type 2 Diabetes

	MECHANISM OF ACTION	EXAMPLES	↓HBA1C (%)	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Dipeptidyl peptidase IV inhibitors	Prolong endogenous GLP-1 action; ↑ Insulin, ↓ glucagon	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 disease

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Sitagliptin
Dosing: Renal Impairment

Cl_{cr} ≥45 mL/minute	No adjustment required
Cl_{cr} ≥30 to <45 mL/minute	50 mg once daily
Cl_{cr}<30 mL/minute	25 mg once daily
ESRD requiring hemodialysis or peritoneal dialysis	25 mg once daily (administered without regard to timing of hemodialysis)

Dosing: Hepatic Impairment
Sitagliptin

- **Mild-to-moderate impairment** (Child-Pugh classes A and B): No dosage adjustment required

- **Severe impairment** (Child-Pugh class C):
- *US labeling:* There are no dosage adjustments provided in the manufacturer's labeling (**has not been studied**).
- *Canadian labeling:* Use is not recommended.

Dosing: Renal Impairment: Adult Linagliptin

- No dosage adjustment necessary.

Dosing: Hepatic Impairment: Adult Linagliptin

- No dosage adjustment necessary.

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects	
				Effect on MACE	HF
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ)	Neutral
				Neutral: exenatide once weekly, lixisenatide	

GLP1RA

Renal effects	
Progression of DKD	**Dosing/use considerations***
Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions

GLP1RA

Oral/SQ	Cost	Clinical considerations
SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected

GLP1RA

	MECHANISM OF ACTION	EXAMPLES[a]	HBA_{1C} REDUCTION (%)[b]	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Parenteral/Oral						
GLP-1 receptor agonists[c,***]	↑ Insulin, ↓ glucagon, slow gastric emptying, satiety	Dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide (oral formulation available)	0.5–1.0	Weight loss, do not cause hypoglycemia (unless combined with another insulin secretagogue or insulin); ↓ CV events	Injection, nausea, pancreatitis[e]	Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid, pancreatic disease

SEMAGLUTIDE

- **Oral: Note:** Administer ≥30 minutes before the first food, beverage, or other medications of the day.
- Initial: 3 mg once daily for 30 days, then increase to 7 mg once daily; may increase to 14 mg once daily after 30 days on the 7 mg dose if needed to achieve glycemic goals. **Note:**The lower initial dose (3 mg daily) is intended to reduce GI symptoms; it does not provide effective glycemic control.
- Missed dose: Missed dose should be skipped; resume at the next scheduled dose.

Dosing: Kidney Impairment: Adult

- **Altered kidney function:** Mild to severe impairment: No dosage adjustment necessary. Use caution when initiating or escalating doses; new-onset or worsening of existing renal failure has been reported, most commonly in patients experiencing volume depletion from GI losses (eg, vomiting, diarrhea, dehydration).
- **Hemodialysis, intermittent (thrice weekly):** Unlikely to be dialyzable (expert opinion): No supplemental dose or dosage adjustment necessary; use with caution due to limited clinical evidence.
- **Peritoneal dialysis:** Unlikely to be dialyzable: No dosage adjustment necessary; use with caution due to limited clinical evidence.

Contraindications
SEMAGLUTIDE

- Hypersensitivity to semaglutide or any component of the formulation; personal or family history of medullary thyroid carcinoma (MTC); patients with multiple endocrine neoplasia syndrome type 2 (MEN2)
- *Canadian labeling:* Additional contraindications (not in US labeling): Pregnancy; breastfeeding

Thiazolidinediones

	Efficacy	Hypoglycemia	Weight change
Thiazolidinediones	High	No	Gain

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	CV effects		Cost
	ASCVD	HF	
Thiazolidinediones	Potential benefit: pioglitazone	Increased risk	Low

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	Oral/SQ	Renal effects	
		Progression of DKD	Dosing/use considerations*
Thiazolidinediones	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention

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	Additional considerations
Thiazolidinediones	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema

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Agents Used for Treatment of Type 1 or Type 2 Diabetes

