

# Antihyperglycemic Agents and Renal Failure

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		CRF Stage				
		5	4	3	2	1
eGFR (mL/min/1.73 m <sup>2</sup> ):		<15	15-29	30-59	60-89	≥ 90
Alpha-Glucosidase Inhibitors	Acarbose (Glucobay)	25				100 mg tid
Biguanides	Metformin (Glucophage)	15	500 mg OD	30	500 mg bid	45
DPP-4 Inhibitors	Alogliptin (Nesina)	6.25 mg		30	12.5 mg	50
	Linagliptin (Trajenta)	Limited experience	15			5 mg OD
	Saxagliptin (Onglyza)	15	2.5 mg		50	5 mg OD
	Sitagliptin (Januvia)	25 mg		30	50 mg	50
GLP-1 Receptor Agonists	Dulaglutide (Trulicity)	Limited experience		30		50
	Exenatide (Byetta)			30		50
	Exenatide QW (Bydureon)			30		50
	Liraglutide (Victoza)	15				50
	Lixisenatide (Adlyxine)			30		50
	Semaglutide (Ozempic)	15	Limited experience	30		50
Insulin Secretagogues	Gliclazide (Diamicon)	15				MR 120 mg die or 160 mg bid
	Glimepiride (Amaryl)	Hypos: start at 1 mg OD		30		4 mg bid
	Glyburide (Diabeta)			30	hypos	50
	Repaglinide (GlucoNorm)					4 mg tid
SGLT2 Inhibitors	Canagliflozin (Invokana)			30	100 mg	60*
	Dapagliflozin (Forxiga)				45	300 mg OD
	Empagliflozin (Jardiance)			30		10 mg OD
	Ertugliflozin (Steglatro)			45	Check renal function	60*
Thiazolidinediones	Pioglitazone (Actos)	Heart failure		30		45 mg OD
	Rosiglitazone (Avandia)	Heart failure		30		8 mg OD
Insulins						

■ Contraindicated   
 ▨ Not recommended   
 ■ Dose adjustment required   
 ■ Caution: reason indicated   
 ▨ Titrate carefully to avoid nausea   
 ■ Safe

\*=Do not initiate if eGFR is < 60 ml/min

The dose indicated is the highest dose that can be used at that eGFR

## Explanatory Notes for the Renal Failure and antihyperglycemic Agents Table

### Medications for which the Recommendations in the Table Differ from the Product Monograph

Metformin	The Health Canada product monograph states « Contraindicated in presence of an eGFR < 60 ml/min. » The US FDA revised its recommendations in 2016 to allow its use down to an eGFR of 30 ml/min. A recent study assessed the use of adjusted dosages down to eGFR of 15 ml/min. The recommendations in this table are based on that study. With these dosages, the circulating levels of metformin are similar to those of usual dosages with normal renal function. (Lalau JD et al. Diabetes Care 2018; 41: 547-553).
Gliclazide	The Canadian Product monograph says: « Contraindicated in case of severe renal failure (< 30 ml/min) ». In fact, gliclazide is metabolized by the liver in inactive metabolites that are excreted by the kidneys. The use of this drug is usual to levels of 15ml/min. Since there are no studies of the use of gliclazide with eGFR under 15 ml/min, its use is not recommended.
Glyburide	The Canadian product monograph states: «In patients with renal insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. ». In fact, glyburide is metabolized by the liver into ACTIVE metabolites that are then excreted by the kidneys. There is therefore a risk of accumulation. Glyburide causes many hospitalisations for hypoglycemia, and should be used with caution at eGFR between 30 and 50 ml/min, and should probably be avoided with eGFR under 30 ml/min considering the available alternatives..
Canagliflozin	The Canadian product monograph states: « Contraindication: Renally impaired patients with eGFR less than 45 mL/min/1.73 m <sup>2</sup> . The CREDENCE trial showed impressive nephro-protective properties and safety of canagliflozin 100 mg per day in patients with an eGFR > 30 ml/min.
Pioglitazone	The Canadian product monograph states: : « No dose adjustment in patients with renal dysfunction is recommended. ». This is because the circulating levels of pioglitazone are not affected by renal function. However, pioglitazone tends to increase fluid retention and edema. In patients with renal failure, this led to more cases of heart failure and extreme caution is therefore recommended if used with an eGFR below 30 ml/min.

### Comments Specific to Some Antihyperglycemic Classes

SGLT2 Inhibitors	Because their action requires glomerular filtration of glucose, the antihyperglycemic efficacy of SGLT2 inhibitors decreases with eGFR. Under 60 ml/min, the effect on glycemia and weight (but not blood pressure) is half of what can be seen at higher eGFR. However, the EMPAREG trial revealed impressive cardiovascular and renal benefits, equivalent at doses of 10 and 25, and equivalent whether the eGFR was between 30 and 60 ml/min or greater than 60 ml/min. On that basis, Health Canada now allows the use of empagliflozin at eGFR above 30 ml/min. The CREDENCE trial showed an impressive nephroprotective effect with canagliflozin 100 mg per day in patients with an eGFR > 30 ml/min. During the first weeks of treatment, the eGFR can be expected to drop by 4-8 ml/min, followed by a stability over time, in contrast to the gradual decline seen in people with diabetes without empagliflozin. Albuminuria will decrease by half very rapidly.
GLP-1 Receptor Agonists	Some GLP-1 receptor agonists are excreted by the kidneys and can accumulate in case of renal failure (lixisenatide, exenatide and exenatide QW). The other GLP-1R agonists are not excreted through the kidneys and do not accumulate (liraglutide, dulaglutide, semaglutide). However, all these agents can cause nausea and/or vomiting, particularly at initiation. In presence of renal failure, dehydration resulting from vomiting could cause acute renal failure (pre-renal). In those circumstances, it is therefore important to titrate very slowly the dosages to avoid nausea.