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Review Article

A justification for less restrictive guidelines on the use of metformin in stable chronic renal failure

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Abstract

Aim The aim was to justify less restrictive use of metformin in stable chronic renal failure, because a literature review reveals metformin is associated with a significantly lower incidence of cardiovascular events and mortality compared with other hypoglycaemic agents, and metformin-associated lactic acidosis is rare and causation uncertain. Studies on intentional metformin overdose and metformin bioavailability, renal clearance and plasma metformin in renal impairment provide evidence in support of a less restrictive use of metformin.

Methods In metformin overdose (n = 22), lactic acidosis was not inevitable with a plasma metformin > 40 mg/l (therapeutic level *c.* 1 mg/l): Severe lactic acidosis (pH ≤ 7.21, plasma lactate ≥ 11 mmol/l, n = 8) did not occur unless plasma metformin was > 40 mg/l. Plasma lactate was a more consistent predictor of pH than plasma metformin, with plasma lactate ≤ 4.7 being associated with a pH ≥ 7.34. A likely 'safe' plasma lactate is < 3.5 mmol/l and plasma metformin < 10 mg/l.

Results Plasma metformin can be predicted from estimated glomerular filtration rate and metformin dose. Reported plasma metformin in renal failure was always less than predicted plasma metformin. Predicted plasma metformin (mg/l), with an estimated glomerular filtration rate of 30 ml/min and metformin 2000 mg/day was 6.8; an estimated glomerular filtration rate of 20 ml/min and metformin 1500 mg/day was 5.1; an estimated glomerular filtration rate of 10 ml/min and metformin 500 mg/day was 4.4.

Conclusion Metformin accumulates in renal failure and, although accumulation does not always lead to lactic acidosis, dose modification to achieve a predicted plasma metformin < 10 mg/l is suggested. As plasma metformin is not routinely available, plasma lactate should be useful in monitoring the use of metformin in renal failure.

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Introduction

If a therapeutic intervention carries a potential rare and non-specific complication, it is difficult to develop a definitive evidence base for the risk–benefit analysis. This may lead to guidelines, in the face of uncertain risk, emphasizing 'first do no harm' rather than balancing the benefits against the risks, potentially unreasonably denying a patient the benefits of that intervention. The guidelines for the use of metformin in patients with impaired renal function [e.g. avoid with an estimated glomerular filtration rate (eGFR) < 30 ml/min and with caution < 40 ml/min)] [1], to our minds, and the minds of others [2–4], reflect a mismatch between the benefits of metformin against the risks of utilization, predominately the risks of lactic acidosis.

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Benefits of metformin

The benefits of the use of metformin as a treatment for patients with Type 2 diabetes are clearly established [5,6], including a long-term benefit (legacy effect) from earlier treatment [7]. Metformin is first-line therapy in most international guidelines [1,8]. Metformin also has significant benefits over many other therapies: low cost, low risk of hypoglycaemia and lack of weight gain [5], and, when compared with insulin, ease of patient education and utilization. In large observational studies, metformin is associated with lower rates of cardiovascular disease and lower overall mortality than is seen with other hypoglycaemic agents, even if patients have renal impairment [9–11]. For example, in a 3.9-year follow-up of 51 675 patients with Type 2 diabetes, adjusted hazard ratios showed that metfor-

min alone, or in combination with other hypoglycaemic agents, was associated with a reduced risk of all-cause mortality, any cardiovascular disease or any serious infection/acidosis when compared with treatment with insulin and also other oral hypoglycaemics [9]. In a cohort of 16 691 patients with diabetes with atherothrombosis, Roussel *et al*. found a mortality rate of 6.3% in patients taking metformin vs. 9.8% in those not receiving the drug [11]. When comparing metformin alone to either insulin alone or other oral hypoglycaemics, the use of metformin is associated with a reduction in all-cause mortality of *c*. 150–175/10 000 person years (our extrapolation of data from Ekstrom *et al*. and Roussel *et al*.) [9,11]. One criticism of observational studies is that patients with renal impairment and consequently higher mortality are under-represented in the metformin group. However, in both of these studies benefits persisted when subjects were stratified by renal function: The effect of metformin, when compared with insulin, on cardiovascular disease/mortality was similar in those with a GFR down to 30 ml/min, compared with those with a GFR $\geq$ 60 ml/min [9]. We acknowledge that there are no outcome data for cardiovascular benefit with the use of metformin in patients with a GFR < 30 ml/min; however, we believe that an expectation of some benefit is a reasonable extrapolation.

