Metformin: time to review its role and safety in chronic kidney disease

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Summary

- Metformin is recommended as first-line therapy for type 2 diabetes because of its safety, low cost and potential cardiovascular benefits.
- The use of metformin was previously restricted in people with chronic kidney disease (CKD) — a condition that commonly coexists with diabetes — due to concerns over drug accumulation and metformin-associated lactic acidosis.
- There are limited data from observational studies and small randomised controlled trials to suggest that metformin, independent of its antihyperglycaemic effects, may be associated with lower risk of myocardial infarction, stroke and all-cause mortality in people with type 2 diabetes and CKD.
- Research into the risk of metformin-associated lactic acidosis in CKD has previously been limited and conflicting, resulting in significant variation across international guidelines on the safe prescribing and dosing of metformin at different stages of renal impairment.
- Present-day large scale cohort studies now provide supporting evidence for the safe use of metformin in mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30–60 mL/min/1.73m^2). However, prescribing metformin in people with severe renal impairment (eGFR < 30 mL/min/1.73m^2) remains a controversial issue. Due to observed increased risk of lactic acidosis and all-cause mortality in people with type 2 diabetes and severe renal impairment, it is generally recommended that metformin is discontinued if renal function falls below this level or during acute renal deterioration.

Diabetes mellitus affects over 1.3 million Australians and is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease.[1,2] Metformin has been used in the treatment of type 2 diabetes mellitus in Australia since 1963, and is recommended as the first-line agent in the management of hyperglycaemia as per the Australian Diabetes Society,[3] the American Diabetes Association guidelines,[4] the European Association for the Study of Diabetes,[4] and the British National Institute for Health and Care Excellence guidelines.[5] It is highly efficacious at improving glycaemic management, with significant reductions in glycated haemoglobin (HbA_{1c}) of up to 2.0% (22 mmol/mol),[6,7] and is very affordable, costing about 15 cents per tablet.[8,9] It works primarily by reducing hepatic glucose production and, to a lesser effect, by enhancing insulin-mediated glucose uptake and utilisation in peripheral tissues.[10] Although gastrointestinal adverse effects such as nausea and diarrhoea are common, metformin is generally well tolerated and serious (life-threatening) adverse events are rare.

There is no clear consensus across international guidelines regarding the safe prescribing and dose adjustment of metformin at different stages of renal impairment (Box 1). When metformin was first approved for use in the United States in 1995, the Food and Drug Administration documented stringent prescribing criteria based on renal function due to concerns over drug accumulation and toxicity-associated lactic acidosis.[13] Even though there is continued debate about the causal relationship between metformin and lactic acidosis, these limitations likely restricted the number of people prescribed metformin. It was only after two independent citizens' petitions,[14,15] which called for a revision of existing prescribing restrictions, that the US Food and Drug Administration revised in 2016 these prescribing restrictions and approved its use in people with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30–60 mL/min/1.73m^2).[13]

For this narrative review, we used PubMed, the Cochrane Library and EMBASE to search original and review articles published between 1979 and 2019, in addition to publications from the Australian Diabetes Society, the American Diabetes Association and the European Association for the Study of Diabetes, to formulate an evidence-based synopsis of metformin, metformin-associated lactic acidosis, and its utility and safety in CKD.

Pharmacokinetics and therapeutic range of metformin

Metformin has unique pharmacokinetics: it is not bound to plasma proteins or metabolised, and is primarily eliminated unchanged via active tubular secretion in the kidney.[16] There is an inverse relationship between eGFR and plasma metformin concentration, and this is evident across all stages of CKD.[17,18] Although metformin has been available for more than 50 years in Australia, the therapeutic range of metformin has never clearly been determined, and the precise serum level that is considered therapeutic or potentially unsafe is unknown. To date, there have been no dose-efficacy studies measuring corresponding plasma metformin concentrations to blood glucose control. In addition, most of the pharmacokinetic parameters for metformin have been derived from single-dose studies, rather than steady state concentrations.[19] The question of therapeutic range is further complicated by interindividual variation in plasma metformin concentrations,[17] which is influenced by differences in oral metformin bioavailability, genetic variability in metformin transporters, and renal clearance.[20]

Metabolic and vascular effects of metformin

Diabetes mellitus, both type 1 and type 2, has long been associated with an increased risk of cardiovascular morbidity and mortality.[21,22] This heightened mortality risk among people with diabetes is, in part, due to the higher incidence of CKD,[23] and cardiovascular disease (CVD) observed in this population.[21,22,24] The risk of a fatal vascular event is two- to threefold higher in people with diabetes compared with those without the disease.[24,25]

