Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency

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A common clinical conundrum faces all U.S. practitioners treating patients with type 2 diabetes. Today's U.S. Food and Drug Administration prescribing guidelines for metformin contraindicate its use in men and women with serum creatinine concentrations ≥1.5 and ≥1.4 mg/dL (≥132 and ≥123 μmol/L), respectively. In a patient tolerating and controlled with this medication, should it automatically be discontinued as the creatinine rises beyond these cut points over time? Stopping metformin often results in poorly controlled glycemia and/or the need for other agents with their own adverse-effect profiles. Moreover, is the now widespread use of estimated glomerular filtration rate (eGFR) in lieu of serum creatinine levels creating even more confusion, especially in those with abnormalities in one but not the other indirect measure of renal function? Indeed, more than a decade and a half after metformin became available in the U.S., debate continues over the best approach in these settings (1–3). How many patients are unable to receive this medication on the basis of guidelines which, although well intentioned, are somewhat arbitrary and outdated based on modern assessments of renal status?

ADVANTAGES OF METFORMIN

—There is some evidence that early treatment with metformin is associated with reduced cardiovascular morbidity and total mortality in newly diagnosed type 2 diabetic patients (4). However, the data come from a small subgroup of a much larger trial. In contrast, despite multiple trials of intensive glucose control using a variety of glucose-lowering strategies, there is a paucity of data to support specific advantages with other agents on cardiovascular outcomes (5–7).

In the original UK Prospective Diabetes Study (UKPDS), 342 overweight patients with newly diagnosed diabetes were randomly assigned to metformin therapy (8). After a median period of 10 years, this subgroup experienced a 39% ($P = 0.010$) risk reduction for myocardial infarction and a 36% reduction for total mortality ($P = 0.011$) compared with conventional diet treatment. Similar benefits were not observed in those randomly assigned to sulfonylurea or insulin. In an 8.5-year posttrial monitoring study, after participants no longer were randomly assigned to their treatments, individuals originally assigned to metformin ($n = 279$) continued to demonstrate a reduced risk for both myocardial infarction (relative risk 33%, $P = 0.005$) and total mortality (relative risk 27%, $P = 0.002$) (9). The latter results are even more impressive when one considers that HbA_{1c} levels in all initially randomly assigned groups had converged within 1 year of follow-up.

Unlike sulfonylureas, thiazolidinediones, and insulin, metformin is weight neutral (10), which makes it an attractive choice for obese patients. Furthermore, the management of type 2 diabetes can be complicated by hypoglycemia, which can seriously limit the pursuit of glycemic control. Here, too, metformin has advantages over insulin and some types of insulin secretagogues; by decreasing excess hepatic gluconeogenesis without raising insulin levels, it rarely leads to significant hypoglycemia when used as a monotherapy (8,11). As a result, metformin is widely considered an ideal first-line agent for the treatment of type 2 diabetes, as recommended by several clinical guidelines (12–14).

In addition to such benefits, metformin reduces the risk of developing diabetes in individuals at high risk for the disease (15) and has been considered as a reasonable "off-label" approach in selected individuals for diabetes prevention (16).

HISTORICAL PERSPECTIVE

—Despite these proven benefits, metformin remains contraindicated in a large segment of the type 2 diabetic population, largely because of concerns over the rare adverse effect of lactic acidosis. For these reasons, the drug has been restricted to individuals with normal creatinine levels as a surrogate for renal competence. Other contraindications (e.g., any significant hypoxemia, alcoholism, cirrhosis, a recent radiocontrast study) also increase the risk for or the consequences of lactic acidosis, but these are not the topic of this review.