Another important potential reason for the use of metformin in patients with renal impairment is improved glycaemic control. Cessation of metformin is frequently associated with an increase in HbA_{1c} levels that in some cases is profound [12]. Metformin remains a useful therapy even in insulin-treated patients; the benefits include improved glycaemic control, reduced insulin dose and low rates of hypoglycaemia for a given HbA_{1c} level [13–15]. And glycaemic control deteriorates if metformin is ceased in insulin-treated patients [15]. Given that good glycaemic control has recently been shown to prevent end-stage renal disease in patients with diabetes and renal impairment [16], physicians may wish to continue metformin in this setting if alternative therapy is suboptimal.

Metformin and lactic acidosis

The initial link between lactic acidosis and metformin was made because metformin is a member of the biguanide class, and the first biguanide, phenformin, was clearly associated with an increased risk of developing lactic acidosis [17]. Metformin has always come under scrutiny, in our view unfairly, as a potential cause of lactic acidosis and, as a consequence, there are multiple case reports in the literature of lactic acidosis associated with metformin. However, metformin and phenformin differ markedly in their rates of uptake into cells and in their metabolism [18], with phenformin having considerably more potential for toxicity. In contrast to the well-documented benefits of metformin, the risks of developing lactic acidosis are not clear for two main reasons: firstly the problem is extremely rare and, secondly, there are multiple causes of lactic acidosis. Indeed, it is questionable whether metformin, when used therapeutically, ever causes lactic acidosis, even in patients with renal failure. Thus, the term metformin-associated lactic acidosis is commonly used, implying a causation is yet to be established.

There is scant evidence of an increased incidence of lactic acidosis in patients treated with metformin in trials and therapeutic use. A substantial meta-analysis of randomized controlled trials, some of which did not exclude subjects with risk factors for lactic acidosis, totalling 18 689 patients, and 36 893 patient years, demonstrated no cases of lactic acidosis in patients on metformin, or in the control group of patients on other hypoglycaemic agents, and no difference in plasma lactate levels between the groups [19]. Based on these data, the authors calculated a probable upper limit for the incidence of lactic acidosis of *c*. 0.9 per 10 000 patient years in both groups [19].

Patients studied under trial conditions do not necessarily reflect the use of metformin in the community where substantial numbers of patients are treated with metformin despite having contraindications to its use, including renal failure. In one study, 19% of patients admitted to hospital on metformin had decreased renal function (creatinine clearance 38.5 $\pm$ 13.4 ml/min) [20] and, in another study, 5% had a creatinine clearance < 30 ml/min [21]. Despite the frequency of renal impairment in metformin-treated patients in clinical practice, there is again no evidence that there is an increased risk of lactic acidosis when compared with other oral hypoglycaemics. The incidence of lactic acidosis in patients with diabetes in the USA on oral hypoglycaemics, prior to the release of metformin, was 0.97 per 10 000 person years (95% CI 0.2–19.1) [22], and this did not change after its introduction in the USA (0.5 per 10 000 person years) [23], despite a significant potential for reporting bias, with metformin carrying a warning of potential lactic acidosis. A similar incidence was reported in a series of papers reviewed elsewhere [24] and a nested case–control study of 50 048 patients with Type 2 diabetes found no difference in the incidence of lactic acidosis between those on metformin and other oral medications (metformin 0.3, sulphonylureas 0.5 cases per 10 000 person years) [25]. Importantly, the incidence of lactic acidosis, at *c*. 0.5/100 000 person years is two orders of magnitude lower than the benefits in mortality associated with the use of metformin, detailed above.