Metformin, independent of its antihyperglycaemic effects, may be associated with lower risk of myocardial infarction and cardiovascular events in people with type 2 diabetes.[9,26–28] This was first demonstrated in the UK Prospective Diabetes Study (UKPDS 34)[9] — a randomised prospective multicentre trial

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1 Comparison of international prescribing guidelines of metformin in renal impairment

Renal impairment	Recommendation	Recommended dose adjustment
Australian Medicines Handbook*[11]		
CrCl 60–90 mL/min	Reduce maximum dose when CrCl < 90 mL/min	2000 mg daily
CrCl 30–60 mL/min		1000 mg daily
CrCl 15–30 mL/min	Metformin is generally not recommended when CrCl < 30 mL/min, but can be considered for people with stable renal function and CrCl > 15 mL/min with careful monitoring	500 mg daily
CrCl < 15 mL/min	Discontinue if CrCl falls below 15 mL/min	
Monitoring: renal function should be measured prior to treatment and every 4–6 months after initiating metformin		
Medsafe — New Zealand Medicines and Medical Device Safety Authority†[12]		
CrCl 60–120 mL/min	Reduce maximum dose when CrCl < 120 mL/min	2000 mg daily
CrCl 30–60 mL/min		1000 mg daily
CrCl 15–30 mL/min		500 mg daily
CrCl < 15 mL/min	Discontinue if CrCl falls below 15 mL/min	
Monitoring: renal function should be measured prior to treatment and at least twice a year in people with renal impairment taking metformin		
National Institute for Health and Care Excellence‡[5]		
eGFR < 45 mL/min/1.73m^2	Review dose of metformin if eGFR < 45 mL/min/1.73m^2 and prescribe metformin with caution for patients at risk of sudden deterioration of renal function and those at risk of eGFR falling below 45 mL/min/1.73m^2	
eGFR < 30 mL/min/1.73m^2	Discontinue if eGFR falls below 30 mL/min/1.73m^2	
Monitoring: renal function should be measured prior to treatment and at least twice a year in people with additional risk factors for renal impairment, or if sudden deterioration is suspected		
United States Food and Drug Administration,[13] American Diabetes Association[4] and European Association for the Study of Diabetes§[14]		
eGFR < 45 mL/min/1.73m^2	Dose reduction of metformin should be considered when eGFR < 45 mL/min/1.73m^2. Starting metformin in people with eGFR 30–45 mL/min/1.73m^2 is not recommended	
eGFR < 30 mL/min/1.73m^2	Metformin is contraindicated in people with eGFR < 30 mL/min/1.73m^2 and should be discontinued if eGFR falls below 30 mL/min/1.73m^2	
Monitoring: renal function should be measured annually in all people on metformin and more frequently in people at increased risk for the development of renal impairment		

CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate. * Australian Medicines Handbook guideline last updated in January 2019. † Medsafe guideline last updated in December 2015. ‡ National Institute for Health and Care Excellence guideline last updated in May 2017. § US Food and Drug Administration guidelines last updated in August 2016. American Diabetes Association and European Association for the Study of Diabetes guidelines last updated in December 2018. ◆

