Should Restrictions Be Relaxed for Metformin Use in Chronic Kidney Disease? Yes, They Should Be Relaxed! What's the Fuss?

George L. Bakris[1] and Mark E. Molitch[2]

Diabetes Care 2016;39:1287–1291 | DOI: 10.2337/dc15-2534

Metformin is and has been considered as first-line therapy for type 2 diabetes for over a quarter of a century. Like other biguanides, metformin can cause a lactic acidosis that is exceptionally rare but fatal. The likelihood of metformin-associated lactic acidosis is substantially higher in patients with kidney impairment and also among those with seemingly normal kidney function who are at risk of acute kidney injury (AKI). Hence, regulatory agencies in many industrialized nations have maintained strict renal restrictions surrounding metformin. However, there have been millions of people exposed to metformin for many years, many of them with serum creatinine values at or close to 1.5 mg/dL with estimated glomerular filtration rates (eGFRs) much below 60 mL/min/1.73 m^2 who have not developed lactic acidosis. Thus, there clearly remains controversy in this area, and there has been heightened pressure to remove the renal restrictions of metformin. To provide a discussion on the pros and cons of relaxing the renal restrictions for metformin use, we provide a Point-Counterpoint. In the preceding point narrative, Drs. Kalantar-Zadeh and Kovesdy provide their argument that although there is little evidence of the potential benefits of metformin in kidney disease, just considering the sheer numbers of metformin users and the high fatality rate of its associated lactic acidosis, the most appropriate practice is to avoid metformin use in people with eGFR <45 mL/min/1.73 m^2 or in those who are at high risk of AKI irrespective of underlying eGFR. In the counterpoint narrative below, Drs. Bakris and Molitch argue that the data from a very large analysis demonstrate clearly that serum creatinine should be supplanted with eGFR as the criteria for metformin use and that the incidence of lactic acidosis is only elevated in those with a reduced eGFR who become dehydrated for various reasons or in those exposed to some toxin resulting in AKI. Otherwise the data clearly support the use of metformin under normal circumstances down to eGFR >30 mL/min/1.73 m^2.

—**William T. Cefalu**
Editor in Chief, *Diabetes Care*

All guidelines within the past decade have endorsed metformin as initial therapy for patients with type 2 diabetes due to its demonstrated efficacy and excellent tolerance (1,2). Because metformin is cleared by the kidney, there has always been concern that it should not be used in people with a serum creatinine above 1.5 mg/dL in men and 1.4 mg/dL in women because of a potential risk of metformin-associated lactic acidosis (MALA), as evidenced by the U.S. Food and Drug

[1]*American Society of Hypertension Comprehensive Hypertension Center, Section of Endocrinology, Diabetes, and Metabolism, The University of Chicago Medicine, Chicago, IL*
[2]*Northwestern University Feinberg School of Medicine, Chicago, IL*

Corresponding author: George L. Bakris, gbakris@medicine.bsd.uchicago.edu.

© 2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

See accompanying article, p. 1281.

Downloaded from http://ada.silverchair.com/care/article-pdf/39/7/1287/625484/dc152534.pdf by guest on 18 April 2024

Administration (FDA) warning label. This concern stemmed from a risk of lactic acidosis with a prior biguanide, phenformin, which is no longer used. However, there was little to no evidence supporting this risk for metformin at the time of the FDA label. Moreover, there are both mechanistic and dosing insights about the effects and use of metformin in kidney disease that show a very different picture (3). Therefore, it is worth reexamining the question of MALA development in patients with impaired kidney function.

Physician practice data suggests that metformin is being used in people with elevated serum creatinine levels in spite of the warnings in the FDA label (4). Moreover, most of the medical community has moved to using estimated glomerular filtration rate (eGFR) rather than serum creatinine to determine safety. This is due to the variation of serum creatinine, primarily based on age. A serum creatinine of 1.5 mg/dL in a healthy 30-year-old male would equal an approximate eGFR of 70–75 mL/min/1.73 m^2, whereas the same creatinine in a 70-year-old male would equate to an eGFR of about 45 mL/min/1.73 m^2. Hence, eGFR stages have been developed to better define groups with kidney disease (5). For the purposes of this discussion, we will be referring to stage 3 chronic kidney disease (CKD), defined as eGFR $<$60 and $\geq$30 mL/min/1.73 m^2.