	MECHANISM OF ACTION	EXAMPLES	↓HBA1C (%)	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Thiazolidinediones	↓ Insulin resistance, ↑ glucose utilization	Pioglitazone, rosiglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, renal/liver insufficiency

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Pioglitazone

- **Administration** Oral: May be administered without regard to meals

Insulin secretagogues: Sulfonylureasc

Agents Used for Treatment of Type 1 or Type 2 Diabetes

	MECHANISM OF ACTION	EXAMPLES	↓HBA1C (%)	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Sulfonylureas	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	1–2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver disease

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	Efficacy	Hypoglycemia	Weight change
Sulfonylureas (2nd generation)	High	Yes	Gain

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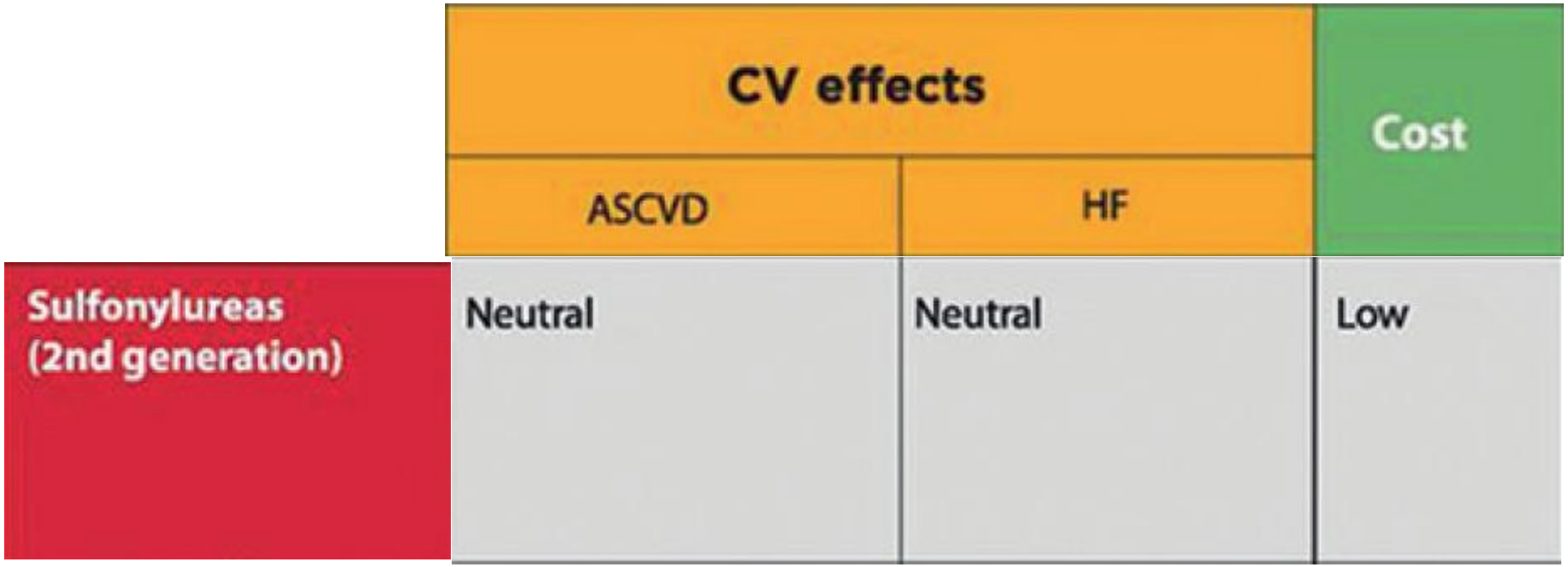
CV effects
Cost
ASCVD
HF
Sulfonylureas (2nd generation)
Neutral
Neutral
Low

	Oral/SQ	Renal effects	
		Progression of DKD	Dosing/use considerations*
Sulfonylureas (2nd generation)	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia

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	Additional considerations
Sulfonylureas (2nd generation)	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycemia

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Glyburide

- **Oral:** Initial: 1.25 to 5 mg once daily administered with the first main meal; in patients whose glycemic levels are close to goal, use lower initial doses (eg, 1.25 to 2.5 mg once daily) to reduce the risk of hypoglycemia.
- *Dosage adjustment:* May increase in increments of ≤2.5 mg/day every 1 to 4 weeks if needed to achieve glycemic goals; usual maintenance dose: 2.5 to 10 mg/day in 1 or 2 divided doses (maximum: 20 mg/day).
- **Note:** For some patients, especially those receiving >10 mg/day, glycemic response may be improved with twice-daily dosing.

