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

Why is metformin considered 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 UKPDS-34 trial. {Metformin + all-cause death; NNT=14/10yrs.}

What is the risk of metformin associated lactic acidosis? 2,13,5
- 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 274 studies in T2DM patients concluded that there was no evidence that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other anti-hyperglycemic treatments.

What conditions or risk factors predispose patients to lactic acidosis? 8
- Currents conditions such as sepsis, renal, & hepatic dysfunction can ↑ the risk of lactic acidosis.
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- Conditions which cause hypoxemia such as cardiovascular, renal, & hepatic dysfunction can ↑ the risk of lactic acidosis.

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.
- The recent 2008 Canadian Diabetes Guidelines & the ADA 2008 state metformin may be used in patients with CrCl <60ml/min, and contraindicated in patients with CrCl<30ml/min. Some references state to avoid at a CrCl <10ml/min. 14
- Suggested Maximum Dosing of Metformin based on renal function 15, (Metformin should be avoided in unstable kidney disease)

<table>
<thead>
<tr>
<th>No renal impairment</th>
<th>CrCl 30-60 ml/min ≤ 850 mg/d</th>
<th>CrCl 60-90 ml/min ≤ 1700 mg/d</th>
<th>CrCl &lt; 30 ml/min (&amp;/or dialysis)</th>
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<tbody>
<tr>
<td>Avoid</td>
<td>Monitoring renal function</td>
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<tr>
<td>At regular intervals (via estimated CrCl):</td>
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<tr>
<td>Every 6 months if CrCl 60-90 ml/min</td>
<td>Every 3-4 months if CrCl 30-60 ml/min</td>
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Can metformin be used in patients with hepatic dysfunction? 2,4
- 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 and alanine transaminase.
- 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 venous function and those at risk of cardiogenic shock.
- Metformin has not been shown to be associated with harm in patients with diabetes & heart failure 2 (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? 5,11,13
- Metformin induced lactic acidosis is rare (and usually other causative factors are present)! However, it is associated with a 30-60% mortality rate. The benefit of metformin on diabetes complications and mortality in T2DM is well established.
- 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).

8. FDA statement (2016): cautious use if eGFR 30-45/60/ml/min; no comment on dose. 21
12. Avoid both acute and chronic excessive alcohol intake, as ethanol may indirectly cause elevated serum lactate and alanine transaminase.
13. Currently there is no clear evidence to support decisions on when to ↓ dose or withhold metformin based on liver function.
14. The ADA 2008 state metformin may be used in patients with CrCl<30ml/min. Some references state to avoid at a CrCl<10ml/min.
15. Suggested Maximum Dosing of Metformin based on renal function 15, (Metformin should be avoided in unstable kidney disease)
16. Metformin induced lactic acidosis is rare (and usually other causative factors are present)! However, it is associated with a 30-60% mortality rate. The benefit of metformin on diabetes complications and mortality in T2DM is well established.
17. For acute exacerbations of heart failure or renal failure.
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.
19. Consider withholding temporarily in an acute illness requiring hospitalization.
20. 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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