

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? ^{2,3,4,5}

- 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 function ¹⁰: (Metformin should be avoided in **unstable** kidney disease)

No renal impairment	≤ 2550 mg/d	CrCl 30-60 ml/min	≤ 850 mg/d	European guideline (2015) ¹⁹ recommends Metformin 500mg daily for CrCl 15-30ml/min if stable. FDA statement (2016): cautious use if eGFR 30-45-60ml/min; no comment on dose. ²⁰
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			

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), and moderate quality evidence favours metformin over sulfonylureas¹⁸. 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).

- Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65.
- Pharmacists Letter February 2008. Clinical use of metformin in special populations – chronic renal insufficiency, heart failure and hepatic dysfunction
- CADTH Health Technology Inquiry Service. Use of metformin in patients with type 2 diabetes who have liver dysfunction: a review of safety, dosing recommendations and guidelines for use. September 3, 2008.
- Salpeter S, Greyber E, Pasternak G, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes. Cochrane Database Syst Rev 2006. CD002967.
- Bolen S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med. 2007;147:386-399
- Glucophage Product Monograph. e-CPS accessed on-line September 2008.
- Herrington WG, Levy JB. Metformin: effective and safe in renal disease? Int Urol Nephrol 2008;40:411-17
- Shaw JS, Wilmot RL, Kilpatrick S. Establishing pragmatic estimated GFR thresholds to guide metformin prescribing. Diabetic Medicine 2007;24:1160-63
- Canadian Diabetes Association Clinical Practice Guidelines 2008. Accessed online: <http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf>
- Lalau J, Race J. Metformin and lactic acidosis in diabetic humans. Diabetes, Obesity and Metabolism 2000;2:131-137
- Tahrani AA, Varughese GI, Scarpello JH, Hanna FW. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? BMJ 2007;355:508-512
- Eurich DT, et al. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. BMJ 2007;335 (7618):497
- Benko AD, et al. Canadian Association of Radiologists: consensus guidelines for the prevention of contrast-induced nephropathy. Can J Assoc Radiol 2007;58:79-87
- Drug Prescribing in Renal Failure 5th Edition 2007. Aronoff GR, Bennett WM, et al.
- Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zimman B. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy : A consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes. Diabetologia. 2008 Oct 22. <http://care.diabetesjournals.org/misc/MedicalManagementofHyperglycemia.pdf>
- Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetic drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. Diabetes Care. 2008 Nov;31(11):2086-91. Epub 2008 Sep 9. Lactic acidosis during current use of oral antidiabetic drugs was very rare and was associated with concurrent comorbidity. Hypoglycemic episodes were substantially more common among sulfonylurea users than among users of metformin.
- Fitzgerald E, Mathieu S, Ball A. Metformin associated lactic acidosis. BMJ. 2009 Sep 16;339:b3660. doi: 10.1136/bmj.b3660.
- Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P. Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.
- ERBP: Guideline development group. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). Nephrol Dial Transplant. 2015 May;30 Suppl 2:ii-142.
- FDA Safety: Metformin-containing Drugs 2016: Drug Safety Communication - Revised Warnings for Certain Patients With Reduced Kidney Function <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/cmn494829.htm>



Thanks to Dr. R. Basi & Dr. J. Kappel for providing cardiology and nephrology input & review. (SHR)