designed to investigate whether intensive glycaemic control with glucose-lowering agents, compared with conventional treatment (diet modifications), reduced the risk of microvascular and macrovascular complications in overweight people with type 2 diabetes. Following an initial 3-month diet, 1704 overweight (mean body mass index, 31.4 kg/m^2) people with type 2 diabetes and raised fasting plasma glucose levels (6.1–15.0 mmol/L) were randomly allocated into conventional treatment (n = 411) or intensive treatment with metformin (n = 342), sulfonylureas (n = 542) or insulin (n = 409). During the 10-year follow-up period, people treated with metformin had a risk reduction of 39% for myocardial infarction (P = 0.010), 36% for all-cause mortality (P = 0.011), and 42% for diabetes-related death (P = 0.017) compared with the conventionally treated group. In addition, metformin was associated with a significantly greater risk reduction in all-cause mortality (P = 0.021), any diabetes-related endpoint (P = 0.003) and stroke (P = 0.032), compared with sulfonylureas or insulin.[9] These protective effects were still evident in the 10-year post-trial observational study, despite loss of between-group differences of HbA_{1c} levels after the first year.[27] In a randomised, placebo-controlled trial, the addition of metformin in people with type 2 diabetes receiving insulin therapy (n = 390) was associated with a reduced risk of secondary macrovascular endpoints, a composite of clinical events that included myocardial infarction, heart failure, stroke and sudden death (hazard ratio [HR], 0.61; P = 0.02).[28] Metformin was also associated with improvements in body weight (mean difference, –3.07 kg; range, –3.85 to –2.28 kg; P < 0.001) and insulin requirements (mean difference, –19.63 IU/day; 95% CI, –24.9 to –14.4 IU/day; P < 0.001) compared with placebo. The improvements in secondary macrovascular endpoints may be partially explained by differences in weight between the two groups. These effects persisted during the 4.3 years of treatment and follow-up. Conversely, the Diabetes Prevention Program study found no statistically significant difference in the cumulative incidence of CVD events or the event rate in individuals on metformin therapy compared with placebo or lifestyle intervention.[29] Although the randomised multicentre study involved individuals (n = 3234) with impaired glucose tolerance, the overall number of fatal and non-fatal CVD events (n = 89) in the study was small.

Recent observational studies suggest metformin use may be associated with reduced cardiovascular events, morbidity and mortality in people with type 2 diabetes and renal impairment. This was first described in a study analysing data from 19 691 people with type 2 diabetes and established atherosclerotic disease.[30] Among the 5031 people with an eGFR of 30–60 mL/min/1.73m^2, mortality rate was lower in metformin users compared with non-users (HR, 0.64; 95% CI, 0.48–0.86; $P = 0.003$), with the greatest effect observed in people with an eGFR of 30–44 mL/min/1.73m^2 (HR, 0.57; 95% CI, 0.35–0.92; $P = 0.02$). Compared with sulfonylureas and other hypoglycaemic agents, metformin has been associated with a statistically significant lower risk of all-cause mortality in people with type 2 diabetes and various stages of CKD, in both a Swedish population-based longitudinal study[31] ($n = 51\,675$) and a large cohort study[32] of veterans ($n = 175\,296$). These results are in line with a newly published retrospective observational study that analysed data on survival, cardiovascular and kidney disease outcomes in metformin users ($n = 591$) and non-users ($n = 3447$) with type 2 diabetes, CKD and anaemia (haemoglobin < 130 g/L) enrolled in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT).[33] Propensity-matched analysis demonstrated an independent association between metformin use and lower risk of all-cause mortality (HR, 0.49; 95% CI, 0.36–0.69; $P < 0.001$), cardiovascular death (HR, 0.49; 95% CI, 0.32–0.74; $P < 0.001$) and cardiovascular events (HR, 0.66; 95% CI, 0.51–0.86; $P = 0.002$), a composite of non-fatal myocardial infarction, congestive heart failure and stroke. Of note, baseline characteristics in metformin users before propensity score matching were statistically different to non-users. Metformin users had a shorter duration of diabetes (mean, 178 ± 109 *v* 194 ± 120 months; $P = 0.002$), were less likely to have CKD stages 4–5 (23.0% *v* 40.8%), and had fewer comorbidities, such as a history of heart failure (23.9% *v* 35.0%; $P < 0.001$) and coronary disease (35.5% *v* 43.7%; $P < 0.001$). This highlights that the individuals selected to receive metformin therapy in the population are largely different from those taking other glucose-lowering medications, which is difficult to adjust for in observational studies.

The potential favourable effects of metformin on cardiovascular outcomes may be attributed, in part, to its actions on metabolic and endothelial factors implicated in the development of CVD. Metformin is associated with a modest reduction in body weight,[6,28] HbA_{1c} levels,[6,7] insulin requirements[28] and total cholesterol and low-density lipoprotein cholesterol levels.[6] Independent of its effects on weight and glycaemic control, several small clinical trials have demonstrated that metformin may improve endothelial function and fibrinolysis by decreasing specific factors, including plasma von Willebrand factor, soluble vascular cell adhesion molecule-1, and soluble E-selectin.[34,35] Higher levels of these factors have been detected in people with atherosclerosis, coronary artery disease and stroke,[36–39] and have been associated with increased risk of cardiovascular mortality in people with type 2 diabetes.[40,41] While the potential vascular and mortality benefits of metformin in people with type 2 diabetes appear promising, most of the data have been derived from small randomised controlled trials and observational studies and this needs to be considered when interpreting the data. Large prospective clinical trials investigating the effects of metformin on cardiovascular outcomes are lacking.

