

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 UKDPS-34 trial. {Metformin ↓ all-cause death; NNT=14/10yrs.}¹

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 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.³

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 include: renal impairment (Creatinine Clearance [CrCl] <60ml/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.
- The recent **2008 Canadian Diabetes Guidelines** (& the ADA 2008¹⁵) state metformin may be used with caution in patients with CrCl <60ml/min. and contraindicated in patients with CrCl<30ml/min.⁹ Some references state to avoid at a CrCl <10ml/min.¹⁴
- Suggested Maximum Dosing** of Metformin based on renal function¹⁰: (Metformin should be avoided in **unstable kidney disease**)

No renal impairment	≤ 2550 mg/d	CrCl 30-60 ml/min	≤ 850 mg/d
CrCl 60-90 ml/min	≤ 1700 mg/d	CrCl < 30ml/min (&/or dialysis)	Avoid

- Monitor renal function** at regular intervals (via estimated CrCl):

Every 6 months if CrCl 60-90 ml/min	Every 3-4 months if CrCl 30-60 ml/min
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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 failure¹² (Meta-analysis). 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)
- 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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Metformin: Precautions with Renal Impairment

A snapshot around the globe

United States: American Diabetes Association

Current Guidelines: Standards of Medical Care in Diabetes—2011

- “Metformin may be used in patients with stable congestive heart failure (CHF) if renal function is normal. It should be avoided in unstable or hospitalized patients with CHF. (C)”
- “Metformin is often contraindicated because of renal insufficiency or significant heart failure.”
- No dosing guidance is provided for renal impairment, and lactic acidosis is not mentioned.

Notes:

- The 2010 Guidelines included the above statements.
- The 2009 Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes stated:
 - “Renal dysfunction is considered a contraindication to metformin use because it may increase the risk of lactic acidosis, an extremely rare (less than 1 case per 100,000 treated patients) but potentially fatal complication (51). However, recent studies have suggested that metformin is safe unless the estimated glomerular filtration rate falls to <30 ml/min (52).”
 - Reference #52: Shaw JS, Wilmot RL, Kilpatrick ES: Establishing pragmatic estimated GFR thresholds to guide metformin prescribing. *Diabet Med* 24:1160–1163, 2007
- Recent article linked on the ADA website:
 - Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency** Lipska, Kasia J, MD; Bailey, Clifford J, PHD, FRCP; Inzucchi, Silvio E, MD *Diabetes Care*; Jun 2011; 34, 6; ProQuest pg. 1431-7.
 - The authors suggest:
 - US Guidelines be updated and include eGFR thresholds that are consistent with the UK, Canadian and Australian Guidelines.

Table 1—Proposed recommendations for use of metformin based on eGFR

eGFR level (mL/min per 1.73 m ²)	Action
≥60	No renal contraindication to metformin Monitor renal function annually
<60 and ≥45	Continue use Increase monitoring of renal function (every 3–6 months)
<45 and ≥30	Prescribe metformin with caution Use lower dose (e.g., 50% or half-maximal dose) Closely monitor renal function (every 3 months)
<30	Do not start new patients on metformin Stop metformin

Additional caution is required in patients at risk for acute kidney injury or with anticipated significant fluctuations in renal status, based on previous history, other comorbidities, or potentially interacting medications.

United Kingdom – NICE Guidelines

Current Guidelines: TYPE 2 DIABETES National clinical guideline for management in primary and secondary care (update) - 2008

- “Lactic acidosis - A Cochrane review (57) looked at the risk of lactic acidosis in patients treated with metformin. There were no cases of fatal or non-fatal lactic acidosis reported. Level 1+ In addition, one RCT (58) did not find a significant difference in plasma lactate levels between metformin-treated patients and patients treated with other antidiabetic agents. Level 1+”
- Metformin dosing recommendations based on renal function:
 - Review the dose of metformin if the serum creatinine exceeds 130 micromol/l or the eGFR is below 45 ml/minute/1.73 m².
 - Stop the metformin if the serum creatinine exceeds 150 micromol/l or the eGFR is below 30 ml/minute/1.73 m².
 - Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73 m².

Note: a partial update of the 2008 Guidelines was completed in 2011, but only focused on newer agents.

Australia: Diabetes Australia

Current Guidelines: DIABETES MANAGEMENT in GENERAL PRACTICE 2011/12

- “Renal impairment is the only absolute contraindication to metformin (ie: a raised serum creatinine which usually reflects significantly impaired renal function). Metformin is contraindicated in people with a GFR <30 ml/min and should be used with caution in people with a GFR of 30–45 ml/min.”
- “Metformin should not be used in patients with diabetic nephropathy if calculated total GFR is <30 ml/min because of the risk of metformin accumulation and lactic acidosis.”

New Zealand: New Zealand Guidelines Group – Diabetes Advisory Group

Current Guideline: Guidance on the management of type 2 diabetes – 2001

- Metformin – stop if eGFR <30ml/min/1.73m²

Summary of above excerpts:

- Caution/review dose when eGFR 30-45ml/min.
- Discontinue metformin when eGFR <30ml/min.