Can J Diabetes 43 (2019) 76–80

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Review

Safe Use of Metformin in Adults With Type 2 Diabetes and Chronic Kidney Disease: Lower Dosages and Sick-Day Education Are Essential

Lori MacCallum BScPhm, PharmD, RPh, CDE [a,b,c,*]; Peter A. Senior BMedSci, MBBS, PhD, FRCP [d]

[a] Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada
[b] Banting & Best Diabetes Centre, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[c] Toronto General Hospital Research Institute, Toronto, Ontario, Canada
[d] Division of Endocrinology, University of Alberta, Edmonton, Alberta, Canada

Key Messages

- The concern about metformin use in patients with type 2 diabetes and chronic kidney disease has been the possibility of an increased risk for lactic acidosis resulting from metformin accumulation.
- New evidence demonstrates that metformin may be used safely in people with chronic kidney disease, provided the dosage is adjusted properly.
- Sick-day management counselling is essential to ensure the safe use of metformin.

ARTICLE INFO

Article history:
Received 27 February 2018
Accepted 16 April 2018

Keywords:
dose
kidney disease
lactic acidosis
metformin
safety
sick day management

ABSTRACT

Metformin, together with lifestyle intervention, is considered first-line treatment for glycemic management in people with type 2 diabetes. Despite this widespread use, one of the areas of longstanding debate has been whether metformin can be used safely in those with chronic kidney disease (CKD). The concern is the possibility of an increased risk for lactic acidosis resulting from metformin accumulation in those with renal impairment. Options in this patient population are limited, and many believe this risk has been overstated, so several organizations around the world have made recommendations to allow for the cautious use of metformin in patients with CKD. Lalau and colleagues have added new evidence with the publication of 3 complementary studies of the use of metformin in people with CKD stages 3A, 3B or 4—a dose-finding study, a chronic metformin treatment study and a pharmacokinetic study. The authors tested adjusted dosage regimens based on level of CKD. The study demonstrates that although there is a relationship between eGFR and metformin levels, there is not a relationship between metformin levels and plasma lactate. In addition, as long as the metformin dosage was adjusted to the level of CKD, pharmacokinetics remained stable. Based on this new evidence, together with past epidemiologic data and systematic reviews, metformin appears to be a safe option for patients with CKD, assuming that the dosage is adjusted individually. Stopping the drug during acute illness is also imperative to ensure its safe use.

Mots clés :
dose
maladie rénale
acidose lactique
metformine
sécurité
gestion de jour de maladie

RÉSUMÉ

La metformine associée à une intervention axée sur le mode de vie est considérée comme le traitement de première intention pour prendre en charge la glycémie des personnes atteintes du diabète de type 2. En dépit de son utilisation généralisée, l'une (1) des questions débattues depuis longtemps est de savoir si la metformine peut être utilisée de façon sécuritaire chez les personnes qui ont une maladie rénale chronique (MRC). Certains sont préoccupés par la possibilité d'un risque accru d'acidose lactique causée par l'accumulation de la metformine chez les personnes qui présentent une détérioration du fonctionnement rénal. Puisque les options de traitement chez cette population de patients sont limitées, et puisque plusieurs croient que l'on a surestimé ce risque, plusieurs organisations du monde entier ont fait des recommandations

* Address for correspondence: Lori MacCallum, BScPhm, PharmD, CDE, Toronto General Hospital, 200 Elizabeth Street, Eaton Building, 12E252, Toronto, Ontario M5G2C4, Canada.
E-mail address: lori.maccallum@uhnresearch.ca

