Metformin in advanced chronic kidney disease: are current guidelines overly restrictive?

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Abstract
Type 2 diabetes mellitus and chronic kidney disease (CKD) frequently co-exist and the increasing burden of both conditions is a global concern. Metformin is established as the first-line treatment for type 2 diabetes because it is associated with improved cardiovascular outcomes and a reduced risk of hypoglycaemia compared with other treatment options. Patients with CKD may benefit in particular because they are at high risk of both cardiovascular disease and hypoglycaemic episodes. However, the use of metformin is restricted in this population due to the concerns over lactic acidosis. Recent reviews have evaluated this risk and concluded that current guidelines for prescribing metformin in CKD may be too restrictive. This narrative review considers this evidence further, but also examines the strength of evidence that favours the use of metformin in CKD patients.

Introduction
Chronic kidney disease (CKD) commonly co-exists with diabetes mellitus; the estimated prevalence of Kidney Disease Outcomes Quality Initiative (KDOQI) stage 3–5 CKD in the UK for those with diabetes is 31%. Diabetic nephropathy is the most common attributed cause of end-stage renal disease (ESRD) in those starting dialysis in the UK, with an incidence of 25.4%. Overt diabetic nephropathy most often occurs 15–20 years after the onset of diabetes and frequently occurs alongside other diabetic microvascular complications such as neuropathy and retinopathy. In addition, macrovascular disease is highly prevalent because both diabetes and CKD are important risk factors for developing cardiovascular disease (CVD).

The increasing burden of type 2 diabetes is a global concern.

The International Diabetes Federation (IDF) estimates that 387 million people worldwide (8.3% of the global population) have diabetes. Type 2 diabetes accounts for 85–95% of diabetes in high-income countries and the prevalence of this disease is increasing. If current trends continue, the IDF calculates a global burden of 592 million people (1 in 10 adults) by 2035. Establishing optimal treatment may therefore produce significant benefits on a population level.

Treatment of type 2 diabetes in those with CKD is aimed at reducing microvascular and macrovascular complications, including the progression of kidney disease. However, management options are restricted because reduced kidney function restricts the use of certain oral hypoglycaemic agents. This is particularly the case with metformin, a biguanide drug that has been established as the first-line treatment for type 2 diabetes in the general population, but which must current guidelines consider to be contraindicated in those with advanced CKD. This is largely due to the perceived increased risk of lactic acidosis, a rare but potentially life-threatening complication associated with biguanide therapy. In addition, a recent observational study has found metformin to be associated with greater mortality in patients approaching ESRD (CKD stage 5).

Recent reviews have focused on metformin and the risk of lactic acidosis in patients with CKD. They concluded that the risk of this complication has been overemphasised in this group and that the current prescribing guidelines may be too restrictive. However, these reviews did not fully consider the strength of evidence that favours the use of metformin in patients with CKD. This narrative review will summarise the evidence for and against metformin use in this population.

Search strategy and selection criteria
References for this review were identified through searches of PubMed for articles published from January 1970 to September 2015, by use of the terms "kidney", "renal", "CKD", "GFR", and "glomerular filtration rate", in combination with the terms "diabetes" and "metformin". Only articles published in English were included. Articles resulting from these searches and relevant references cited in those articles were reviewed.

The importance of glycaemic control
Metformin is the first-line hypoglycaemic drug for those with type 2 diabetes. Its glucose-lowering effect is attributed to increased insulin sensitivity, decreased hepatic glucose output and enhanced peripheral glucose uptake. The importance of glycaemic control has been demonstrated in large trials that have shown a reduction in diabetic microvascular complications. In
the landmark United Kingdom Prospective Diabetes Study (UKPDS), over 4,000 participants with newly diagnosed type 2 diabetes were randomly assigned to receive conventional diet-based therapy or intensive glycaemic control with a sulphonylurea or insulin.\textsuperscript{14} Mean glycated haemoglobin (HbA\textsubscript{1c}) was 7.0% (53 mmol/mol) in the intensive group and 7.9% (63 mmol/mol) in the conventional group. Over 10 years, intensive therapy substantially reduced the risk of diabetic microvascular complications by 25%. This effect persisted at a further 10 years post-trial, despite the differences in HbA\textsubscript{1c} levels being lost after a year.\textsuperscript{15} In addition, there was a 15% \( p=0.01 \) risk reduction for myocardial infarction and a 13% \( p=0.007 \) risk reduction for death from any cause in the intensive glycaemic control group.