Metformin is filtered at the glomerulus and secreted in the proximal tubule, with a resultant very high clearance of 507 $\pm$ 129 mL/min in normal subjects (6). Cimetidine, which blocks tubular secretion, inhibits metformin clearance by about 50%, emphasizing the role of tubular secretion in addition to glomerular filtration (6). The clearance of metformin decreases by about 75% when the GFR is $<$60 mL/min/1.73 m^2, without further change when the GFR declines to 30 mL/min/1.73 m^2 (7). Median serum concentration ranges of metformin are 4.5 (0.1–20.7), 7.71 (0.12–15.5), and 8.88 (5.99–18.6) μmol/L (1 μg/mL = 7.8 μmol/L) at GFR levels $>$60, 30–60, and $<$30 mL/min/1.73 m^2, respectively (8). In patients presenting with MALA, metformin levels are 5- to 15-fold higher than the aforementioned levels and serum creatinine levels are generally more than 3 mg/dL (9).

There are a number of very large analyses that assess the incidence of MALA from metformin; some of the main studies are reviewed in this article (Table 1). In the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) study, 4,838 patients with type 2 diabetes received metformin; of these, 17.7% of women and 13.4% of men had eGFR $\leq$60 mL/min/1.73 m^2 (10). These findings are not limited to primary care. At the University of Chicago Diabetes Center, 36 of 234 (15.3%) patients with eGFR of $<$60 mL/min/1.73 m^2 were receiving metformin; none developed lactic acidosis (11). Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2006 of patients with diabetes aged $>$18 years and with eGFR $<$60 mL/min/1.73 m^2 (N = 1,870) demonstrated that 14% with a serum creatinine $>$1.5 mg/dL were receiving metformin (11). The incidence of lactic acidosis in these patients taking metformin was estimated at eight cases per 100,000 person-years (11). In contrast, the risk of lactic acidosis, with a mortality rate of 30–50%, from phenformin is 40–64 cases per 100,000 patient-years (12).

The overall incidence of lactic acidosis with metformin use is quite rare. A Cochrane Database review of 347 prospective trials and observational cohort studies showed no cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin users or in 55,451 patient-years of users of other antihyperglycemia agents (13). In a nested case-control analysis of 50,048 patients with type 2 diabetes participating in the U.K. General Practice Research Database, only six cases of lactic acidosis were found, giving incidence rates of 3.3 cases per 100,000 person-years among metformin users and 4.8 cases per 100,000 person-years among users of sulfonylureas (14). In the Swedish National Diabetes Register of 51,675 patients with type 2 diabetes, compared with other diabetes treatments, there were significantly lower risks for any acidosis/serious infection associated with metformin in patients with eGFR $>$60 (n = 41,048) and 45–60 mL/min/1.73 m^2 (n = 6,960) and a slightly higher albeit insignificant risk among those with eGFR 30–45 mL/min/1.73 m^2 (n = 2,044) (15). A systematic review that included a search of comparative trials, observational cohort studies, and meta-analyses to assess lactic acidosis risk with metformin in CKD found one randomized controlled trial, one meta-analysis, one case-control study, and three prospective cohort studies, representing about 150,000 patients (16). The data demonstrated that metformin is safe in patients with stable mild-to-moderate renal impairment (eGFR $>$30 mL/min/1.73 m^2). The incidence of lactic acidosis was 3.3 per 100,000 person-years, which was similar to that found in patients taking sulfonylureas (4.8 per 100,000 person-years). In addition, reduced risks of cardiovascular disease, all-cause mortality, or any acidosis/serious infection were seen with metformin in people with eGFR 30–60 mL/min/1.73 m^2 compared with sulfonylureas. The authors concluded that data over the past decade refute the idea that there is an increased risk of MALA in patients with stable stage 3 CKD, stating that the risk is similar to the risk found with other types of diabetes medications in patients with similar degrees of renal impairment (16). Last, metformin use was examined in kidney transplant recipients. A retrospective cohort study of over 46,000 patients garnered from a database linking the Scientific Registry of Transplant Recipients of all incident kidney transplants in 2001–2012 and national pharmacy claims (17). The study compared recipients having one or more pharmacy claims for a metformin-containing product (n = 4,609) and recipients having one or more claims for a nonmetformin glucose-lowering agent (n = 42,305). The authors found the median serum creatinine levels of metformin claims were 1.6 mg/dL (range 1.2–2.5). Metformin was associated with lower mortality in transplant recipients; moreover, lactic acidosis was not noted in this series. The authors concluded that despite metformin being contraindicated in renal dysfunction many kidney transplant recipients receive it and it is not associated with worse patient or allograft survival (17).