The association between metformin and lactic acidosis

Lactic acidosis is the greatest perceived risk with metformin use and this association originated from phenformin, a predecessor of metformin. Phenformin was withdrawn from the United States market in 1977 due to the high incidence of lactic acidosis (40–64 cases per 100 000 person-years) and the associated mortality.[42] Compared with metformin, phenformin is more lipophilic, has a higher affinity for mitochondrial membranes and a greater tendency to impair oxidative phosphorylation in the liver, thereby increasing lactate production through anaerobic pathways. Phenformin also inhibits lactate oxidation and increases lactate release by muscle — effects not exhibited by metformin.[43]

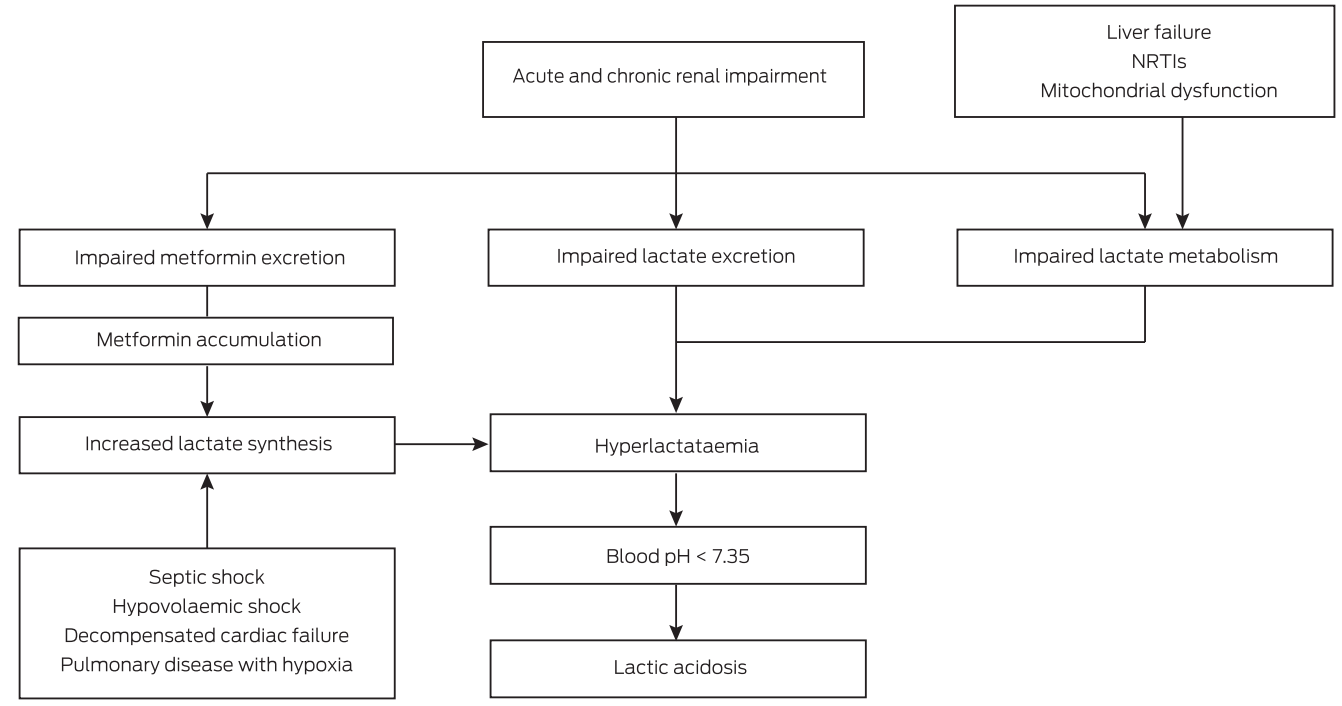
There remains considerable debate and question about the correlation between metformin use and lactic acidosis. Most of the data have been derived from poor quality case reports and observational studies, with varying criteria to diagnose metformin-associated lactic acidosis and conflicting results. Pharmacovigilance reporting of cases of metformin-associated lactic acidosis in a database of the license holder for metformin was reviewed.[44] Of the 869 cases reported in a 15-year period, only 41% met the criteria for lactic acidosis (pH < 7.35; hyperlactataemia > 5 mmol/L) and metformin plasma levels were measured in 14% of cases. Criteria using pH, lactate and metformin concentration were met in 10% of cases. A large Cochrane systematic review[8] of cohort studies and prospective trials (347 studies, representing 70 490 person-years of metformin use) found no cases of fatal or non-fatal lactic acidosis. Compared with other glucose-lowering treatments, metformin was not associated with hyperlactataemia or risk of lactic acidosis. However, 191 of the 334 prospective studies analysed excluded people with CKD.