Metformin belongs to the biguanide drug class (previous members include phenformin and buformin), developed for lowering glucose in the 1950s. Initial enthusiasm for biguanides was tempered over the next two decades by the growing recognition of their risk of lactic acidosis. A marked reduction in biguanide use occurred in the mid-1970s because phenformin, extensively adopted in clinical practice, was implicated in a number of fatal cases of this severe metabolic decompensation (17). The association with lactic acidosis eventually led to its withdrawal from the market. Importantly, lactic acidosis with phenformin seems to occur ~10–20 times more frequently than with metformin (18). In contrast to metformin, modestly raised phenformin concentrations may reduce peripheral glucose oxidation and enhance peripheral lactate production, which can increase circulating lactate levels. In fact, phenformin levels correlate with lactate concentration,

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whereas metformin levels do not (19). In addition, ~10% of European Caucasians have an inherent defect in phenformin hydroxylation, which may lead to drug accumulation and, as a result, elevated lactate levels (20).

The experience with phenformin resulted in cautious use of metformin in Europe. In the 1980s, the creatinine cut points for contraindication to metformin were considered to be appropriate at 1.4 mg/dL in women and 1.5 mg/dL in men. This was based on the calculated ability to remove 3 g of metformin (an amount slightly beyond the maximum daily U.S. dose) at steady-state levels within 24–48 h. In fact, the ability to comfortably remove the drug extends up to creatinine levels of 1.8–2.0 mg/dL, but the cut points chosen were intentionally set lower to ensure that those patients who may be lost to follow-up and whose creatinine levels increase over time would not be at risk for appreciable drug accumulation.

Metformin was not approved in the U.S. until December of 1994 and was marketed in 1995. The experience with phenformin led to judicious labeling and recommendations for careful monitoring of adverse events. Its new-drug application was the subject of extensive review. The risk for lactic acidosis was estimated to be ~3 cases per 100,000 patient-years based on cases reported from France, the U.K., and other countries where pharmacovigilance information was available (21). Similar estimates were quoted from Sweden (2.4 cases per 100,000 patient-years), where the number of cases appeared to be decreasing despite rising clinical use of metformin. After careful deliberation, metformin was approved by the U.S. Food and Drug Administration, with lactic acidosis risk seen as small, although inevitable with future widespread availability of the drug.

CLINICAL PRACTICE GUIDELINES

—The prescribing information for metformin in the current label is explicit with respect to renal contraindications, based on serum creatinine cut points. It proscribes use at or above the 1.4 and 1.5 mg/dL levels in women and men, respectively. The recently updated Kidney Disease Outcomes Quality Initiative guidelines from the National Kidney Foundation are perfectly consistent with the label (22). Yet, certain U.S. practice guidelines substantially differ in their recommendations for metformin use related to renal status. The annually updated clinical practice guidelines issued by the American Diabetes Association, for example, do not actually discuss renal thresholds (16) but refer the reader to a separate consensus statement for prescribing details. This statement, authored by members of the American Diabetes Association and European Association for the Study of Diabetes, reports that metformin seems safe unless eGFR falls to <30 mL/min per 1.73 m^2 (12).

Clinical guidelines outside of the U.S. incorporate the eGFR for determination of metformin safety. In the U.K., for example, prescribing guidelines consider both creatinine and eGFR for assessing treatment eligibility. The National Institute for Health and Clinical Excellence recommends reviewing the clinical circumstances when serum creatinine exceeds 130 μmol/L (1.5 mg/dL) or eGFR falls below 45 mL/min per 1.73 m^2. The National Institute for Health and Clinical Excellence further specifies that metformin be stopped if serum creatinine exceeds 150 μmol/L (1.7 mg/dL) (a higher threshold than in the U.S.) or eGFR is below 30 mL/min per 1.73 m^2 (14). In contrast, the Canadian Diabetes Association practice guidelines are now based solely on eGFR, recommending caution with eGFR <60 mL/min per 1.73 m^2 and contraindicating its use with eGFR <30 mL/min per 1.73 m^2 (23). The Australian Diabetes Society practice guidelines similarly recommend against metformin with eGFR <30 mL/min per 1.73 m^2 and caution with eGFR 30–45 mL/min per 1.73 m^2 (24). Thus, although there is clear recognition that renal failure may be a risk factor for adverse events with metformin use, there is significant divergence in opinion across the globe regarding the optimal definition of safety.