Despite the very low incidence in these studies, MALA certainly does occur, but it is quite rare. In retrospective series evaluating MALA, hypotension, sepsis, hypoxia, and, very commonly, acute kidney injury (AKI) related to abrupt volume loss were the primary causes of lactic acidosis when metformin was used (9,18–23). Loss of tubular secretion does not occur in stable CKD

Downloaded from http://ada.silverchair.com/care/article-pdf/39/7/1287/625484/dc1525534.pdf by guest on 18 April 2024

Table 1—Summary of studies

Study, year (reference)	Study design	Study groups	Baseline characteristics of metformin users	Results
GOAL A1C, 2005 (10)	Randomized, open label	Metformin-treated subjects with elevated vs. nonelevated serum creatinine levels	Of the 4,838 patients receiving metformin, 219 (4.5%) had elevated baseline serum creatinine levels.	1 of 22 (4.5%) patient treated with metformin in general practice had serum creatinine levels exceeding predefined safety limits.
Vashisht et al., 2010 (11)	Retrospective database review of diabetes center and separate NHANES 1999–2006 analysis	Patients with type 2 diabetes followed in diabetes center over 3 years of receiving metformin	36 of 234 (15.3%) patients receiving metformin had eGFR $<$60 mL/min/1.73 m^2; NHANES, patients with type 2 diabetes aged $>$18 years and with eGFR $<$60 mL/min/1.73 m^2 (N = 1,870)	There were no cases of lactic acidosis in diabetes center; NHANES reported 14% receiving metformin with a serum creatinine $>$1.5 mg/dL. Incidence of lactic acidosis was estimated at 8 cases per 100,000 person-years.
Cochrane Database review, 2010 (13)	347 prospective trials and observational cohort studies reviewed	Multiple different groups	Multiple different baselines	No cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin users.
Bodmer et al., 2008 (14)	Nested case-control study	50,048 patients with type 2 diabetes in the U.K. General Practice Research Database	Not clearly defined	There were incidence rates of 3.3 cases per 100,000 person-years among metformin users.
Swedish National Diabetes Register, 2012 (15)	Observational study (registry)	51,675 patients with type 2 diabetes	9,004 of 51,675 (17.4%) patients had eGFR 30–60 mL/min/1.73 m^2	People with eGFR 45–60 (n = 6,960) had significantly lower risk of any acidosis/ serious infection and those with eGFR 30–45 mL/min/1.73 m^2 (n = 2,044) had a slightly higher but insignificant risk of lactic acidosis.
Lu et al., 2013 (16)	Systematic review of 1 randomized controlled trial, 1 meta-analysis, 1 case-control study, and 3 prospective cohort studies (N = 150,000 patients)	Multiple groups	Multiple baselines	Metformin was safe in patients with renal impairment (eGFR $>$30 mL/min/1.73 m^2). The incidence of lactic acidosis was 3.3 cases per 100,000 person-years. People with eGFR 30–60 mL/min/1.73 m^2 on metformin had reduced risks of cardiovascular disease, all-cause mortality, or any acidosis/serious infection compared with those on sulfonylureas.
Stephen et al., 2014 (17)	Retrospective, observational cohort study (registry)	All postrenal transplant	More than 46,000 patients from a database linking the Scientific Registry of Transplant Recipients 2001–2012 and national pharmacy claims	Median serum creatinine of metformin claims were 1.6 mg/dL (range 1.2–2.5). Metformin was associated with lower mortality in transplant recipients, and lactic acidosis was not noted in this series.

but is a characteristic feature of AKI due to rapid volume depletion associated with an intercurrent illness (23). It is possible that this loss of tubular secretion in addition to the loss of GFR contributes to the substantial rise in metformin levels in cases associated with AKI. High levels of metformin, either from an overdose or from accumulation due to AKI, can cause lactic acidosis through multiple mechanisms, including inhibition of mitochondrial electron transport, acceleration of glycolysis, and activation of anaerobic metabolism of glucose in the intestine (9,24,25).