In addition to the above evidence, most reported cases of metformin-associated lactic acidosis are in patients who also have significant risk factors for lactic acidosis, other than renal failure. In a collection of 47 cases of metformin-associated lactic acidosis only one patient had no risk factors for lactic acidosis (and no metformin accumulation, with a plasma metformin of 0.89 mg/l) and, of the 12 patients with chronic renal failure, only one had no other risk factors (acute renal failure, cardiovascular disease, hepatic failure, intravenous contrast, shock, sepsis) (and no plasma metformin recorded) [26]. In this study, there was a low level of

inter-observer agreement on the cause of the lactic acidosis and no correlation between plasma levels of metformin and plasma lactate [26]. In another series of 49 cases of metformin-associated lactic acidosis, all patients had other risk factors [27]. There were only three patients with chronic renal failure and no other risk factors: The plasma metformin in these patients was 7, 37 and 63 mg/l [27]. In addition, the mean metformin levels were higher in the survivors than in those who died, suggesting lack of causality [27]. These data do not exclude metformin as a cause of lactic acidosis in any of the cases, it just makes attribution more difficult and, in most cases, unlikely.

In another review of 67 patients with lactic acidosis in intensive care, the lactic acidosis was attributed to metformin in four patients, because no other cause was discerned [28]. These patients had severe renal failure, with an eGFR < 11 ml/min (possibly an overestimate if there was a rising plasma creatinine in an acute setting) and plasma metformin levels, measured in three patients, were > 40 mg/l [28]. Lactic acidosis carries a high mortality rate, but observational studies suggest that mortality in metformin-associated lactic acidosis is lower than that observed in lactic acidosis not associated with metformin [27]. Indeed, this has led to speculation that metformin could actually have a protective effect, via mechanisms such as diminution in oxidative stress, and repression of mitochondrial permeability transition [27].

Determining any association between metformin and lactic acidosis seems more possible following intentional metformin overdose, although many of these patients may have ingested other drugs as well [29]. Following metformin overdose in 22 patients, there was no clear relationship between plasma metformin and pH or lactate (Fig. 1) [29]. In nine of the patients with a metformin overdose, a pH ≤ 7.2 was associated with a peak lactate of > 20 mmol/l and a plasma metformin level ranging from 42 to 188 mg/l [29] (Fig. 1). However, in another 13 patients with a metformin overdose, a pH ≥ 7.21 was associated with a plasma lactate < 15 mmol/l, but with plasma metformin ranging from 0.3 to 140 mg/l. Indeed, four patients with a plasma metformin ≥ 36 mg/l and a plasma lactate ranging from 3 to 7 mmol/l had a normal pH (> 7.35) [29] (Fig. 1). In contrast to the lack of relationship between plasma metformin and pH in these patients, there was a good correlation between plasma lactate and pH (Fig. 2). While lactic acidosis is not an inevitable consequence of a high plasma metformin, a plasma metformin above 40 mg/l, some 40 times the therapeutic level, may possibly cause/facilitate the development of lactic acidosis in susceptible individuals.

If there is any susceptibility to lactic acidosis in some patients, with high plasma metformin levels, this may reflect a variable relationship between intracellular and plasma metformin concentration or may reflect a variable susceptibility of lactate metabolism to metformin accumulation, either innate or induced by associated conditions that increase the risk of lactic acidosis.