METFORMIN PHARMACOKINETICS

—The principal reason for carefully setting renal thresholds is that metformin is eliminated unchanged primarily by the kidneys. Thus, one of the most important risk factors for elevated metformin concentrations (which are proposed to lead to lactic acidosis) is the inability to clear the drug efficiently. Metformin has a 50–60% bioavailability and is absorbed mainly in the small intestine. It does not appear to bind appreciably to plasma proteins. The maximum plasma concentration is observed ~2 h after oral dosing, typically reaching a C_{max} of 1–2 μg/mL (~10 μmol/L). Metformin accumulates in the walls of the small intestine and salivary glands as well as in the kidney (25). It has a plasma elimination half-life of 6.2 h and is renally eliminated both by filtration and active tubular secretion (26).

In careful experiments, Tucker et al. (27) studied metformin kinetics in 4 healthy subjects and 12 type 2 diabetic subjects and found that plasma renal clearance of metformin highly correlated with creatinine clearance (CrCl; $r = 0.85$, $P < 0.001$). However, the relationship between physiological clearance of an actual oral dose and CrCl was much weaker ($r = 0.66$, $P < 0.01$). Therefore, the investigators postulated that other factors may impact this relationship, such as perhaps gastrointestinal absorption of metformin in patients with renal failure and/or nonrenal clearance of a small amount of the drug.

In another pharmacokinetic study (28), a single 850-mg dose of metformin was given to 21 healthy subjects and 13 subjects with renal insufficiency (mild to severe). In the control group (data presented are mean ± SD) (mean CrCl 112 ± 8 mL/min), average renal metformin clearance was 636 ± 84 mL/min, whereas in mild chronic kidney disease (CKD) (CrCl 61–90 mL/min; mean 73 ± 7) clearance was reduced at 384 ± 122 mL/min. The mean renal clearance of metformin was lower in subjects with moderate (CrCl 31–60 mL/min; mean 41 ± 9) and severe (CrCl 10–30 mL/min; mean 22 ± 6) CKD, measuring 108 ± 57 and 130 ± 90 mL/min, respectively. Similarly, maximum concentration and the area under the concentration time curve were increased in individuals with moderate to severe CKD compared with those with mild CKD or normal renal function. Based on the regression analysis, both CrCl and age were found to be important predictors of metformin clearance. This study did not provide evidence for specific thresholds at which lactate production may begin to rise.

These reports have relied on information derived from single doses of metformin, which may not reflect chronic-treatment pharmacokinetics. In contrast, few reports have assessed the impact of renal insufficiency on metformin clearance during long-term use. Indeed, one such study (29) concluded that metformin can be efficiently cleared in mild-to-moderate CKD. In this investigation, 24 older patients (aged 70–88 years) were administered metformin 850 mg/day or 1,700 mg/day based on CrCl of 30–60 mL/min ($n = 11$) or >60 mL/min ($n = 13$),

respectively. After 2 months, metformin remained in the therapeutic range and lactate within the reference limits in all participants. In addition, the measured levels of metformin and lactate were not statistically different between those with and without renal impairment (29).