Taken together, these data support the concept that metformin use is quite safe in patients with stage 3 CKD and that MALA is very rare. As Herrington and Levy (26) point out, metformin use is much safer than insulin and/or sulfonylurea use, citing the incidence of MALA as 6.3 per 100,000 patient-years, with a 50% mortality, yielding a predicted number of deaths of 3 per 100,000 patient-years, in contrast to the incidence of hypoglycemia of 1,000 for sulfonylureas and 18,000 for insulin per 100,000 patient-years, with a 4.3% mortality, yielding predicted numbers of deaths of 43 for sulfonylureas and 77 for insulin per 100,000 patient-years.

Many have suggested changing from a strict dosing based on creatinine levels to dosing based on progressive decreases in eGFR (25,27,28). If the eGFR is 45–59 mL/min/1.73 m^2 (stage 3a CKD), one can

Downloaded from http://ada.silverchair.com/care/article-pdf/39/7/1287/625484/dc152534.pdf by guest on 18 April 2024

continue use of metformin without dosage change but the physician must follow kidney function more closely, such as every 3–4 months, and warn the patient about volume depletion–associated problems, such as diarrhea or prolonged reduction of fluid intake. If the eGFR is 30–44 mL/min/1.73 m^2 (stage 3b CKD), the physician should limit the maximum dose to 1,000 mg in two divided doses and follow kidney function every 3 months. One should avoid initiating metformin in patients with stage 3b CKD. Last, metformin should not be used if the eGFR $<$30 mL/min/1.73 m^2 (stage 4 CKD) (29,30).

A key point is that metformin should be stopped when prolonged hypoxia or an acute decline in kidney function occurs from any cause, including sepsis/shock, hypotension, acute myocardial infarction, or use of radiographic contrast or other nephrotoxic agents (25,28). Patients with eGFR$<$60 mL/min/1.73 m^2 should withhold metformin if they experience intercurrent illness that could lead to rapid volume depletion and should alert their health care providers of their situation. If lactic acidosis occurs in stage 3 CKD, then it will mostly be in the aforementioned settings. In patients taking metformin are admitted to the hospital, consideration should be given to holding the drug if their medical condition is unstable or they experience any of the issues discussed above.

