Published in final edited form as:

JAMA. 2014 December 24; 312(24): 2668–2675. doi:10.1001/jama.2014.15298.

Metformin in Patients With Type 2 Diabetes and Kidney Disease:

A Systematic Review

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Abstract

IMPORTANCE—Metformin is widely viewed as the best initial pharmacological option to lower glucose concentrations in patients with type 2 diabetes mellitus. However, the drug is contraindicated in many individuals with impaired kidney function because of concerns of lactic acidosis.

OBJECTIVE—To assess the risk of lactic acidosis associated with metformin use in individuals with impaired kidney function.

EVIDENCE ACQUISITION—In July 2014, we searched the MEDLINE and Cochrane databases for English-language articles pertaining to metformin, kidney disease, and lactic acidosis in humans between 1950 and June 2014. We excluded reviews, letters, editorials, case reports, small case series, and manuscripts that did not directly pertain to the topic area or that met other exclusion criteria. Of an original 818 articles, 65 were included in this review, including pharmacokinetic/metabolic studies, large case series, retrospective studies, meta-analyses, and a clinical trial.

RESULTS—Although metformin is renally cleared, drug levels generally remain within the therapeutic range and lactate concentrations are not substantially increased when used in patients with mild to moderate chronic kidney disease (estimated glomerular filtration rates, 30-60 mL/min per 1.73 m^2). The overall incidence of lactic acidosis in metformin users varies across studies from

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Author Contributions: Drs Inzucchi and McGuire had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Inzucchi, Bailey, McGuire.
Acquisition, analysis, or interpretation of data: Inzucchi, Lipska, Mayo, Bailey.
Drafting of the manuscript: Inzucchi, Mayo, Bailey, McGuire.
Critical revision of the manuscript for important intellectual content: Inzucchi, Lipska, Mayo, McGuire.
Administrative, technical, or material support: Inzucchi.

Supplemental content at jama.com

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

approximately 3 per 100 000 person-years to 10 per 100 000 person-years and is generally indistinguishable from the background rate in the overall population with diabetes. Data suggesting an increased risk of lactic acidosis in metformin-treated patients with chronic kidney disease are limited, and no randomized controlled trials have been conducted to test the safety of metformin in patients with significantly impaired kidney function. Population-based studies demonstrate that metformin may be prescribed counter to prevailing guidelines suggesting a renal risk in up to 1 in 4 patients with type 2 diabetes mellitus—use which, in most reports, has not been associated with increased rates of lactic acidosis. Observational studies suggest a potential benefit from metformin on macrovascular outcomes, even in patients with prevalent renal contraindications for its use.

CONCLUSIONS AND RELEVANCE—Available evidence supports cautious expansion of metformin use in patients with mild to moderate chronic kidney disease, as defined by estimated glomerular filtration rate, with appropriate dosage reductions and careful follow-up of kidney function.

Metformin has been prescribed in the United States for the management of type 2 diabetes for 20 years. It is widely endorsed as initial therapy by professional organizations because of its low cost, safety profile, and potential cardiovascular benefits.[1] Another biguanide, phenformin, was withdrawn in 1977 owing to risk of lactic acidosis. Because metformin is cleared by the kidneys, it may accumulate when renal function decreases, with the potential for exposure-dependent toxicity that could precipitate lactate accumulation. At its US approval of metformin in 1994, the Food and Drug Administration (FDA) stipulated stringent prescribing criteria based on kidney function that remain in place today (**Box**).[2] Given the aging population as well as the most recent estimate of adults with diagnosed type 2 diabetes in the United States (21 million[3]) and the rate of this degree of impaired kidney function in these individuals (estimated at 12%[4]), it is possible that prescribing criteria may preclude metformin use in many patients with renal clearance rates sufficient for adequate drug elimination.