Another recent study (30) evaluated metformin levels in patients with type 2 diabetes and varying renal function. GFR was estimated based on cystatin C levels. The median dose of metformin was 1,500 mg/day. The median serum level of metformin was 4.5 μmol/L (~0.6 μg/mL) (range 0.1–20.7) in patients with eGFR >60 mL/min per 1.73 m^2 (n = 107), 7.7 μmol/L (~1.0 μg/mL) (0.1–15.2) with eGFR 30–60 mL/min per 1.73 m^2 (n = 21), and 8.9 μmol/L (~1.1 μg/mL) (6.0–18.6) with eGFR <30 mL/min per 1.73 m^2 (n = 9). Notably, there were wide variations in these levels within each group, with few patients having serum levels >20 μmol/L (>~2.6 μg/mL). However, the "unsafe" metformin concentration is not really known. At usual clinical doses and schedules, steady-state plasma concentrations are generally <1 μg/mL (<7.8 μmol/L). Maximum plasma levels during controlled clinical trials do not generally exceed 5 μg/mL (38.8 μmol/L), but these have not typically enrolled CKD patients. Moreover, whether measurement of metformin levels actually can aid in the prediction of lactic acidosis risk remains unclear. Therefore, although these studies provide some information on the relationship between renal function and metformin concentrations, they do not clarify the issue of toxicity and lactic acidosis risk.

Many of the early pharmacokinetic studies with metformin actually relied on CrCl based on 24-h urine collection for creatinine. How well the current serum creatinine cut points reflect the ability to effectively clear the drug also is unknown. Creatinine levels, in general, vary inversely with GFR. However, important limitations to the estimation of renal function with creatinine should be considered. First, serum creatinine can only be used reliably in patients with stable kidney function. Second, variation in creatinine production may differ among and within individuals over time, especially if there are significant changes in muscle mass or in physical activity. Variability in creatinine secretion, extrarenal creatinine excretion, assay method, and equipment can all affect serum measurements. Calculated estimates (clearance from the Cockroft-Gault and eGFR from the Modification of Diet in Renal Disease equation) have been developed to incorporate known demographic and clinical factors affecting serum concentrations. These equations have their own inherent shortcomings, such as residual limitations with respect to age and race, underestimation of GFR in the context of diabetic renal disease (Cockroft-Gault and Modification of Diet in Renal Disease) (31), and in obese individuals (Modification of Diet in Renal Disease) (32). However, they provide better estimation of renal function than creatinine alone. Moreover, development of new estimating equations, such as the Chronic Kidney Disease Epidemiology Collaboration equation, may allow for even more accurate estimates of renal function in the future. Finally, dosing considerations by the Food and Drug Administration for other medications (e.g., sitagliptin, fenofibrate) are generally based on CrCl estimated from such calculations and not on creatinine levels themselves.

LACTIC ACIDOSIS ASSOCIATED WITH METFORMIN THERAPY

Even though elevated metformin concentrations have been proposed to lead to lactic acidosis, there are few data regarding the level predisposing to hyperlactatemia. In fact, multiple studies suggest that elevated circulating lactate levels, often attributed to metformin, may actually not be caused by the drug. First, lactic acidosis occurs in patients with type 2 diabetes more frequently than in the general population; in some reports, the observed rate appears to be similar in patients on metformin versus other glucose-lowering agents (11). Second, metformin and lactate levels do not necessarily appear to correlate, such that higher metformin concentrations do not consistently occur in those with more severe degrees of lactic acidosis (33,34). Finally, metformin levels are not linked to mortality in those who develop lactic acidosis, perhaps reflecting the primary effect of the underlying cause of the acidosis (e.g., hypoxia, hemodynamic compromise) on outcomes rather than incriminating metformin itself (33–35).

Although lactic acidosis remains a recognized, albeit rare, adverse event associated with metformin, the number of lactic acidosis cases continues to be very small, particularly when one considers the widespread use of this drug. In the largest updated Cochrane meta-analysis, Salpeter et al. (36) pooled data from 347 comparative trials and cohort studies. Not a single case of lactic acidosis was found in >70,000 metformin patient-years or >55,000 nonmetformin person-years. In this analysis, 53% of prospective studies allowed for inclusion of renal insufficiency, but patient-level serum creatinine concentrations were not available for review. Based on statistical inference, the estimated upper limit of true incidence was 4.3 and 5.4 cases per 100,000 patient-years in the metformin and nonmetformin groups, respectively. This investigation suggests that lactic acidosis is extremely rare and the incidence does not differ in those treated with metformin versus other agents.