In most cases of metformin-associated lactic acidosis reported in the literature, at least one or more predisposing medical conditions or risk factors for lactic acidosis could be identified at the time of diagnosis. These included conditions associated with increased lactate synthesis (eg, cardiogenic or septic shock, myocardial infarction), impaired lactate metabolism (eg, severe liver disease) and reduced lactate excretion (eg, renal impairment) (Box 2).[8,45,46] A nested case–control study based on the UK General Practice Research Database was used to identify cases of lactic acidosis in people with type 2 diabetes taking oral hypoglycaemic agents with or without concomitant insulin use.[8] Six cases of lactic acidosis were identified among the study population of 50 048 individuals with type 2 diabetes, producing a crude incident rate of 3.3 cases per 100 000 person-years of treatment with metformin and 4.8 cases per 100 000 person-years of treatment with sulfonylureas. In all cases, risk factors for lactic acidosis could be identified. It is generally recommended that metformin is withheld in people who present with an acute deterioration in renal function or conditions associated with increased lactate synthesis (Box 2).

Metformin use and the risk of lactic acidosis in people with chronic kidney disease

Until recently, studies addressing the safety of metformin in people with mild to severe renal impairment have been inconclusive and contradictory. In one of the first large scale retrospective observational studies, data from 77 601 people with type 2 diabetes on metformin was analysed in the British Clinical Practice Research Datalink (CPRD) database (www.cprd.com) to evaluate the risk of lactic acidosis by renal function.[47] There were 35 lactic acidosis events in the study population between 2007 and 2012, corresponding to an overall incident rate of 10.4 cases per

2 Risk factors for lactic acidosis



NRTIs = nucleoside reverse transcriptase inhibitor. ◆

100 000 person-years. Twenty-three cases occurred in people with moderate renal impairment, 16 of which had a condition independently associated with an increased risk of lactic acidosis (eg, acute kidney injury, ischaemic heart disease). The incidence rates of lactic acidosis in metformin-treated people across normal (eGFR > 90 mL/min/1.73m^2), mild (eGFR 61–90 mL/min/1.73m^2), moderate (eGFR 31–60 mL/min/1.73m^2) and severe (eGFR ≤ 30 mL/min/1.73m^2) renal impairment were 7.6, 4.6, 17.2, and 39.0 per 100 000 person-years, respectively. Despite the numerical trends for increasing lactic acidosis events with lower eGFRs, these differences were not found to be statistically significant.[47] In contrast, another cohort study (n = 233 698) using the CPRD database, found that metformin use was associated with an increased risk of lactic acidosis in people with an eGFR below 60 mL/min/1.73m^2 (adjusted HR, 6.37; 95% CI, 1.48–27.5).[48] However, this study had several limitations. The eGFR dataset was incomplete (missing data in 27.4% of metformin users) and did not account for changes in eGFR over time. Furthermore, diagnoses were captured through standardised clinical codes and not substantiated by medical record review. In a previous study of the same CPRD database, about 50% of the lactic acidosis diagnoses were excluded after manual review of medical records.[8]