The association of reduced microvascular complications with improved glycaemic control is of particular relevance in the CKD population because of the potential to slow the progression of diabetic nephropathy. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial randomised 11,140 patients with type 2 diabetes to undergo standard glucose control (mean HbA\textsubscript{1c} 7.4% or 57 mmol/mol) or intensive glucose control (mean HbA\textsubscript{1c} 6.5% or 48 mmol/mol).\textsuperscript{16} At baseline the mean creatinine was normal, 27% had microalbuminuria and 3.6% had macroalbuminuria. There was a significantly lower incidence of major microvascular events in the intensive control group over a median follow-up of five years, primarily due to a reduction in the incidence of nephropathy. The use of most classes of oral hypoglycaemic and insulin had increased in the intensive treatment group. Later analysis revealed significant reductions in the risk of developing ESRD (65%), microalbuminuria (9%) and macroalbuminuria (30%).\textsuperscript{17} Furthermore, the progression of albuminuria was significantly reduced by 10% and its regression significantly increased by 15%. The number needed to treat over five years to prevent one ESRD event ranged from 410 in the overall study to 41 in participants with pre-existing macroalbuminuria. In support of these findings, another trial – the Veterans Affairs Diabetes Trial (VADT) – also demonstrated a benefit in reducing microalbuminuria with intensive glycaemic control.\textsuperscript{18}

There are limited data in those with more advanced CKD, and it is uncertain whether glycaemic control is as effective for this group of patients, many of whom have established diabetic complications. Observational studies have associated glycaemic control with improved outcomes but they do not establish causality.\textsuperscript{19-21}

**Implications of current recommendations**

It is now widely acknowledged that the US Food and Drug Administration prescribing guidelines for metformin are too restrictive. They state that its use is contraindicated with a creatinine >1.5 mg/dL (133 \( \mu \)mol/L) in men or >1.4 mg/dL (124 \( \mu \)mol/L) in women.\textsuperscript{22} This approximately equates to an estimated glomerular filtration rate (eGFR) of <45 mL/min, or CKD stage 3B or more. In the UK, the British National Formulary states that metformin should be used “with caution in renal impairment” and should be avoided “in significant renal impairment”.\textsuperscript{9} The National Institute for Health and Care Excellence (NICE) recommends that the dose of metformin is reviewed if the creatinine exceeds 130 \( \mu \)mol/L or eGFR falls to <45 mL/min.\textsuperscript{1} NICE goes on to recommend that metformin is stopped once serum creatinine exceeds 150 \( \mu \)mol/L or if the eGFR is <30 mL/min (CKD stage 4 or more). In the USA the American Diabetes Association is in agreement with this position.\textsuperscript{23}

It is uncertain whether these recommendations are adhered to and there is likely to be variability in prescribing practice. There are few data available to estimate the additional number of patients who may benefit from metformin therapy if its use was to be expanded in those with more advanced CKD. Dreyer et al performed a cross-sectional study of 34,359 patients with diabetes in three primary care trusts in the UK.\textsuperscript{24} They found that the prevalence of people with an eGFR of <45 mL/min was 5.4%. However, this may be an underestimate because the study population contained a significant number of non-white individuals (who have a lower prevalence of CKD stage 3). Indeed, Bailey et al used National Health and Nutrition Examination Survey (NHANES) data to find a prevalence of 9% in the USA, whilst a study from Spain estimated the prevalence to be 6.4%.\textsuperscript{25,26} Given the large burden of type 2 diabetes, these data suggest that there are a large number of diabetics with CKD who might benefit from even a mild relaxation of the eGFR cut-off for continuing metformin.