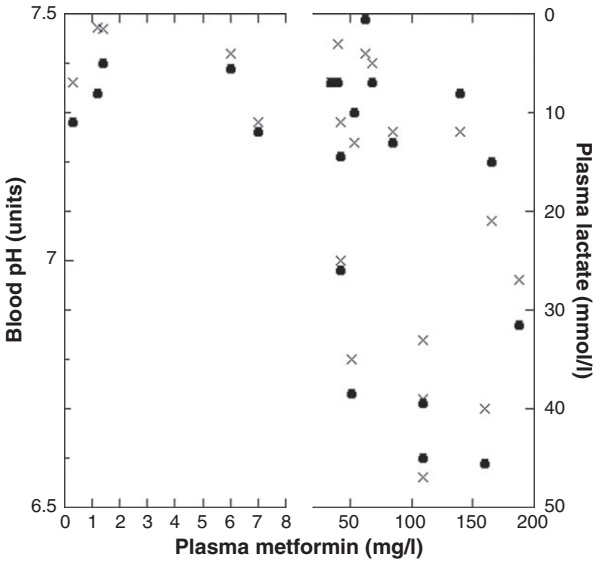

FIGURE 1 The relationship between plasma metformin and pH (X) and plasma lactate (O) in 22 patients following an intentional overdose of metformin (and other drugs) (Dell'Aglio *et al*. [29]). There was a poor correlation between plasma metformin and pH or plasma lactate. Lactic acidosis was only present when plasma metformin levels were > 40 mg/l, and then only in some patients.

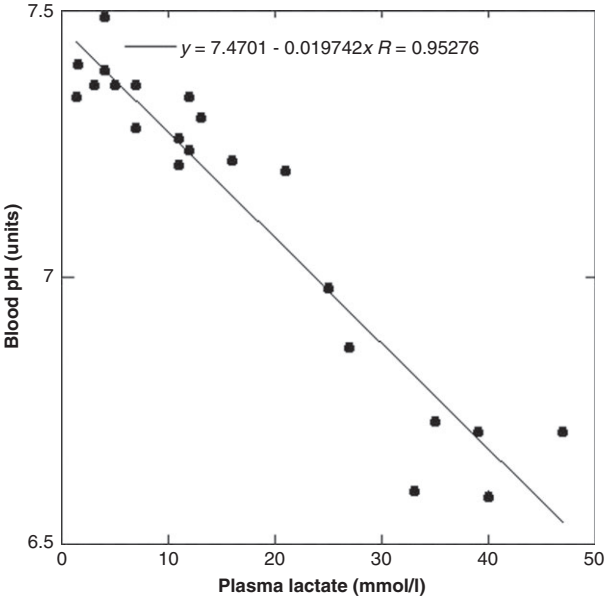

FIGURE 2 The relationship between blood pH and plasma lactate in 22 patients following an intentional overdose of metformin (and other drugs) (Dell'Aglio *et al*. [29]). There was a better correlation between plasma lactate and pH (R = 0.95) than plasma metformin and pH (Fig. 1).

To summarize, while nearly all cases of metformin-associated lactic acidosis can be attributed to causes other than metformin, we cannot exclude the possibility that metformin may cause/facilitate lactic acidosis in certain susceptible individuals. If metformin does cause/facilitate lactic acidosis, this may be completely idiosyncratic, but it seems much more

likely that metformin-associated lactic acidosis occurs in susceptible individuals only when plasma metformin levels are very high (> 40 mg/l). Further, plasma lactate is a better predictor of acidosis than plasma metformin. Given the therapeutic benefits of metformin, and the low incidence and uncertain cause of lactic acidosis, a metformin dosage regime in renal failure that maintained maximum plasma metformin levels < 10 mg/l may be sufficient to minimize the risk of metformin-associated lactic acidosis and should also reduce the risk of other side effects.

Metformin and renal function

These data raise two important consequent questions. What degree of renal failure, and metformin dose, are required to achieve a plasma metformin of ≤ 10 mg/l? Can the risk of metformin-associated lactic acidosis be anticipated by using the GFR to predict the likely plasma metformin, given the drug's pharmacokinetics?

Following intravenous administration of metformin, there is both transport into cells (hepatic, bowel, red blood cells) and a renal clearance at a rate 4–5 times glomerular filtration [30,31], requiring active tubular secretion.

The bioavailability of oral metformin is *c*. 50–60% [31] and no metabolites of metformin have been discovered, with renal excretion, over 72 h, accounting for 80–100% of intravenously administered metformin [30,310. Specifically, there was no faecal excretion of intravenous metformin.

The absence of metabolites and the predominant renal excretion of metformin mean that, following continuing oral metformin, plasma metformin will depend on metformin dose, bioavailability and renal clearance. The renal clearance of metformin approximates renal plasma flow (4–5 times the GFR) and suggests possible dependence of metformin clearance on renal plasma flow [31,32]. Organic cation transporter 2 (OCT 2) are likely candidates for the renal transporter responsible for the near first pass clearance of metformin [33]. The low Michaelis Constant (Km) of OCT 2 *in vitro* for metformin (*c*. 1 ug/l), if realized *in vivo*, is consistent with near first-pass clearance [33].