The view that metformin can be safely prescribed in mild to moderate CKD has been substantiated in a newly published study, which found metformin was associated with lactic acidosis only with an eGFR below 30 mL/min/1.73m^2 (adjusted HR, 2.21; 95% CI, 1.42–3.44).[49] The risk of acidosis with metformin use was assessed in a community-based cohort of 75 413 people with type 2 diabetes receiving primary care in the United States over a median of 5.7 years. At enrolment, 14 662 people had an eGFR below 60 mL/min/1.73m^2 and 1765 had an eGFR below 30 mL/min/1.73m^2. Compared with other glucose-lowering agents, metformin was not associated with increased risk of lactic acidosis in people with an eGFR above 30 mL/min/1.73m^2, even after accounting for change in eGFR stage over time and potential confounding variables (eg, cardiovascular risk factors, HbA_{1c} level and time-dependent concomitant medications). The mean daily dose of metformin at baseline (1.34–1.38 g/day) was similar across all stages of renal impairment, but adjustment of metformin dose with time and changes in eGFR was not specifically reported. In both metformin users and non-metformin users, lower eGFR was associated with a higher incidence of acidosis. The incidence rates of acidosis in people with CKD stage 2 (eGFR 60–89 mL/min/1.73m^2), 3A (eGFR 45–59 mL/min/1.73m^2), 3B (eGFR 30–44 mL/min/1.73m^2), and 4–5 (eGFR ≤ 30 mL/min/1.73m^2) were 4, 7, 10, and 24 per 1000 person-years, respectively. These results were reproducible when new metformin users were compared with new sulfonylurea users, in propensity score-matched cohort, and in the replication cohort of 82 017 people from a nationwide database.[49] Similarly, a Taiwanese population-based, observational cohort study demonstrated that metformin use was associated with a 35% higher risk of all-cause mortality in people with type 2 diabetes and serum creatinine concentrations greater than 530 μmol/L (equivalent to end-stage kidney disease).[50] The highest risk was noted in individuals prescribed metformin at a dose higher than 1000 mg/day. Complementary open-label, single-centre studies investigating the use of metformin in people with type 2 diabetes and varying CKD stages have been recently published.[17] In the dose-finding study, all patients (n = 69) underwent three one-week blocks of metformin treatment at an increasing dosage (500 mg/daily, 1000 mg/daily and 2000 mg/daily), with a one-week washout period after each block. Metformin concentrations, both plasma and erythrocyte, were assayed 12 hours after the last metformin dose and lactate concentrations were measured in people with CKD stages 3–5. There was a significant inverse relationship between eGFR and metformin concentration for each dose level (P < 0.001), but no observed

association between metformin and lactate levels. In the second study, participants ($n = 46$) underwent 4 months of metformin treatment at a fixed dosage adjusted for CKD stage: 1500 mg/day for CKD stage 3A, 1000 mg/day for CKD stage 3B, and 500 mg/day for CKD stage 4. Plasma and erythrocyte metformin levels remained stable throughout the study and, like in the previous study, no statistically significant relationship was observed between metformin and lactate concentrations.

Conclusion

Despite its multiple benefits, metformin use in patients with kidney disease remains limited by the perceived, albeit rare, risk of lactic acidosis. Lactic acidosis associated with metformin use is a complex issue and the causal relationship, which is often muddied by the presence of coexisting medical conditions, remains open to debate. The data on the safety of metformin in mild to moderate renal impairment (eGFR 30–60 mL/min/1.73m^2) have been limited until recently and sometimes conflicting, despite increased laxity in prescribing guidelines. Recent studies provide further evidence that metformin does not appear to increase the risk of lactic acidosis in mild to moderate renal impairment.[49] However, prescribing metformin in people with moderate to severe renal impairment remains a controversial issue and this is reflected in the conflicting advice in the different international prescribing guidelines (Box 1), with some authorities providing more conservative advice. In the consensus report on the management of hyperglycaemia in type 2 diabetes[4] published in December 2018, both the American Diabetes Association and the European Association for the Study of Diabetes recommend against prescribing metformin in people with an eGFR of 30–45 mL/min/1.73m^2. Conversely, the New Zealand Medsafe guidelines recommend discontinuing when creatinine clearance is less than 15 mL/min, but these were last updated in May 2015. Metformin has been associated with a heightened risk of lactic acidosis and mortality in people with type 2 diabetes and severe renal impairment (eGFR < 30 mL/min/1.73m^2). However, metformin dose was not adjusted for renal function in the Taiwanese population-based cohort study,[50] and adjustment of metformin dose with time and changes in eGFR was not specifically reported in a 2018 study.[49] Dose-efficacy studies to determine metformin therapeutic and safety levels in people with renal impairment are warranted to further guide our prescribing of metformin in this population. Thus, with appropriate dose reduction, precautionary use in patients acutely unwell and close monitoring of renal function, metformin can be sensibly prescribed in individuals with type 2 diabetes and stable renal function with eGFR values above 30 mL/min/1.73m^2. There is currently insufficient evidence to support the safe prescribing of metformin in people with eGFR values below 30 mL/min/1.73m^2 and, therefore, it is generally recommended that it is discontinued if renal function falls below this level.

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