The original prescribing label was intended to provide a safety margin to minimize the risk of metformin-associated lactic acidosis (MALA). The label warnings were based on a modest amount of pharmacokinetic data about reduced metformin clearance in the setting of kidney impairment, but the clinical relevance of these observations remains uncertain. The incidence of lactic acidosis is estimated at approximately 1 per 23 000 to 30 000 person-years among metformin users compared with approximately 1 per 18 000 to 21 000 person-years among patients with type 2 diabetes using other agents.[5,6] These data and the safety profile after several decades of clinical experience have led to less restrictive policy revisions outside the United States. Whether the FDA guidelines should be expanded to allow greater access to metformin in the United States is under consideration.

Literature Search

We conducted a search of the MEDLINE and Cochrane databases (Database of Systematic Reviews, Central Register of Controlled Trials, and DARE [Database of Abstracts of Reviews of Effects]) for articles on metformin in patients with chronic kidney disease (CKD) using the search terms *metformin*, *kidney*, *renal*, *CKD*, *lactic acidosis*, and

glomerular filtration rate. We retrieved English-language human studies published between January 1950 and June 2014. Eight hundred twelve manuscripts were supplemented by an additional 6 found on review of bibliographies of included studies and other sources. Reviews, letters, editorials, case reports, series involving fewer than 10 patients, and animal or in vitro studies were excluded, leaving 414 manuscripts. These were hand-searched; those not pertaining to the topic (338), pharmacokinetic studies in patients without diabetes (1), observational studies with cohorts not defined by kidney function (5), and older meta-analyses later updated (5) were excluded. Thus, the final number of manuscripts was 65 (pharmacokinetic/metabolic investigations [10]; case series [20]; cross-sectional, observational, and pharmacosurveillance studies [31]; metaanalyses [3]; and a clinical trial [1]). (PRISMA diagram in eFigure in the Supplement.)

Box

Current US Food and Drug Administration Prescribing Guidelines for Metformin as Related to Kidney Function

- Metformin is contraindicated in "renal disease or renal dysfunction (eg, as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females]) or abnormal creatinine clearance (CrCl)."
- Metformin "should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced."

Source: Metformin final printed labeling.[2]

Results

Major Findings

Metformin, CKD, and Lactate Metabolism—Biguanides such as metformin inhibit the mitochondrial respiratory chain, impairing the main site of energy generation through aerobic metabolism. This results in a shift toward anaerobic metabolism, of which lactate is a by-product, and less energy for gluconeogenesis. Reduced hepatic glucose production is a major mechanism of the antihyperglycemic effect of metformin, although it has been recently proposed that some glucose lowering may be mediated through the enteroendocrine axis.[7] Metformin is eliminated unchanged in the urine, and the drug may accumulate in patients with kidney failure.[8,9] Although mild to moderate CKD reduces metformin clearance, drug levels typically remain within a safe range. Sambol et al[9] found that, in single-dose studies, mild CKD (creatinine clearance, 60-90 mL/min) was associated with 23% to 33% reductions in medication clearance and moderate CKD (30-60 mL/min) with 74% to 78% reductions. Metformin levels, however, were generally maintained in the therapeutic range (0.47-2.5 mg/L [≈ 4-20 μmol/L]). Frid et al[10] measured metformin levels in 137 patients with diabetes mellitus receiving long-term therapy. Median trough levels (upper therapeutic range, 20 μmol/L) were 4.50 μmol/L (range, 0.10-20.70) for estimated glomerular filtration rates (eGFRs) greater than 60 mL/min per 1.73 m^2, 7.71 μmol/L (range,

0.12-15.15) for eGFRs of 30 to 60 mL/min per 1.73 m^2, and 8.88 μmol/L(range, 5.99-18.60) for eGFRs less than 30 mL/min per 1.73 m^2.