In a large, nested, case-control analysis of the U.K. general practice research database (11), the crude incidence of lactic acidosis was even lower at 3.3 cases per 100,000 person-years among metformin users and 4.8 cases per 100,000 person-years among sulfonylurea users (in very close agreement to the estimates of 3 and 2.4 cases per 100,000 patient-years from Europe and Scandinavia before metformin's U.S. approval). Given all of these findings, some (37) have argued that the occurrence of lactic acidosis with metformin use is merely coincidental and that there is no tangible evidence from prospective observational studies or clinical trials that the drug increases its incidence. Of course, all these data have been collected in the context of contemporaneous strict metformin-prescribing guidelines. It is possible that looser restrictions may have led to more frequent occurrence of lactic acidosis.

In summary, lactic acidosis remains exceedingly rare in clinical trials and cohort studies of metformin therapy. Moreover, the available data suggest that lactate levels and risk of lactic acidosis do not differ appreciably in patients taking this versus other glucose-lowering agents. Thus, the long-proclaimed causal relationship between metformin and lactic acidosis remains in question.

CURRENT USE OF METFORMIN IN CKD

Given the current contraindications in the U.S., some might consider it a challenge to conduct a new clinical trial to evaluate the use of metformin in individuals with various degrees of impaired renal function, taking into account new criteria for assessing glomerular filtration. Yet, evidence suggests that metformin is often

already used in practice outside of the current labeling contraindications, prescribed in full knowledge of the relevant cutoffs (38–41). For example, in a review (41) of restrictions to metformin therapy conducted in Scotland, 24.5% of metformin users had filled a prescription despite active contraindications (3.4% had the specific local exclusion of a serum creatinine ≥1.7 mg/dL recorded twice on different days within 4 weeks). A single case of lactic acidosis during 4,600 patient-years of follow-up occurred in a patient with an extensive acute myocardial infarction who developed acute renal failure and died the same day. Given the clinical scenario, the authors intimated that acidosis had occurred because of hemodynamic compromise related to the infarct and not to metformin accumulation. In a U.S. study (42) performed in the primary care practice setting, 4.5% of patients treated with metformin had creatinine levels >1.4 and 1.5 mg/dL in women and men, respectively. Two other studies (38,40) of sicker patients admitted to hospitals in Germany and the U.S. confirmed high frequency of metformin use despite various contraindications (73 and 27%, respectively).

When one considers the imperfect reflection of actual renal function by serum creatinine, metformin is likely used even more frequently in patients with impaired GFR than that suggested by the above studies. In the aforementioned U.S. primary practice setting, where 4.5% of patients were given metformin despite creatinine-based contraindications, 17.7% of women and 13.4% of men receiving metformin actually had an abnormally low eGFR (≤60 mL/min per 1.73 m^2) (42). Likewise, in another single U.S. center cross-sectional study (43), 15.3% of patients with type 2 diabetes and eGFR <60 mL/min per 1.73 m^2 were receiving metformin. Such frequent "inappropriate" use of metformin in patients is further suggested by data from the National Health and Nutrition Examination Survey (1999–2006) (43). Among individuals with eGFR <60 mL/min per 1.73 m^2 and diabetes, 32.2% were treated with metformin and had a normal creatinine level (<1.5 mg/dL), whereas 13.4% were treated with metformin despite a frankly elevated creatinine level (>1.5 mg/dL). The use of metformin in mild-to-moderate CKD clearly is not at all uncommon.