The implications of excretion by a transporter, as compared with glomerular filtration, are that the process may be saturable (i.e. excretion could be limited by a V_{max}), despite any further increase in plasma metformin, and excretion is susceptible to competition from other drugs; for example, proton pump inhibitors [34]. That is, variations in renal clearance of metformin could occur with intrinsic or acquired variations in the number of transporters (e.g. as a result of tissue damage), the V_{max} of the transporter or competition for transport (by other drugs)—potentially limiting the utility of glomerular filtration rate as a predictor of plasma metformin. The decreased renal clearance of metformin with ageing, independent of GFR [32], may be explained by a decrease in transporter activity, although the decrease in renal plasma flow, relative to GFR, in the elderly, may also be a contributor [28].

Table 1 Predicted upper limits of plasma metformin, based on daily dose and estimated glomerular filtration rate (eGFR)

Metformin, daily dose (mg)	500	1000	1500	2000
eGFR (ml/min)				
40	1.4	2.8	4.2	5.6
30	1.7	3.4	5.1	6.8
20	2.2	4.4	6.6	8.8
10	4.4	8.8	13.2	17.6

The results were calculated assuming a bioavailability of 60% and a regression analysis of the linear relationship between metformin renal clearance and creatinine clearance [31], down to a creatinine clearance of 20 ml/min, and then a linear extrapolation, forced through 0, for creatinine clearance < 20 ml/min and a range of estimated plasma metformin of ± 50%, to allow for variation in bioavailability (± 20%) [31],and a ± 30% error in the relationship between eGFR, creatinine clearance and actual GFR.

Can we use a measure of GFR to predict metformin clearance and, by extrapolation, plasma metformin in renal failure? In one study in patients with creatinine clearance varying from 160 to 20 ml/min, the relationship between metformin renal clearance (y) and creatinine clearance (x) (both ml/min) was described by $y = 61 + 3.8x$, $r = 0.88$ [31]. Although, in another study, after oral metformin, the metformin–creatinine clearance relationship was higher [32], the lower estimate seems validated by data in patients with a mean creatinine clearance of 20 ml/min (range 10–30 ml/min), where the mean renal metformin clearance was 130 ml/min [32], compared with a predicted value of 137 ml/min. Using this more conservative estimate of metformin clearance, mean daily plasma metformin can be predicted from daily metformin dose and eGFR (Table 1).

Support for the safety of our predicted plasma metformin levels comes from a number of sources. First, predictions based on a population pharmacokinetic study, derived from pooled measurements of plasma metformin in 305 patients with a GFR ranging from 15 to 178 ml/min, where peak plasma metformin (95% confidence interval) was estimated to be < 3.5 mg/l with either a metformin dose of 500 mg and a GFR of 15 ml/min (our predicted plasma metformin 3.3 mg/l), or < 4.5 mg/l with a metformin dose of 1000 mg and a GFR of 30 ml/min (our predicted plasma metformin 3.4 mg/l) [35]. Second, peak (4-h post-dose) plasma metformin levels (135 measures) in 22 patients with creatinine clearances ranging from 15 to 39 ml/min, and two patients on dialysis, and metformin doses ranging from 250 to 2000 mg, were always below 5 mg/l, and below 3 mg/l in 98% [36]. Third, in a study of 35 patients on peritoneal dialysis with residual renal function (creatinine clearance 5.5–7.1 ml/min) on metformin (500 or 1000 mg/day), mean plasma metformin was 2.6 ± 1.5 mg/l compared with our predicted upper limit of 7–14 mg/l) [37]. Fourth, estimates of plasma metformin, using this formula, exceed actual measurements in patients with metformin-associated lactic

acidosis at varying times since last dose [38], and in patients with varying contraindications to metformin use, after fasting [21] (Fig. 3): All these give some reassurance that our predicted levels in renal failure are a reasonable basis for dosage recommendations. It should be emphasized that using eGFR in predicting plasma metformin requires a stable plasma creatinine, and overestimates GFR when the plasma creatinine is increasing, as in acute renal failure.