**The case for metformin use in CKD**

**Improved cardiovascular outcomes**

Metformin has become firmly established as the first-line oral hypoglycaemic agent in patients with type 2 diabetes mellitus, in large part due to the UKPDS. The original study found intensive therapy with a sulphonylurea or insulin reduced the risk of diabetic microvascular complications but not macrovascular disease when compared with conventional treatment.\textsuperscript{14} This is in keeping with the results of the ADVANCE trial that also showed no reduction in cardiovascular events with intensive glycaemic control.\textsuperscript{16} However, in the UKPDS, metformin was included as a randomisation option in 1,704 participants who were overweight.\textsuperscript{27} Only 342 individuals received metformin, but they were found to have a 39% lower risk \( p=0.010 \) of myocardial infarction compared with conventional treatment. They also had a 30% lower risk \( p=0.020 \) of all macrovascular disease including myocardial infarction, sudden death, angina, stroke and peripheral vascular disease. The risk reduction in the metformin group was greater than in those assigned intensive therapy with a sulphonylurea or insulin, although the difference was not statistically significant. It should be noted that other trials have failed to show reductions in cardiovascular events or mortality with metformin therapy, but these have been of shorter duration than the UKPDS.\textsuperscript{28-30}

A number of mechanisms have been proposed to explain the improved cardiovascular outcomes observed with metformin, including weight loss and an improved lipoprotein profile.\textsuperscript{13,28} These effects may be of particular benefit in CKD because the risk of CVD increases as renal disease becomes more ad-
vanced. However, it is by no means certain that the findings of the UKPDS is applicable to CKD patients because it examined metformin use in a small subgroup of overweight patients who did not have established CVD. This is in contrast to the CKD population, which has a complex cardiovascular risk profile that includes traditional risk factors as well as atypical factors such as vascular calcification. In a prospective observational study, Ekström et al examined metformin therapy in 51,675 patients with type 2 diabetes and differing levels of renal function (eGFR 30–44 mL/min, 45–59 mL/min and ≥60 mL/min). In this study, metformin-based therapy was not associated with a reduced risk of CVD when compared with other therapies, independent of renal function.

The above notwithstanding, there is evidence that metformin may be beneficial for those with pre-existing cardiovascular disease. In a trial of 304 people with type 2 diabetes and coronary artery disease, metformin monotherapy significantly reduced composite cardiovascular events in comparison to glipizide over five years of follow-up (HR 0.54, 95% CI 0.30 to 0.90). Furthermore, Roussel et al examined data from 19,691 participants with diabetes and established atherothrombosis in the Reduction of Atherosclerosis for Continued Health (REACH) registry. They found that mortality was lower for patients with an eGFR ≥30 mL/min who had been prescribed metformin compared with those who were not. Statistical significance was reached only in those with an eGFR <60 mL/min and there was a greater reduction in mortality in the group with an eGFR of 30–44 mL/min (HR 0.57, 95% CI 0.35 to 0.92) than for the group with an eGFR of 45–59 mL/min (HR 0.75, 95% CI 0.52 to 1.10).

Fewer hypoglycaemic episodes
A well-established benefit of metformin therapy compared with most other oral hypoglycaemic agents is the lower risk of hypoglycaemia. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study compared intensive glucose control (mean HbA1c 6.4% or 46 mmol/mol) with standard glucose control (mean HbA1c 7.5% or 59 mmol/mol) in patients with type 2 diabetes. The study was stopped after 3.5 years due to a significantly higher mortality rate in the intensive therapy group. Although a direct link was not established, there was a significantly higher rate of hypoglycaemia in the intensive therapy group, a finding that was in common with the ADVANCE study and VADT. Hypoglycaemia is a potentially life-threatening complication of diabetes treatment and recent observational data have found an association between hypoglycaemia in insulin-treated patients and increased cardiovascular risk.

Hypoglycaemia is particularly important for those with CKD because it occurs more frequently. This is likely due to a combination of reduced insulin clearance, lower glycogen stores, decreased renal gluconeogenesis and reduced clearance of hypoglycaemic medication. For this reason, international guidelines have recommended less stringent glycaemic control targets for patients with CKD than for those without CKD. Indeed, in a post hoc analysis of the ACCORD data, intensive glycaemic control was found to significantly increase cardiovascular and all-cause mortality in CKD patients, but not in non-CKD patients. Therefore, metformin may have a particular advantage over other therapies in this high-risk population.