Circulating lactate levels among metformin-treated patients are typically normal, even among patients with kidney dysfunction. Liu et al[11] measured lactate levels (normal, 5-15 mg/dL [0.6-1.7 mmol/L]) in 1024 patients with type 2 diabetes and normal kidney function. Mean lactate was higher in patients taking metformin compared with those taking other agents (1.32 [SD, 0.52] vs 1.14 [0.45] mmol/L, $P < .01$), and elevated concentrations (>2.0 mmol/L) were nearly 3 times more common in metformin-treated patients (9.2% vs 3.8%, $P < .001$). However, none met diagnostic criteria for lactic acidosis. Lin et al[12] found mean lactate concentrations to be similar between 66 patients with type 2 diabetes older than 80 years and taking metformin (mean age, 83.6 years; mean creatinine clearance, 48.9 [SD, 12.9] mL/min), compared with 79 younger individuals (mean age, 59.9 years; mean creatinine clearance, 80.3 [SD, 30.1] mL/min, $P < .01$): 1.47 [SD, 0.58] vs 1.50 [SD, 0.53] mmol/L. Lim et al[13] studied a group of 97 patients taking metformin and found no association between plasma lactate levels and kidney status (1.7 [SD, 0.3] mmol/L in groups with eGFRs less than 60 mL/min per 1.73 m^2, 1.8 [SD, 0.3] mmol/L in groups with eGFRs of 60 through 90/mL/min per 1.73 m^2, and 1.8 [SD, 0.4] mmol/L in groups with eGFRs greater than 90 mL/min per 1.73 m^2). Similar findings were reported by Duong et al[14] and Connolly and Kesson[15] in studies that included patients with more advanced kidney dysfunction. Among 493 patients with type 2 diabetes, Mongraw-Chaffin et al[16] found slightly higher (but still normal) lactate levels in those using metformin vs those using other agents (1.00 [95% CI, 0.94-1.06] vs 0.93 [range, 0.88-0.97] mmol/L; $P < .05$). Similar findings were reported by Davis et al[17] in 272 patients (1.86 [SD, 1.34-2.59] for metformin vs 1.58 [1.09-2.30] mmol/L for no metformin; $P < .001$.) Abbasi et al[18] reported mildly elevated lactate levels (mean, 2.17 [SD, 0.57] mmol/L) in 57% of 110 patients taking metformin with normal kidney function, but there was no control group.

The pharmacokinetics of metformin differ substantially from those of phenformin, an original biguanide whose removal from the market nearly 4 decades ago was based on a significantly increased risk of lactic acidosis. Metformin is entirely renally cleared (half-life, 6.5 hours)[19]; phenformin is both hepatically metabolized and more slowly renally excreted (half-life, 7-15 hours). Compared with metformin, phenformin is also lipophilic, with a higher affinity for mitochondrial membranes and more powerful inhibitory effect on the mitochondrial respiratory chain. Phenformin increases muscle lactate release and inhibits lactate oxidation, effects not shared by metformin.[20] Three early investigations found a relationship between phenformin and lactate levels not demonstrable with metformin.[21-23] These data may explain reduced incidence of lactic acidosis in Swedish patients with diabetes during 1977-1991, comparing rates when phenformin was available (1.5 cases/10 000 patient-years) vs when metformin was the exclusive biguanide prescribed (0.24 cases/10 000 patient-years).[24,25]

In summary, although metformin clearance is decreased in the setting of CKD, drug levels remain within therapeutic range when eGFR is greater than 30 mL/min per 1.73 m^2 and do not significantly affect circulating lactate levels. These conclusions are based on small

studies; larger data sets could reveal a closer alignment between metformin, kidney function, and predisposition to hyperlactatemia.

The Relationship Between Metformin and Lactic Acidosis—Lactic acidosis is an anion-gap metabolic acidosis defined by plasma lactate level greater than 5 mmol/L and pH less than 7.35. When severe, it is associated with multisystem organ dysfunction—particularly neurologic (stupor, coma, seizures) and cardiovascular (hypotension, ventricular fibrillation)—and carries a high mortality risk. Small series involving patients hospitalized with lactic acidosis have explored associations with metformin exposure.[19,26-44] In each, the patients had a supervening illness that precipitated the metabolic decompensation, usually infection, acute kidney or liver failure, or cardiovascular collapse. Although a possible role for metformin could not be excluded, it was viewed predominately as a bystander—ie, not causally implicated—by most authors. When metformin levels were measured, they were normal or elevated but did not consistently correlate with the degree of acidosis.[28,34,45,46] Lactate concentrations were not different than in patients who did not take metformin but were contemporaneously admitted with lactic acidosis.[38] In addition, drug concentrations carried neither diagnostic nor prognostic significance. In one series, higher metformin levels were associated with reduced mortality.[35] In some studies[30,31,34] the majority of patients with metformin-associated lactic acidosis had antecedent normal kidney function—suggesting that prescribing limitations based on renal parameters would not necessarily prevent lactic acidosis, even if the drug were responsible.