It is also important to note that clearance of metformin by dialysis is by filtration, with no contribution from tubular secretion. As a consequence, in patients on dialysis, any residual renal function will be the main determinant of plasma metformin. The lower levels of plasma metformin reported in dialysis patients (< 5 mg/l) [36,37] probably reflect the contribution to metformin clearance by residual renal function, but decreased bioavailability of metformin is another possible contributor.

Metformin and plasma lactate

An additional safeguard to predicting plasma metformin in patients with renal failure would be to measure plasma lactate concentrations. In the study on collected cases of metformin overdose, there was a poor correlation between plasma metformin and pH and also between plasma metformin and plasma lactate. However, there was, not suprisingly, a good correlation between plasma lactate and pH (Fig. 2) [29]. A routine plasma lactate measurement might be a better predictor of risk for metformin-associated lactic acidosis than eGFR. The mean plasma lactate for patients with diabetes on metformin is similar [39] or slightly higher than normal [40], with 1/3 of 272 metformin-treated patients having a fasting plasma lactate above the upper limit of the reference range (2 mmol/l) and 1% with a plasma lactate above 3.5 mmol/l [40]. A small study in 24 patients on metformin (dose 250–2000 mg daily) with a creatinine clearance of 15–40 ml/min found no association between plasma metformin and plasma lactate; and only three patients with a raised plasma lactate level (range of 2.7–5.5 mmol/l), none of whom had acidosis or adverse consequence [35]. Based on the above, a plasma lactate of < 5 mmol/l in a patient on metformin should give little cause for concern and a lactate level < 3.5 mmol/l no concern at all. Routine measurements of plasma lactate in patients with renal impairment on metformin should provide evidence, or not, of their utility in predicting the risk of lactic acidosis.

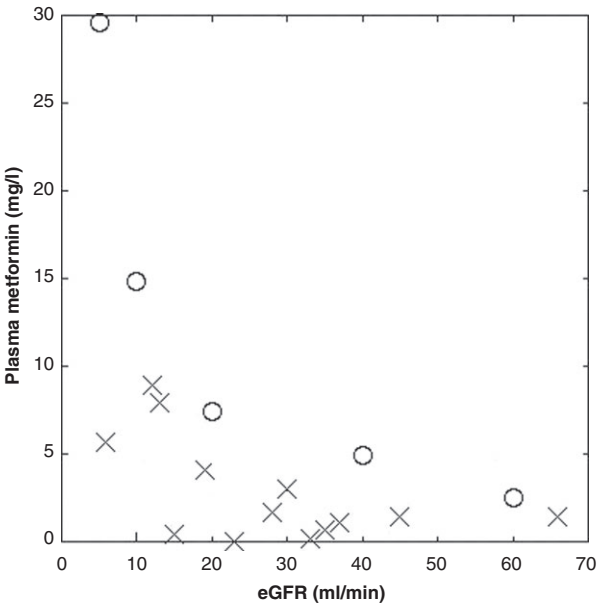

FIGURE 3 The predicted (O) (upper limit) and measured (X) plasma metformin in renal failure. Predicted plasma metformin assumes a bioavailability of 60% and is then based on a regression analysis of the linear relationship between metformin renal clearance and creatinine clearance, down to a creatinine clearance of 20 ml/min (Tucker *et al.* [31]), and then a linear extrapolation, forced through zero, for a creatinine clearance < 20 ml/min. The error in prediction is likely to be *c.* ± 50%, based on variations in bioavailability (± 20%) and errors in the relationship between estimated glomerular filtration rate (eGFR), creatinine clearance and actual GFR. Measured plasma metformin is derived from Awadhi *et al.* [21] and Lalau *et al.* [38], adjusted when necessary to a nominal dose of 1700 mg/day, and using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate eGFR from plasma creatinine.