GLICLAZID

- **Oral:** Initial: 40 to 80 mg once daily with the first main meal.
- *Dosage adjustment:* May increase dose in 40 to 80 mg increments every 1 to 4 weeks if needed to achieve glycemic goals; usual maintenance dose: 40 to 160 mg/day (maximum: 320 mg/day).
- **Note:** Administer doses ≥160 mg/day in 2 divided doses.

GLICLAZID
Modified-release tablet:

- **Oral:** Initial: 30 mg once daily with the first main meal.
- *Dosage adjustment:* May increase dose in 30 mg increments every 1 to 4 weeks if needed to achieve glycemic goals; usual maintenance dose: 30 to 60 mg/day (maximum: 120 mg/day) .

GLICLAZID
Dosing: Kidney Impairment: Adult

- Gliclazide is primarily metabolized in the liver to several inactive metabolites, with <1 % excreted unchanged in the urine
- eGFR >60 mL/minute/1.73 m^2: No dosage adjustment necessary (Campbell 1991).

GLICLAZID
eGFR 15 to 60 mL/minute/1.73 m^2:

- **Note:** Use with caution. Initiate at low doses, and titrate gradually with close monitoring. Consider further dose reductions for hypoglycemia or with worsening kidney function.
- *IR tablet:* **Oral:** Initial: 40 once daily; may gradually increase dose in 40 mg increments every 2 to 4 weeks if needed to achieve glycemic goals .
- *Modified-release tablet:* **Oral:** Initial: 30 once daily; may increase dose in 30 mg increments every 2 to 4 weeks if needed to achieve glycemic goals.
- **Note:** Gliclazide MR 30 mg is considered bioequivalent to gliclazide IR 80 mg; initiation with immediate release product may be preferred in some patients (expert opinion).

GLICLAZID
eGFR <15 mL/minute/1.73 m^2:

- Avoid use if possible (expert opinion); use is contraindicated in the manufacturer's labeling; if hypoglycemia should occur, it may be prolonged

GLICLAZID
Dosing: Hepatic Impairment: Adult

- Mild to moderate impairment
- *Immediate-release tablet:* There are no specific dosage adjustments provided in the manufacturer's labeling; however, a dosage reduction may be required.

- Severe impairment: Use is contraindicated.

Insulin secretagogues: Nonsulfonylureasc

Agents Used for Treatment of Type 1 or Type 2 Diabetes

	MECHANISM OF ACTION	EXAMPLES	↓HBA1C (%)	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Insulin secretagogues: Nonsulfonylureas	↑ Insulin secretion	Mitiglinide nateglinide, repaglinide	0.5 – 1.0	Short onset of action, lower postprandial glucose	Hypoglycemia	Renal/liver insufficiency (except repaglinide)

α-Glucosidase inhibitorsc

Agents Used for Treatment of Type 1 or Type 2 Diabetes

	MECHANISM OF ACTION	EXAMPLES	↓HBA1C (%)	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
α-Glucosidase inhibitorsc	↓ GI glucose absorption	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, liver function tests	Reduced dose with renal disease

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Dosing: Renal Impairment: Adult Acarbose

- **Serum creatinine ≤2 mg/dL or CrCl ≥25 mL/ minute/1.73 m^2:** There are no dosage adjustments provided in the manufacturer's labeling.
- **Serum creatinine >2 mg/dL or CrCl <25 ml/minute/1.73 m^2:**
- Use is not recommended

Dosing: Hepatic Impairment: Adult Acarbose

- There are no dosage adjustments provided in the manufacturer's labeling; ***contraindicated*** in patients with ***cirrhosis***.