Several larger observational studies have explored the relationship between metformin and lactic acidosis.[6,45,47-49] Stang et al[47]conducted an historical cohort analysis of the Saskatchewan Health database, including information on metformin therapy during a 15-year period. In that study, 11 797 patients received at least 1 prescription, for a total exposure of 22 296 years. Two patients were hospitalized for lactic acidosis (approximately 9/100 000 person-years); in both, other factors were identified to be primarily responsible. For context, Brown et al[50] studied 3 Kaiser Permanente databases prior to availability of metformin in the United States. Among 41 000 patients with type 2 diabetes, 4 cases of lactic acidosis were confirmed, resulting in a risk estimate of approximately 10 per 100 000 person-years. Bodmer et al[6] conducted a nested case-control study using a general practice database in the United Kingdom and identified 6 cases of lactic acidosis among 50 048 patients with type 2 diabetes. The estimated incidence was approximately 3.3 per 100 000 person-years among metformin users and approximately 4.8 per 100 000 person-years among sulfonylurea users. One Dutch study found a higher rate of lactic acidosis in metformin-treated patients (47 per 100 000 person-years), the majority ascribed to underlying illnesses.[51] The investigators did not estimate corresponding rates with other antihyperglycemic drugs, however.

Kajbaf and Lalau[49] examined the quality of pharmacovigilance reporting of cases of metformin-associated lactic acidosis in Europe. Of 869 cases during a 15-year period, only 41.3% met appropriate diagnostic criteria and in only 14% were metformin levels measured. It was therefore impossible to assess whether metformin was causatively involved in 90% of cases. In a more detailed study, Stades et al[45] convened 6 critical care experts to review 47 case reports of suspected metformin-associated lactic acidosis published between

1959-1999. There was generally very low interobserver agreement as to causation (κ = 0.041), challenging the notion of a simple, causal relationship between metformin and lactic acidosis.

In conclusion, no consistent link between metformin and lactic acidosis has been found. However, observational studies may underestimate the risk of MALA because of confounding by indication. Patients prescribed metformin despite kidney dysfunction in these studies may be healthier, and this may explain the low risk for lactic acidosis observed in this group. On the other hand, ascertainment bias may overestimate the risk of MALA in observational studies. Clinicians may be more likely to measure lactate levels in patients taking metformin. Similarly, in pharmacosurveillance studies, the perception of risk for MALA could lead to increased adverse event reporting. Accordingly, it is difficult to make firm conclusions from these studies about metformin and lactic acidosis in patients with kidney disease.

Clinical Trials and Large Retrospective Studies—Salpeter et al[5] compiled trials and observational studies evaluating metformin therapy compared with placebo or other antihyperglycemic drugs. The authors pooled data from 347 studies of type 2 diabetes and discovered no cases of lactic acidosis during 70 490 patient-years in the metformin group or during 55 451 patient-years in the nonmetformin group. The upper 95% confidence limit for the true incidence of lactic acidosis per 100 000 patient-years was 4.3 cases with and 5.4 cases without metformin. Given the prevailing contraindications, many participants with kidney dysfunction may have been excluded. It would therefore be inappropriate to use absence of MALA cases therein as proof of drug safety in CKD—yet of the 334 prospective trials examined, 43% did not exclude kidney disease at baseline.

More recent observational studies suggest clinical benefits of metformin in patients with impaired kidney function. Roussel et al[52] analyzed data from 19 691 patients with type 2 diabetes with established atherosclerotic disease. Propensity scores for metformin prescription were used to statistically account for differences in baseline characteristics. Mortality rates were 6.3% (95% CI, 5.2%-7.4%) with and 9.8% (95% CI, 8.4%-11.2%) without metformin therapy. The adjusted hazard ratio (HR) was 0.76 (95% CI, 0.65-0.89) in metformin users. In prespecified subgroup analyses, apparent benefit persisted in those with creatinine clearance of 30 to 60 mL/min per 1.73 m^2 (adjusted HR, 0.64 [95% CI, 0.48-0.86]). The authors concluded that metformin therapy might reduce mortality in patients with renal contraindications.