Suggestions for metformin dosage in renal failure

Given the benefits of metformin therapy, the weak association of metformin with lactic acidosis—except possibly at very high plasma metformin levels, a reasonable ability to predict plasma metformin from dose and eGFR, and the

Table 2 Suggested dosage regimen for the use of metformin in stable chronic renal failure

eGFR (ml/min)	Suggested daily maximum metformin dose	Additional precautions
≥ 40	No restriction	
30–39	2000 mg	
20–29	1500 mg	Measure venous plasma lactate. Reduce dose or cease if the plasma lactate is > 3.5 mmol/l
10–19	500 mg	Measure venous plasma lactate. Reduce dose or cease if the plasma lactate is > 3.5 mmol/l
< 10	Do not use	
Stable dialysis	500 mg, but only if residual GFR > 5 ml/min	Measure venous plasma lactate regularly. Cease if the plasma lactate is > 3.5 mmol/l

Suggested monitoring would be an estimated glomerular filtration rate (eGFR) and plasma lactate 1 week after commencement, with any intercurrent illness or relevant change in medication, and on routine reassessment.

more ready availability, and utility, of measurements of plasma lactate, we think it reasonable to reduce the restrictions on the use of metformin in renal failure. Our suggestions for metformin use in patients with stable impaired renal function and diabetes are shown in Table 2. Our suggested dose schedule for metformin aims to maintain a mean plasma metformin < 10 mg/l. An alternative more conservative approach would be to maintain a plasma metformin < 5 mg/l [35], which could be achieved by reducing the suggested dose by 50%. It should be emphasized that these suggestions are for patients with stable renal function, or with a predictable, and slow enough, loss of renal function that would allow continuing timely dose modification.

The suggested dose schedule for dialysis patients (Table 2) is less certain, as it is very dependent on the level of residual renal function, but is supported by the lower than predicted levels in dialysis patients [35,37] and the opportunity for close monitoring available in dialysis programmes.

Another important issue is whether to cease metformin in patients at risk of acute renal failure, such as those receiving iodinated X-ray contrast media. A sudden reduction in GFR to < 5 ml/min in a patient on 2000 mg would rapidly lead to plasma metformin levels approaching 20 mg/l, and potentially expose the patient to risk of lactic acidosis. Post-contrast metformin-associated lactic acidosis is so rare, in patients with normal pre-existing renal function, that metformin does not need to be suspended [41]. This has been recognized in the most recent guidelines of the Royal College of Radiologists [42]. For patients with pre-existing renal impairment (eGFR < 60 ml/min), the question is not about the need to reduce metformin intake, it is the ability, or willingness, to readily detect early acute renal failure after a potentially nephrotoxic insult (e.g. iodinated contrast) in the absence of oliguria. The use of new biomarkers for acute renal failure using an early spot urine sample (approximately 12 h after insult) may provide an early diagnosis that would allow early post-insult metformin dose reduction, but remain to be tested [43]. We suggest that continuation of metformin, with measurement of plasma lactate and creatinine at 24 and 48 h post-procedure, and cessation of metformin if creatinine is rising (> 10%) or lactate exceeds 3.5 mmol, is a logical alternative to current recommendations, which may lead to recommencement of metformin after 2 days, with a yet-undiagnosed episode of acute renal failure. Continuation of metformin, with monitoring, would facilitate the maintenance of glycaemic control during the peri-procedure period.

These suggestions are much less restrictive than current guidelines and would allow access to the clear-cut benefits of metformin treatment to many more patients. We believe any increased risk of lactic acidosis that might exist because of errors in our estimates (unlikely to exceed 10 times the whole population risk of nine cases of lactic acidosis per 100 000 person years), or unknown other factors that might reduce metformin excretion (e.g. competition for OCT 2 by other drugs), is insignificant relative to the population benefits of metformin treatment (*c*. 20 lives saved per 1000 person years). It is our view that the advantages of providing more patients with stable renal impairment, the benefits of metformin, allowed under our proposed comprehensive suggestions, greatly outweigh the minute risk of lactic acidosis in this population.

Previous publication

A component of this paper was presented at the 49th Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology, Brisbane, Australia, 9–11 September 2013, and appeared in abstract form in *Nephrology* 2013; **18**: S42.

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Competing interests

None declared.

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