Disadvantages of other treatment options
Metformin may have additional advantages over other hypoglycaemic agents including a lower risk of renal function decline and of solid cancers. However, it is also important to consider the specific disadvantages of the alternative treatment options. Although the treatment of diabetes is evolving, many agents are contraindicated or unlicensed for use in advanced CKD. Other drugs such as the dipeptidylpeptidase-4 inhibitors lack long-term and hard outcome data, whilst pioglitazone has been associated with heart failure and bladder cancer (although a recent pooled analysis has challenged the latter). Therefore, when metformin is contraindicated, the alternative is often to switch to a sulphonylurea or insulin. Both of these are associated with weight gain, an important side-effect that has implications for both body image and cardiovascular risk. Insulin in particular is unpopular with patients and associated with its own risks and costs. Indeed, observational studies have associated adverse cardiovascular outcomes and increased mortality with both sulphonylureas and insulin, albeit the data from clinical trials are less conclusive.

This is not to say that metformin does not have its own problems: in addition to the association with lactic acidosis, gastrointestinal side-effects limit its tolerability in some patients and it has been associated with vitamin B12 deficiency. But when tolerated and appropriately monitored, metformin is cheap, simple to administer and safe.

The case against metformin use in CKD
The risk of lactic acidosis
Metformin and phenformin, the two main biguanides, were introduced in the late 1950s but the latter was withdrawn in many countries in the late 1970s due to its association with lactic acidosis. Metformin also causes a small increase in serum lactate concentrations, probably because of conversion of glucose to lactate by the intestinal mucosa and reduced uptake of lactate in the liver. However, significant lactic acidosis associated with metformin use is rare and has been overemphasised in the literature. In a meta-analysis of 347 comparative trials and cohort studies, no cases of lactic acidosis were identified in 70,490 patient-years of metformin use. Individual studies have reported crude incidence rates of 3.3–10.4 cases per 100,000 patient-years. This risk may be comparable to rates of lactic acidosis in those taking sulphonylureas or in those with type 2 diabetes in general.

Metformin is primarily eliminated unchanged by the kidneys and therefore kidney disease is associated with higher drug levels that could increase the risk of lactic acidosis as renal function declines. Metformin has also been shown to accumulate in enterocytes of the small intestine in a mouse model of diabetes. This may explain the long half-life of metformin elimination in cases of metformin-associated lactic acidosis and may
be of particular concern in those with CKD. Indeed, case reports have frequently identified kidney failure (both acute and chronic) as a risk factor. Despite this, only a few experimental studies have tried to establish whether reduced metformin clearance in CKD is associated with an increased serum lactate level. In the only randomised control trial, Rachmani et al randomly assigned 393 type 2 diabetics with a serum creatinine of 130–200 μmol/L to continue or stop metformin. A close correlation between serum creatinine and lactate levels was observed (r=0.78, p<0.001). In other small studies, however, this correlation has not been seen. The relevance of these experimental findings is uncertain, given the rarity of significant metformin-associated lactic acidosis in clinical practice. For instance, in the large meta-analysis mentioned above, 45% of the studies reviewed did not exclude patients with a creatinine of >133 μmol/L. This meant there were no cases of metformin-associated lactic acidosis identified amongst 37,360 patient-years of metformin use in patients with CKD.

To further determine the risks of metformin use with kidney disease, retrospective observational studies have investigated the frequency of lactic acidosis in those with CKD. In the aforementioned study by Ekström et al, metformin prescription was not associated with an increased risk of acidosis or serious infection in patients with an eGFR of 30–44 ml/min when compared with other hypoglycaemic treatments. Conversely, metformin was associated with a significantly lower risk of this composite outcome compared with other agents in those with an eGFR ≥45 ml/min. In a recent study by Hung et al, metformin use in 3,254 patients with advanced CKD approaching ESRD (creatinine >530 μmol/L) was not associated with a significantly greater risk of metabolic acidosis (adjusted HR 1.30, 95% CI 0.88 to 1.93). Two large studies have analysed UK patient records from the Clinical Practice Research Datalink (CPRD) database. Richy et al examined the records of 77,601 patients treated with metformin for type 2 diabetes between 2007 and 2012. They found no statistically significant increase in the incidence of lactic acidosis in patients with more advanced CKD compared to those with normal renal function. Eppenga et al investigated a larger cohort of 223,968 patients with type 2 diabetes prescribed metformin between 2004 and 2012. Evaluating lactic acidosis either by CPRD Read code or a serum lactate concentration of >5 mmol/L, they found an overall crude incidence rate of metformin-associated lactic acidosis of 7.4 events per 100,000 patient-years. These data suggest that, although the relative risk of lactic acidosis in those taking metformin does increase with CKD, the absolute risk remains low.