From the Swedish National Diabetes Register, Ekström et al[53] studied 51 675 patients with type 2 diabetes across a spectrum of kidney function, with mean follow-up of 3.9 years. Using patients receiving metformin monotherapy as the referent group and propensity scoring, the hazard ratios for fatal or nonfatal cardiovascular disease events and all-cause mortality were numerically (and in some circumstances statistically) higher in those treated with other agents (sulfonylureas: HR, 1.02 [95% CI, 0.93-1.12] and 1.13 [95% CI, 1.01-1.27]); insulin: HR, 1.18 [95% CI, 1.07 to 1.29] and 1.34 [95% CI, 1.19 to 1.50]). Among patients with eGFRs of 45 to 60 mL/min per 1.73 m^2, those using metformin monotherapy had a lower risk of acidosis, serious infection, or both (HR, 0.85 [95% CI,

0.74-0.97]) and all-cause mortality (HR, 0.87 [95% CI, 0.77-0.99]) compared with those using other single agents.

Other observational data appear to confirm those findings, although the lack of propensity score adjustments make them more susceptible to confounding by indication.[54,55] Solini et al[54] analyzed data from 15 733 individuals with type 2 diabetes in an observational cohort study. Cardiovascular disease prevalence was lower in patients taking metformin (20.2%) vs other agents (32.4%), an observation consistent across all eGFR categories (including <60 mL/min per 1.73 m^2) and age quartiles.

Two recent studies using a UK general practice database have added further controversy, however. Eppenga et al[56] analyzed data from 223 968 patients using metformin and 34 571 using other oral agents between 2004-2012. The primary outcome was lactic acidosis defined by clinical code, lactate level greater than 5 mmol/L, or both. The overall incidence rate was 7.4 vs 2.2 per 100 000 person-years among metformin users vs nonusers. The adjusted HR for patients using metformin was 4.06 (95% CI, 0.97-16.81). The investigators reported an HR of 6.37 (95% CI, 1.48-27.5) in patients using metformin with eGFR less than 60 mL/min per 1.73 m^2, whereas the HR was not significantly increased (2.87 [95% CI, 0.67-12.3]) in those with eGFR greater than 60 mL/min per 1.73 m^2. Using the eGFR cut-point of 45 mL/min per 1.73 m^2, the corresponding HRs were 6.74 (1.34-33.8) vs 3.16 (0.75-13.3). The risk among persons with impaired kidney function was increased further in those taking higher daily doses (≥2 g/d) (HR, 13.0 [95% CI, 2.36-72.0]). The authors concluded that the risk of lactic acidosis or elevated lactate level was significantly higher in metformin-treated patients with mild to moderate CKD as compared with those using other therapies, a risk compounded at higher doses.

This study has several limitations. The number of events was small, and kidney function was not documented in more than 25% of individuals. Lactic acidosis diagnoses were captured through standardized terminology codes and not substantiated by chart review. Prior work with this database reported that approximately 50% of diagnoses could not be confirmed on manual medical record review.[6] Last, the inclusion of increased lactate levels as part of the composite end point (26% in this analysis) would tend to increase the estimate of risk among metformin users, because clinicians may be more likely to measure lactate in patients taking the drug. Conversely, patients using metformin tended to be younger with overall better kidney function and may have been selected for therapy because their risk for lactic acidosis appeared low.