We conclude that MALA is a very rare phenomenon and that metformin can be used safely in patients down to eGFR of 30 mL/min/1.73 m^2 with no increased risk of lactic acidosis. However, when stage 3 CKD (eGFR $<$60 mL/min/1.73 m^2) is reached, caution is needed, so that the drug can be stopped immediately when increased risk factors for lactic acidosis itself (e.g., hypoxia, sepsis, hypotension) or AKI occur. Hospitalized patients must be followed closely for the development of such potential risks, and many clinicians feel that hospitalization itself is fraught with so many risks that metformin should be held routinely upon hospital admission. Thus, our position is consistent with current guidelines statements of both American Diabetes Association and European Association for the Study of Diabetes (29,30). Very recently, a delayed-release metformin (Met DR) was formulated to deliver the drug to the lower bowel to leverage the gut-based mechanisms of metformin and reduce plasma exposure. These studies found a dissociation of the glycemic effect from plasma exposure with gut-restricted Met DR, supporting a predominantly lower bowel–mediated mechanism of metformin action (31). Last, in keeping with these data the FDA recently revised its warning regarding metformin, stating that use of metformin in patients who have an eGFR $<$60 mL/min/1.73 m^2 can now be done safely but starting metformin when the eGFR is $<$45 ml/min/1.73 m^2 is not recommended and metformin is contraindicated when the eGFR is $<$30 ml/min/1.73 m^2 (32).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35:1364–1379
2. Hirst JA, Farmer AJ, Ali R, Roberts NW, Stevens RJ. Quantifying the effect of metformin treatment and dose on glycemic control. Diabetes Care 2012;35:446–454
3. Buse JB, DeFronzo RA, Rosenstock J, et al. The primary glucose-lowering effect of metformin resides in the gut, not the circulation: results from short-term pharmacokinetic and 12-week dose-ranging studies. Diabetes Care 2016;39:198–205
4. Becquemont L, Bauduceau B, Benattar-Zibi L, et al. Cardiovascular drugs and metformin drug dosage according to renal function in non-institutionalized elderly patients. Basic Clin Pharmacol Toxicol. 17 November 2015 [Epub ahead of print]. DOI: 10.1111/bcpt.12526
5. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 2014;63: 713–735
6. Graham GG, Punt J, Arora M, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet 2011;50:81–98
7. Sambol NC, Chiang J, Lin ET, et al. Kidney function and age are both predictors of pharmacokinetics of metformin. J Clin Pharmacol 1995; 35:1094–1102
8. Frid A, Sterner GN, Löndahl M, et al. Novel assay of metformin levels in patients with type 2 diabetes and varying levels of renal function: clinical recommendations. Diabetes Care 2010; 33:1291–1293
9. Duong JK, Furlong TJ, Roberts DM, et al. The role of metformin in metformin-associated lactic acidosis (MALA): case series and formulation of a model of pathogenesis. Drug Saf 2013;36: 733–746
10. Kennedy L, Herman WH; GOAL A1C Study Team. Renal status among patients using metformin in a primary care setting. Diabetes Care 2005;28:922–924
11. Vasisht KP, Chen S-C, Peng Y, Bakris GL. Limitations of metformin use in patients with kidney disease: are they warranted? Diabetes Obes Metab 2010;12:1079–1083
12. Pernicova I, Korbonits M. Metformin–mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol 2014;10:143–156
13. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010;4: CD002967
14. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. Diabetes Care 2008;31: 2086–2091
15. Ekström N, Schiöler L, Svensson A-M, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open 2012;2:e001076
16. Lu WR, Defilippi J, Braun A. Unleash metformin: reconsideration of the contraindication in patients with renal impairment. Ann Pharmacother 2013;47:1488–1497
17. Stephen J, Anderson-Haag TL, Gustafson S, Snyder JJ, Kasiske BL, Israni AK. Metformin use in kidney transplant recipients in the United States: an observational study. Am J Nephrol 2014;40:546–553
18. Lalau JD, Lacroix C, Compagnon P, et al. Role of metformin accumulation in metformin-associated lactic acidosis. Diabetes Care 1995; 18:779–784
19. Runge S, Mayerle J, Warnke C, et al. Metformin-associated lactic acidosis in patients with renal impairment solely due to drug accumulation? Diabetes Obes Metab 2008;10:91–93
20. Seidowsky A, Nseir S, Houdret N, Fourrier F. Metformin-associated lactic acidosis: a prognostic and therapeutic study. Crit Care Med 2009;37:2191–2196
21. Friesecke S, Abel P, Roser M, Felix SB, Runge S. Outcome of severe lactic acidosis associated with metformin accumulation. Crit Care 2010; 14:R226
22. Renda F, Mura P, Finco G, Ferrazin F, Pani L, Landoni G. Metformin-associated lactic acidosis requiring hospitalization. A national 10 year survey and a systematic literature review. Eur Rev Med Pharmacol Sci 2013;17(Suppl. 1):45–49
23. Schrier RW, Wang W, Poole B, Mitra A. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. J Clin Invest 2004;114:5–14
24. Lalau J-D, Arnouts P, Sharif A, De Broe ME. Metformin and other antidiabetic agents in renal failure patients. Kidney Int 2015;87:308–322
25. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34:1431–1437
26. Herrington WG, Levy JB. Metformin: effective and safe in renal disease? Int Urol Nephrol 2008;40:411–417

Downloaded from http://ada.silverchair.com/care/article-pdf/39/7/1287/625484/dc1525534.pdf by guest on 18 April 2024

27. Tuot DS, Lin F, Shlipak MG, et al.; CDC CKD Surveillance Team. Potential impact of prescribing metformin according to eGFR rather than serum creatinine. Diabetes Care 2015;38:2059–2067
28. Stacul F, van der Molen AJ, Reimer P, et al.; Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol 2011;21:2527–2541
29. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015;58:429–442
30. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
31. Buse JB, DeFronzo RA, Rosenstock J, et al. The primary glucose-lowering effect of metformin resides in the gut, not the circulation: results from short-term pharmacokinetic and 12-week dose-ranging studies. Diabetes Care 2016;39:198–205
32. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function [Internet], 2016. Available from http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm. Accessed 8 April 2016

Downloaded from http://ada.silverchair.com/care/article-pdf/39/7/1287/625484/dc152534.pdf by guest on 18 April 2024