Following on from this, it is reasonable to question whether the excess risk of metformin-associated lactic acidosis in CKD patients can be offset by reducing the dose of metformin as opposed to stopping it. In the study by Eppenga et al, the risk of lactic acidosis was lower in those prescribed smaller doses of metformin, especially in those with an eGFR <60 ml/min. There is also experimental evidence to support this finding. In a study of 24 patients aged 70–88 years, those with a creatinine clearance (CrCl) of >60 ml/min were prescribed 1,700 mg/day metformin and those with a CrCl of 30–60 ml/min were prescribed 850 mg/day. After two months there was no significant difference in the serum levels of metformin and lactate between the two groups. Similarly, Lin et al compared lactate levels in 66 patients with type 2 diabetes aged over 80 years and taking metformin (mean age 83.6 years, mean CrCl 48.9 ml/min) with 79 younger individuals (mean age 59.9 years, mean CrCl 80.3 ml/min). There was no difference between the groups, although it should be recognised that the patients in the elderly group had a significantly lower daily metformin dose. However, the evidence does not support the routine measurement of serum lactate to guide metformin dosing in CKD. In a study of 22 patients with eGFR readings of 15–40 ml/min (as well as two dialysis patients), three patients developed a high lactate concentration (>2.7 mmol/L) but no correlation was observed with the serum metformin level.

The lack of a clinically useful relationship between metformin levels and lactate concentration in those with CKD has also been demonstrated elsewhere. The explanation for this finding is that there is unlikely to be a simple causal relationship. The difficulty with interpreting the studies using CPRD data is their observational nature and the fact that there are other causes of lactic acidosis. In a series of 49 metformin-treated patients with lactic acidosis, Lalau and Race found that neither serum metformin levels nor lactate levels were of prognostic value with regard to mortality. They concluded that death in these patients appeared to be associated with other hypoxic injury or underlying ill health rather than the accumulation of metformin. Patients with both diabetes and CKD frequently have other co-morbidities that predispose to lactic acidosis, irrespective of the use of metformin. These include more advanced diabetes and CVD, both of which may predispose to sepsis and/or vascular insufficiency. In addition, these patients are at increased risk of acute kidney injury (AKI). AKI is frequently associated with acute presentations that can result in lactic acidosis (e.g. sepsis, ischaemia, hypovolaemia), as well as being an independent risk factor for the accumulation of metformin due to reduced renal excretion.

Further support for the view that metformin use is not an isolated risk factor for developing lactic acidosis was found in a study by Bodmer et al. They examined the records of 50,048 patients with type 2 diabetes from the UK General Practice Research Database between 1994 and 2005 and identified only seven cases of lactic acidosis, of which five were in current users.
of metformin. In four of these, lactic acidosis was associated with the worsening of other factors known to contribute to the risk of lactic acidosis: acute heart failure, urosepsis, AKI, hypovolaemia or seizure. Similarly, in a review of 47 cases of metformin-associated lactic acidosis, a panel of six critical care experts came to the conclusion that there was not a simple causal relationship between metformin use and lactic acidosis in diabetic patients. It therefore may be more logical and sufficient to suggest that metformin be stopped in specific groups of patients at high risk of lactic acidosis rather than avoiding its use in all patients with CKD.