Richy et al[57] also used this database to determine whether, among metformin-treated patients, those with abnormal kidney function experienced any increased risk for lactic acidosis. A total 35 events were identified during 2007-2012 among 77 601 metformin users, for an overall incidence of 10.37 (95% CI, 7.22–14.42) per 100 000 patient-years. Corresponding rates were 7.6 (95% CI, 0.9-27.5) per 100 000 patient-years among patients with normal kidney function (eGFR >90 mL/min per 1.73 m^2), 4.6 (95% CI, 2.00-9.15) per 100 000 patient-years among those with mildly impaired function (eGFR 60-90 mL/min per 1.73 m^2), 17 (95% CI, 10.89-25.79) per 100 000 patient-years among those with moderately impaired function (eGFR 30-60 mL/min per 1.73 m^2), and 39 (95% CI, 4.72-140.89) per

100 000 patient-years among those with severely impaired function (eGFR <30 mL/min per 1.73 m^2). The incidence rate ratios, compared with the normal kidney function group, were 0.61 (0.12-5.26) for those with mildly impaired function, 2.27 (0.56-20.00) for those with moderately impaired function, and 5.26 (0.37-71.43) for those with severely impaired function. The authors concluded that lactic acidosis is rare with metformin and that differences in the incidence rates between patients with normal and reduced kidney function were not significant. However, numerical trends for increasing lactic acidosis events begin with eGFRs less than 60 mL/min per 1.73 m^2. With such small numbers of events, conclusive statements cannot be made.

In summary, the frequency of lactic acidosis in the setting of metformin therapy is very low and numerically similar to what appears to be the background rate in the population with type 2 diabetes. Data from 2 recent observational studies suggest possible trends toward a higher risk of either lactic acidosis or elevated lactate levels in patients taking metformin and with eGFRs less than 45 to 60 mL/min per 1.73 m^2. For context, other studies have suggested a significant clinical benefit for macrovascular outcomes from metformin,[58-61] with a pooled odds ratio from a single systematic review of 0.74 (95% CI, 0.62-0.89) for cardiovascular mortality compared with other oral agents or placebo.[59]

Adherence to Current Prescribing Guidelines—Eppenga et al[56] and Richy et al[57] have observed that current prescribing guidelines for kidney dysfunction are not consistently followed in real-world practice, and others have made similar observations (Table 1).[31,62-75] In some studies, metformin was used despite recommendations concerning renal risk in up to 1 of 4 patients. So, current regulatory cautions to avoid metformin in patients with mild to moderate CKD apparently are not being followed. Yet lactic acidosis developed rarely and, when it occurred, was considered primarily related to underlying disease.

Other Treatment Options

During the past 15 years, many other glucose-lowering agents have become available, each with unique safety profiles.[1] Adverse effects are a particular concern in chronic diseases, in which the treatment course is open ended and quality of life, drug cost, and safety are critical components of patient-centered care. If metformin is discontinued or avoided because of the development of mild to moderate CKD (a frequent scenario in diabetes, particularly in elderly patients), other therapies may be required. Whether the alternatives available are any safer in this setting is uncertain.[76] There are concerns related to hypoglycemia with sulfonylureas and insulin among patients with CKD. Kidney dysfunction is associated with increased risk for peripheral edema and heart failure with the thiazolidinediones.[77] Sodium-glucose cotransporter 2 inhibitors are less effective as glucosuric agents if kidney function is impaired.[78]

Discussion

Summary of Key Findings

Because of concerns regarding MALA in the setting of CKD, guidelines in the United States prohibit the use of metformin for at least 2.5 million individuals.[4] The incidence of lactic

acidosis in the setting of metformin therapy is, however, low, and the drug is not necessarily responsible when lactic acidosis occurs in patients taking this medication. Although drug levels are higher in those with kidney dysfunction, levels are still maintained largely within the therapeutic range[9,10] and lactate levels are not substantially increased when metformin is used in those with reduced GFR.[11-14] The risk of lactic acidosis is essentially nil in the context of clinical trials, including those that did not specify kidney disease as an exclusion criterion.[5] Data from observational clinical practice data sets are conflicting, with most appearing to confirm the drug's overall safety profile, finding lactic acidosis rates not different from those in the general population of patients with diabetes treated with other agents.[6,47] Current guidelines regarding use of metformin in patients with CKD are commonly disregarded, but when the drug is prescribed despite renal contraindications, it is associated with no greater occurrence of adverse events and may potentially have clinical benefits in this population.[52-54,79] Some recent data suggest that the risk of lactic acidosis or elevated lactate levels may be increased in metformin users with more advanced kidney dysfunction compared with users of other drugs, although the absolute risk remains extremely low. A conservative synthesis of these data is that, as long as kidney function is stable and the patient is observed closely, metformin is un-likely to measurably increase the risk of lactic acidosis in those with mild to moderate CKD (ie, eGFR 30-60 mL/min per 1.73 m^2).

