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

Why is metformin considered in patients with 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 UKPDS-34 trial. [Metformin ↓ all-cause death; NNT=14/10yrs.]
- 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]

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. 1,4 [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/truma, 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.

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

*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 15-30/ml/min if stable. 17
FDA statement (2016): cautious use if eGFR 30-45-60/ml/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.

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 (UKPDS). Meta-analysis, and moderate quality evidence favours metformin over sulfonylureas. 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.
  - For 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.)
References:

16. Bodmer M, Meier C, Kahan E, Sjogren J, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis: a nested case-control analysis. Diabetes Care. 2008 Nov;31(11):2086-91. Epub 2008 Sep 9. Lactic acidosis during current use of oral antidiabetes drugs was very rare and was associated with concurrent comorbidity. Hypoglycemic episodes were substantially more common among sulfonylurea users than among users of metformin.
20. Efficacy and safety of metformin in patients with type 2 diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). Nephrol Dial Transplant. 2005 May;20 Suppl 2:i1-42.