A lack of evidence for metformin in CKD

It is important to note that there have been no comparative trials in the CKD population in order to establish the potential benefit of metformin compared with alternative treatment options. This group differs substantially from the majority of participants in these studies because patients with kidney disease frequently have long-standing diabetes with established complications, as well as atypical cardiovascular risk factors. Indeed, in the aforementioned study by Hung et al, metformin was associated with increased mortality in those with advanced CKD approaching ESRD (KDIGO CKD stage 5) that was not explained by an increased risk of acidosis. This is in contrast to observational studies in the wider population that have shown metformin monotherapy to be associated with lower mortality compared with other hypoglycaemic agents. Interpreting this study should be done with caution, given the observational design and potential for confounding factors. Nevertheless, it may be incorrect to assume that the results of trials that have established the benefits of metformin therapy, as well as glycaemic control in general, apply to those with CKD.

The UKPDS remains the most important of these studies, but the trial results have attracted some controversy. Boussageon et al point out that the beneficial effects of metformin were limited to a small subgroup of overweight patients and that these findings have not been replicated in other studies. They highlight methodological flaws in the study, particularly the lack of double blinding and a placebo control. Another concern has been the paradoxical finding that all-cause mortality was higher when metformin was added to a sulphonylurea compared with a sulphonylurea alone (RR 1.60, 95% CI 1.02 to 2.52). In support of this, a meta-analysis of observational studies reported an increased risk of cardiovascular hospitalisation and mortality with the combination of metformin plus a sulphonylurea. This presents a potential dilemma when considering the expansion of metformin use in CKD: the improved renal outcomes observed in the ADVANCE trial were achieved with a largely sulphonylurea-driven protocol and so combination therapy could be argued to be the most evidence-based approach in this population. However, despite the combination of metformin and a sulphonylurea being more frequent in the intensive control group of this study, an increase in mortality was not observed. Taken together with the results of other trials, the possibility of an adverse interaction between these agents remains uncertain.

Discussion

The absolute risk of lactic acidosis with metformin use is low. In CKD this risk is probably increased, but epidemiological evidence suggests that the overall incidence remains low. The excess risk may, in part, be circumstantial because CKD is associated with other factors that predispose to lactic acidosis. However, discontinuing metformin in this group of patients needs to be balanced against the advantages of metformin over other treatment options. Those with CKD and diabetes are at high risk of CVD, and metformin could be especially beneficial for these patients because, in contrast to other hypoglycaemic drugs, metformin may reduce cardiovascular risk. Furthermore, the alternative to continuing metformin is often to switch to a sulphonylurea or insulin, both of which are associated with weight gain and hypoglycaemic episodes. It is reasonable therefore to question whether it is better to accept the small risk of lactic acidosis with continuing metformin than the morbidity and mortality that may come with switching to an alternative hypoglycaemic agent.

There is a lack of objective outcome data to guide the use of metformin in the CKD population itself and further studies are needed. The existing evidence is largely extrapolated from studies involving participants with normal or mildly impaired renal function. Furthermore, the improved cardiovascular outcomes observed in the UKPDS were confined to those who were overweight. As such, it could be argued that there are insufficient data to support the initiation of metformin in all type 2 diabetics with advanced CKD. However, for the majority of patients with CKD, the question is not whether to start metformin but whether to continue. In patients who have been well maintained on metformin, particularly those who are overweight, the evidence is not strong enough to support its routine withdrawal upon reaching an eGFR of 30 mL/min, as per current guidelines. Indeed, other authors have put forward the case for metformin to be continued with lower levels of renal function and there is some evidence that this reflects current clinical practice. In our experience, many prescribers adopt a pragmatic approach
and continue metformin until eGFR falls below 20 mL/min or less, depending on patient age, weight, stability and co-morbidities. Recent observational data have suggested that continuing metformin beyond this may be associated with adverse outcomes, and so it is difficult to justify continued use in those with an eGFR of <20 mL/min except in the context of a clinical trial.

A sensible strategy for the extended use of metformin in CKD might be to reduce the prescribed dose of metformin, with close attention to risk factors for developing lactic acidosis such as heart failure and the risk of AKI. Given that patients with CKD are more likely to develop AKI, they should be fully informed of the risk associated with metformin and advised to have a lower threshold to seek medical advice should they become unwell. This situation is similar to that of inhibitors of the renin-angiotensin system, which are associated with a higher risk of hyperkalaemia and renal injury, and so should be withheld in the face of acute intercurrent illness.

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