Current Clinical Practice Guidelines

The US FDA prescribing guidelines for metformin regarding kidney function are noted above. In some other parts of the world, use of the drug extends to those with mild to moderate CKD. In the United Kingdom, guidelines allow for use with eGFRs less than 60 mL/min per 1.73 m^2,[80] with the recommendation that dosing be reviewed if serum creatinine levels increase to more than 1.5 mg/dL or eGFR decreases to less than 45 mL/min per 1.73 m^2 and that the drug be stopped with creatinine levels more than 1.7 mg/dL or eGFRs less than 30 mL/min per 1.73 m^2. The European Medicines Agency stipulates that metformin is contraindicated with creatinine clearance less than 60 mL/min.[81] The Canadian Diabetes Association allows for metformin use with creatinine clearance less than 60 mL/min but with a maximum dose of 1700 mg/d for patients with creatinine clearance of 60 to 90 mL/min and of 850 mg/d for patients with creatinine clearance of 30 to 60 mL/min.[82] The 2012 American Diabetes Association–European Association for the Study of Diabetes position statement on antihyperglycemic therapy in type 2 diabetes favors the eGFR-based National Institute for Health and Care Excellence guidelines.[1] The Kidney Disease Outcomes Quality Initiative clinical practice guidelines recommend that metformin safety be assessed in patients with stage 4 and stage 5 CKD.[83]

There have been increasing calls to update the US metformin-prescribing guidelines to allow for use of this agent in patients with mild to moderate CKD,[84-87] with 2 citizens' petitions being considered by the FDA.[88,89]

Controversial/Unresolved Issues, Areas for Future Research

There have been no randomized clinical trials to test the specific hypothesis that metformin is safe in patients with mild to moderate CKD. Randomized trials would help to better

inform evidence-based guidelines. However, given the rarity of lactic acidosis in the setting of metformin therapy, a study would need to examine hundreds of thousands of patients for many years to demonstrate non-inferiority compared with other agents, which is clearly impractical. National patient registries might be a reasonable alternative. However, for regulatory bodies at this time, the best available evidence is limited to meta-analyses, retrospective studies, and smaller mechanistic investigations reported herein.

Recommendations

Our review supports consideration of a change to metformin's prescribing guidelines, with use allowed in patients with mild to moderate CKD. Table 2 proposes a possible strategy, but it has not been evaluated or validated in a clinical trial. It should be noted that, while generally increasing access to metformin for many, this strategy may actually make treatment in some older individuals more complex, with certain subgroups (mainly nonblack women with eGFRs of 30-44 mL/min per 1.73 m^2) requiring dosage reductions not currently specified in the US label (eg, a white woman aged 61 years with a serum creatinine level of 1.3 mg/dL but an eGFR of 44 mL/min per 1.73 m^2). Any new expansion of metformin use in patients with mild to moderate CKD will need to be accompanied by appropriate dosage reductions and careful follow-up assessments of kidney function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr Inzucchi reported serving as a consultant for Merck, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, and Novo Nordisk; serving as a speaker for Merck; and receiving nonfinancial support from Takeda. Dr Lipska reported receiving a grant from the National Institutes of Health and receiving a Yale Center for Clinical Investigation Scholar Award and a Pepper Center Research Career Development Award. Dr Bailey reported serving as a consultant for, and receiving honoraria and travel expenses from, AstraZeneca/Bristol-Myers Squibb, sanofi, Merck Sharp & Dohme, Takeda, Boehringer Ingelheim/Lilly, and Novo. Dr McGuire reported receiving personal fees from Boehringer Ingelheim, Janssen Research and Development LLC, sanofi-aventis Groupe, Genentech, Merck Sharp & Dohme, Medscape Cardiology, Pri-Med Institute, The Brigham and Women's Hospital, Inc, Duke Clinical Research Institute, The Cleveland Clinic Coordinating Center for Clinical Research, The University of Oxford, Daiichi Sankyo, Lilly USA, Novo Nordisk, F. Hoffmann La Roche, Axio Research, INC Research LLC, GlaxoSmithKline, Takeda Pharmaceuticals North America, Bristol-Myers Squibb, AstraZeneca, Orexigen, Lexicon, Eisai, and Regeneron and receiving nonfinancial support from Gilead Sciences.