Two studies have attempted to translate creatinine into corresponding eGFR cut points in the context of metformin therapy. In a review (44) of prescribing practices in the U.K., appropriate use of the drug was defined on the basis of creatinine level ≤1.7 mg/dL. Of 11,297 patients meeting those criteria, 82% had an eGFR <90, 25.5% <60, and 2.8% <30 mL/min per 1.73 m^2. The authors calculated that the eGFR threshold of 36 mL/min would result in a similar number of patients becoming ineligible for metformin compared with the serum creatinine threshold of 1.7 mg/dL (although some patients would become newly eligible and some who previously qualified would now become ineligible). The authors proposed that if the current practice is considered safe (and based on the review by Salpeter et al. [36], this appears to be so), then a switch to an eGFR-based cut point may be both a more practical and a more accurate way to limit metformin access in those with significantly impaired renal function. In another British study of 12,482 patients with diabetes, an eGFR cutoff of 41 mL/min per 1.73 m^2 in men and 30 mL/min per 1.73 m^2 in women resulted in a similar proportion of patients having metformin withheld compared with the serum creatinine threshold of 1.7 mg/dL (45). The investigators therefore proposed the pragmatic eGFR limit of 30 mL/min per 1.73 m^2 to denote absolute contraindication to therapy.

Limited data specifically address metformin's long-term safety in patients with mild-to-moderate renal failure (46–48). These studies found no increased risks in various degrees of renal insufficiency but were limited by small size and significant methodological shortcomings. Recently, an analysis of the Reduction of Atherothrombosis for Continued Health Registry suggests that the proposed cardiovascular benefits of metformin may extend to patients with established atherosclerosis and moderate CKD (49). In this large, observational study of >19,000 subjects with a history of atherothrombotic disease, 1,572 patients were using metformin with eGFR 30–60 mL/min per 1.73 m^2. After adjustment for baseline factors and propensity score, metformin use was associated with a significant reduction in 2-year mortality in the overall population (hazard ratio 0.76 [95% CI 0.65–0.89]), including in those with moderate CKD (0.64 [0.48–0.86]). However, lack of information with respect to the duration of metformin use and HbA_{1c}, as well as the observational nature of the study, require further confirmation of the mortality benefit in similar patient cohorts in prospective trials.

Although these data are reassuring, we must note that there are no randomized clinical trials that specifically evaluated the safety of metformin use and potential cardiovascular benefits in patients with CKD.

PROGRESSION OF CKD IN PATIENTS WITH DIABETES—Renal function is dynamic, and renal dysfunction in diabetes is typically progressive (50). Even in the absence of an acute event, glomerular function slowly declines with aging as nephron mass is lost. The renal thresholds for the acceptability of metformin therapy should therefore ideally account for the tempo of CKD progression. The assessment of renal function in clinical practice occurs periodically, and the degree of renal dysfunction may change appreciably between these assessments. Therefore, it is important to know how quickly GFR declines in the typical spectrum of nephropathy among diabetic patients, particularly when considering metformin therapy.

Few studies have, however, systematically evaluated the rate of progression of renal dysfunction in the general diabetic patient population by directly measuring GFR over time. Some data suggest that eGFR tends to underestimate the rate of GFR decline by as much as 28% when compared with direct measurement (51). Nevertheless, most of the available data are based on estimations. A recent British population-based cohort study (52) of 3,431 diabetic patients examined renal decline as measured by changes in eGFR (Modification of Diet in Renal Disease). The analysis of data collected over 7 years demonstrated that the rate of progression was lowest among individuals who were normoalbuminuric (0.3% or ~0.2 mL/min per 1.73 m^2 decline in eGFR per year), intermediate in those with microalbuminuria (1.5% or ~1.2 mL/min per 1.73 m^2 per year), and highest in those with macroalbuminuria (5.7% or 4.5 mL/min per 1.73 m^2 per year). In a large Dutch study (53), eGFR fell by 0.5 mL/min per 1.73 m^2 per year in the general population but to a greater extent in those with hypertension,diabetes,andmacroalbuminuria (1.9 mL/min per 1.73 m^2 per year). Based on these and other results (31), average annual progression of renal dysfunction in diabetes appears to be in the range of −1 to −4 mL/min per 1.73 m^2

of filtration capacity, dependent in part on other risk factors and the use of renoprotective therapies. The decline is slow, but, importantly, the majority of patients in these studies had normal kidney function at the outset. There is less information available on diabetic patients with CKD. It should also be noted that diabetes places an individual at increased risk for other causes of renal disease (54). Thus, all diabetic patients, especially those with CKD, may be at risk for more rapid decline in their renal function or acute kidney injury.

