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Metformin: Precautions with Renal Impairment, Hepatic Disease and Heart Failure

Why consider metformin in patients with a potential caution or contraindication?

- The benefit of metformin in reducing mortality and macrovascular complications in obese patients with Type 2 diabetes (T2DM) was established in the UKDPS-34 trial. {Metformin ↓ all-cause death; NNT=14/10yrs.}[1]
- After long term follow-up of ~20 years, early glucose lowering to A1C ~7% may reduce long-term macrovascular disease even when between group differences in A1C did not persist in the UKPDS-80. {Metformin ↓ all-cause mortality NNT=14/~20 yr}[2,3]

What is the risk of metformin associated lactic acidosis? [2,3,4,5]

- The incidence of metformin-induced lactic acidosis is rare and is estimated to be 1-9 cases per 100,000 patient-years. Some have suggested that the link between metformin and lactic acidosis is coincidental rather than causal.[3,4] {The incidence of lactic acidosis associated with metformin is at least 10 - 20-fold lower than seen with its predecessor phenformin.}
- A Cochrane review of 347 studies revealed no cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin use, with lactate levels similar between patients receiving metformin and other anti-hyperglycemic treatments.[26]

What conditions or risk factors predispose patients to lactic acidosis? [6]

- Conditions which cause hypoxemia such as cardiovascular, renal, & hepatic dysfunction can ↑ the risk of lactic acidosis.
- Current cautions/*official contraindications* for metformin: renal impairment (Creatinine Clearance [CrCl] <60ml/min) [HC; FDA <30mL/min], heart failure (HF), severe hepatic dysfunction, excessive alcohol intake, severe infection, surgery/trauma, severe dehydration, gastrointestinal illness, age >80yr, cardio-respiratory insufficiency, & those receiving contrast media for diagnostic purposes. (**Onset** is often subtle, accompanied by nonspecific symptoms such as malaise, myalgias, respiratory distress, ↑ somnolence & abdominal distress. **Lab** abnormalities include low pH, ↑ anion gap & elevated blood lactate.)

Can metformin be used in patients with reduced kidney function/chronic kidney disease? [7,8,9,10]

- Metformin may be used in patients with reduced but stable renal function, however, at a reduced dose.

Renal Function	Suggested Metformin dose	Monitor renal function
eGFR ≥60mL/min	≤2550 mg/day	Every 6 to 12 months
eGFR 45-59 mL/min	≤2000 mg/day	Every 3 to 6 months
eGFR 30-44 mL/min	≤1000 mg/day	Every 3 months
eGFR <30 mL/min	Avoid**	N/A
Peritoneal Dialysis	250mg/d	N/A
Hemodialysis	500mg after dialysis	N/A

**Diabetes Canada and ADA Guidelines suggest to avoid if CrCl <30mL/min due to risk of lactic acidosis. However, given the outcome benefits seen with metformin, and the rare & controversial association with lactic acidosis, it is sometimes used cautiously (e.g. 500mg daily) in individuals with stable renal function between 15 to 30mL/min.

European guideline (2015): recommends Metformin 500mg daily for CrCl 15-30ml/min if stable. [19]
FDA statement (2016): cautious use if eGFR 30-45-60ml/min; no comment on dose. [20]
New Zealand Medicines and Medical Devices Safety Authority (2015): recommends metformin 500mg daily in stable renal function 15-30 ml/min

- Metformin should be held in acute illness or dehydration; follow **SADMANS** "sick-day medication list" to avoid decreasing kidney function further and increasing adverse effects.

S= sulfonylureas	**M**= metformin
A= ACE inhibitors	**A**= angiotensin receptor blockers
D= diuretics, direct renin inhibitors	**N**= nonsteroidal anti-inflammatory
	S= SGLT2 inhibitors

Can metformin be used in patients with hepatic dysfunction? [2,3]

- Impaired hepatic function may significantly limit the ability to clear lactate, thus the product monograph recommendation to avoid metformin use in patients with hepatic failure.
- Avoid both acute and chronic excessive alcohol intake, as ethanol may indirectly cause elevated serum lactate levels.
- Currently there is no clear evidence to support decisions on when to ↓ dose or withhold metformin based on liver function.

Is metformin safe to use in patients with heart failure? [2, 11,12]

- Patients with unstable or acute HF are predisposed to lactic acidosis. Risk factors include those patients who require aggressive diuresis, deteriorating ventricular function and those in cardiogenic shock.
- Metformin has not been shown to be associated with harm in patients with diabetes & heart failure[12] (Meta-analysis), and moderate quality evidence favours metformin over sulfonylureas[18]. In patients with stable HF, even those requiring maintenance diuretics, metformin has been shown to be safe. (HF, no longer a contraindication in the USA.) In acute exacerbations of heart failure, metformin should be held temporarily.

What are some key points to remember regarding metformin and the risk of lactic acidosis? [6,11,13]

- Metformin induced lactic acidosis is **rare** (and usually other causative factors are present)! However, it is associated with a 50-60% mortality rate. The benefit of metformin on diabetes complications and mortality in T2DM is well established. (UKPDS-34)
- Lactic acidosis in patients with severe CKD is likely mediated by accumulation of excessive levels of metformin, which is renally cleared, but metformin is not itself renally toxic.
- **Withhold** metformin temporarily:
  - For acute exacerbations of heart failure or renal failure.
  - Acute gastrointestinal illness (nausea, vomiting, diarrhea) leading to dehydration and/or volume depletion.
  - For at least 48 hours post procedure in patients receiving contrast media for diagnostic purposes.
- Consider withholding temporarily in an acute illness requiring hospitalization.
- Determine individual benefit-risk of initiating or continuing metformin in patients with T2DM and **potential risk factors** for development of lactic acidosis. (**NSAIDs** & sometimes ACE or ARBS can worsen renal function in select patients).

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