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Table 1

Retrospective Studies Examining the Frequency of Metformin Use in Patients With Active Renal Contraindications

			Renal Contraindication		
Source	**No.**	**Setting**	**Frequency, No. (%)**	**Definition[a]**	**Frequency of Lactic Acidosis**
Kosmalski et al,[62] 2012	335	Hospital	56 (16.7)	eGFR <60	No cases
Vasisht et al,[63] 2010	234	Outpatient	36 (15.4)	eGFR <60	No cases
Scotton et al,[31] 2009	283	Hospital	17 (6.0)	SCr >1.5 (men) SCr >1.4 (women)	Not reported
Kamber et al,[64] 2008	425	Outpatient	78 (8.4)	eGFR <60	No cases[b]
Runge et al,[65] 2008	92	Outpatient	4 (4.4)	SCr ≥ 1.5 (men) SCr ≥ 1.3 (women)	Not reported
Sweileh et al,[66] 2007	124	Outpatient	34 (27.4)	Renal impairment	Not reported
Warren et al,[67] 2007	11 297	Outpatient	880 (25.5)	eGFR <60	Unknown
Kennedy et al,[68] 2005	4838	Outpatient	219 (4.5) 290 (13.4) [men] 362 (17.7) [women]	eGFR <60 SCr ≥1.5 (men) SCr ≥1.4 (women)	Not reported
Millican et al,[69] 2004	83	Hospital	12 (14.5)	eGFR <50 or SCr >1.7	Not reported
Horlen et al,[70] 2002	22	Outpatient	8 (36.4)	SCr ≥1.5 (men) SCr ≥1.4 (women)	Not reported
Calabrese et al, [71] 2002	263	Hospital	32 (12.2)	SCr ≥1.5 (men) SCr ≥1.4 (women)	3 cases (metformin could not be ruled out as the cause)
Emslie-Smith et al,[72] 2001	1347	Outpatient	63 (4.7)	SCr ≥1.7	1 case, unrelated (extensive myocardial infarction, renal function previously normal)
Holstein et al,[73] 1999	308	Hospital	59 (19.2)	eGFR <60	No cases
Selby et al,[74] 1999	9875	Outpatient	128 (1.3)	SCr ≥1.5	1 case, likely unrelated (renal function normal)
Sulkin et al,[75] 1997	89	Outpatient	2 (2.3)	SCr ≥1.4	Not reported

Abbreviations: eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

SI conversion factor: To convert serum creatinine values to μmol/L, multiply by 88.4.

[a] Estimated glomerular filtration rate values reported in mL/min per 1.73 m^2; serum creatinine values reported in mg/dL.

[b] During study follow-up (1993 to 2001); authors reported 3 patients with metformin-associated lactic acidosis during extended follow-up via data linkage through 2006, each of whom had at least 1 major comorbidity associated with lactic acidosis (estimated incidence similar to that of patients not treated with metformin [$P = .4$]).

Table 2

Possible Approach to Metformin Prescribing in the Setting of CKD[a]

CKD Stage	eGFR, mL/min per 1.73 m^2	Maximal Total Daily Dose, mg	Other Recommendations
1	≥90	2550	
2	60 -<90	2550	
3A	45 -<60	2000	Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
3B	30 -<45	1000	Do not initiate therapy at this stage but drug may be continued Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function
4	15 -<30	Do not use	
5	<15	Do not use	

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

[a]This strategy has not been evaluated or validated in a clinical trial; there are no data to support its efficacy, safety, or potential to improve clinical outcomes.