Antihyperglycemic Agents and Renal Failure

Yale JF, version October 2019
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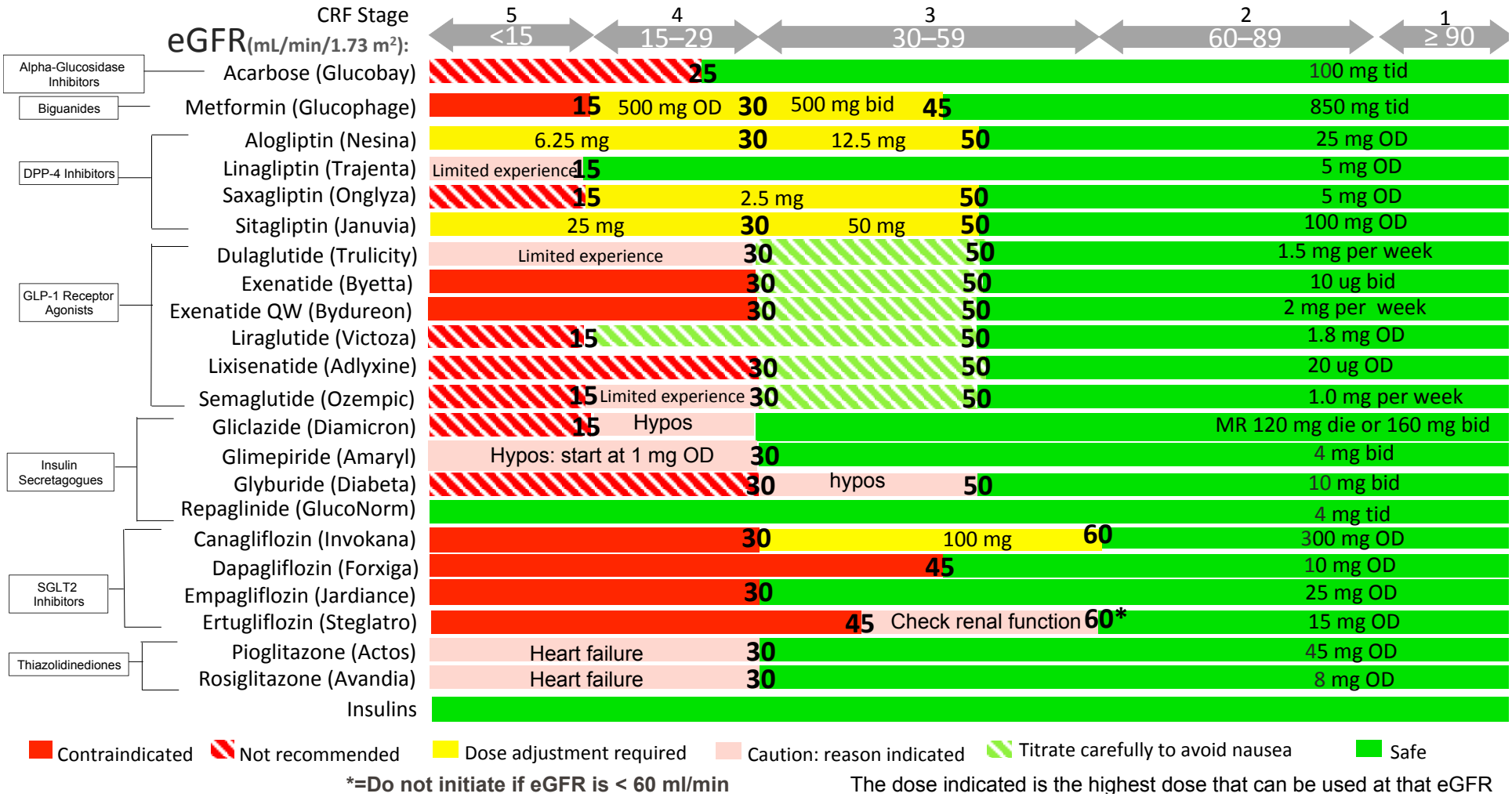

*=Do not initiate if eGFR is < 60 ml/min

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

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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..
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. This is why initially, these molecules could only be initiated at an eGFR above 60 ml/min. However, the EMPAREG (empa), CANVAS (cana) and DECLARE (dapa) trials, and particularly the CREDENCE (cana) trial revealed impressive cardiovascular and renal benefits. On that basis, Health Canada now allows the use of empagliflozin and canagliflozin at eGFR above 30 ml/min, and dapagliflozin above 45 ml/min. In CREDENCE, the primary outcome (ESKD, doubling of serum creatinine or renal or CV death) was reduced by an impressive 30%. In this trial, with an entry criteria of an eGFR 30-90, canagliflozin was limited to 100 mg/day, and the drug was continued even if the eGFR dropped below 30 during the evolution. 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.