Despite these appropriate concerns, most of the available data would suggest that, on average, eGFR declines slowly in diabetes, although it can be accelerated to some degree in the presence of albuminuria. If eGFR is calculated annually (and more frequently in those at high risk for deterioration in renal function), it is unlikely that patients will experience changes in their eGFR levels large enough to rapidly alter the safety of metformin therapy.

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

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

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

CONCLUSIONS AND RECOMMENDATIONS

Although metformin is eliminated renally, and accumulation may conceivably lead to lactic acidosis, there currently is limited systematic evidence to substantiate continued reliance on the creatinine-based contraindications in use in the U.S. Indeed, in the modern era of eGFR, this measure of glomerular filtration appears to give a more reliable estimate of renal dysfunction. Metformin-associated lactic acidosis is exceedingly rare based on the available literature, and even though the use of metformin has not been comprehensively assessed in individuals with CKD, there is extensive evidence that this agent often is used without adverse effects in those with mildly to moderately reduced renal function. In the context of rising concerns regarding other glucose-lowering therapies (55), safety restrictions over the use of metformin in this population may result in the drug being stopped prematurely and unnecessarily in some patients. This may lead to significant deterioration in glycemic control and/or the need for other glucose-lowering medications, which present their own safety concerns. An evidence-based approach to prescribing metformin in this group appears warranted, taking into account the current pervasive use of eGFR in clinical care.

We therefore suggest that the current guidelines for metformin use in the U.S. be updated. These recommendations should include eGFR thresholds that are generally consistent with the National Institute for Health and Clinical Excellence guidelines in the U.K. and those endorsed by the Canadian Diabetes Association and the Australian Diabetes Society (Table 1). Metformin may be continued (or initiated) with eGFR <60 mL/min per 1.73 m^2, but renal function should be monitored closely (every 3–6 months). The dose of metformin should be reviewed and reduced (e.g., by 50% or to half-maximal dose) in those with eGFR <45 mL/min per 1.73 m^2, and renal function should be monitored closely (every 3 months). Metformin should not be initiated in patients at this stage, however. The drug should be stopped once eGFR falls to <30 mL/min per 1.73 m^2. Additional caution is required in patients with anticipated significant fluctuations in renal status or those at risk for abrupt deterioration in kidney function, based on previous history, other comorbidities, albuminuria, and medication regimen (e.g., potent diuretics or nephrotoxic agents).

Without question, such a treatment program could not be implemented without meticulous clinical follow-up, clear communication with patients regarding risks and benefits of therapy, and adherence to frequent monitoring. The plan, therefore, should be modified in patients with suboptimal adherence to medical instructions or regular follow-up. It is clear that vigilance would be required so that cases of lactic acidosis do not emerge because of inappropriate use of metformin in patients with more advanced and/or unstable CKD.

Given the frequency with which clinicians must decide whether to continue or initiate metformin in mild-to-moderate CKD, these recommendations would have a profound impact on clinical practice. Such proposals, being consistent with the sentiments of several well-respected national guideline committees, should be reviewed by professional medical organizations in the U.S., such as the American Diabetes Association. If a consensus emerges, perhaps the Food and Drug Administration might reconsider the current metformin-prescribing guidelines, which, like those of other nonbranded compounds, tend to remain static despite emerging evidence and changes in clinical care.

In the future, more research in this important area is needed, including prospective, randomized trials of metformin at varying degrees of renal impairment and/or closer examination of registries of CKD patients receiving metformin.

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