1499-2671
https://doi.org/10.1016/j.jcjd.2018.04.004

pour favoriser l'utilisation prudente de la metformine chez les patients atteints de MRC. Lalau et ses collègues ont apporté de nouvelles données probantes lors de la publication de 3 études complémentaires (1 étude destinée à l'établissement de la posologie, 1 étude sur le traitement à long terme par metformine et 1 étude de la pharmacocinétique) sur l'utilisation de la metformine chez les personnes atteintes de MRC de stades 3A, 3B ou 4. Les auteurs ont examiné les régimes posologiques ajustés selon le stade de la MRC. L'étude démontre que bien qu'il y ait un lien entre le DFGe (débit de filtration glomérulaire estimé) et les concentrations de la metformine, il n'existe pas de lien entre les concentrations de la metformine et les concentrations plasmatiques de lactate. De plus, tant que la posologie de la metformine était ajustée au stade de la MRC, la pharmacocinétique demeurait stable. Selon ces nouvelles données probantes, ainsi que selon les données épidémiologiques et les revues systématiques, la metformine semble être une option sécuritaire chez les patients atteints de MRC, dans l'hypothèse où la posologie est ajustée de façon individuelle. L'interruption du médicament durant une maladie d'évolution rapide est également impérative pour s'assurer de son utilisation sécuritaire.

Introduction

Metformin, together with lifestyle intervention, is considered a first-line therapy for glycemic management in people with type 2 diabetes by organizations around the world (1–4). Owing to its low cost, safety and effectiveness, metformin is the most widely used antihyperglycemic agent and the most common therapeutic ingredient available in fixed-dose combinations. Despite this widespread use, one of the areas of longstanding debate has been whether metformin can be used safely by those with chronic kidney disease (CKD). The concern is the possibility of an increased risk for lactic acidosis resulting from metformin accumulation in those with renal impairment (5–7). There are, however, many who believe this risk has been greatly overstated (8).

Diabetes continues to be the leading cause of kidney disease in Canada, and as much as 50% of people with diabetes will have signs of kidney damage in their lifetimes (9–12). The question of whether metformin is safe is important because options in this patient population are limited. If the risks have been overstated, are we depriving patients of a safe and effective medication? Metformin withdrawal is associated with worse glycemic control, blood pressure and lipid levels and increased use of secretagogues or insulin, with risk for weight gain and hypoglycemia (13–16). Access to newer agents without renal cautions is limited in many places.

In part, metformin's glucose-lowering action is mediated by inhibiting the conversion of lactate into glucose in the liver. Because metformin is eliminated unchanged by the kidneys (by glomerular filtration and tubular secretion), the same glucose-lowering effect can be achieved with smaller dosages of metformin in people with reduced glomerular filtration rates (GFRs) because of reduced elimination of the drug. Of concern is the potential for metformin to cause excessive accumulation of lactate, resulting in lactic acidosis (LA), which was observed with a related drug (phenformin) that was subsequently taken off the market in 1978 (17). Fortunately, LA is rare (despite the widespread use of metformin) and is generally associated with acute, severe illnesses that cause excess production or reduced ability to oxidize lactate (e.g. ischemia or hypoxia), which are often associated with acute kidney injury and to which people with CKD are more susceptible (Figure 1).

There is little evidence to link metformin, low GFRs and LA directly. Although the clearance of metformin is reduced by approximately 75% when the estimated glomerular filtration rate (eGFR) is <60 mL/min/1.73 m^2, without further change when the eGFR declines to 30 mL/min/1.73 m^2, serum levels do not reach the levels seen in patients with true metformin-associated lactic acidosis (MALA) (18). In patients presenting with MALA, metformin levels were 5- to 15-fold higher (5). The evidence for metformin-induced LA stems mainly from case reports of patients who also had severe underlying illness, and systematic reviews have not shown an increased risk for LA with metformin (5,19–22). In studies of patients continuing to receive metformin, even when they have an eGFR of 30 to 60 mL/min/1.73 m^2, LA is very rare and the risk for it is similar to the risk seen with other agents in patients with similar degrees of renal impairment (23).

Although regulators provide frameworks to the pharmaceutical industry to guide study design, data analysis and interpretation of study results for product labeling in renal impairment, it is unlikely that manufacturers will perform such studies for metformin or other drugs that are approved and are now off patent (24,25). However, because of the weak association with MALA, several organizations have developed new recommendations to extend the use of metformin in people with CKD.

In 2013, the Canadian Diabetes Association (now Diabetes Canada) clinical practice guidelines changed the recommendation for metformin from the official product labeling, advising that it could be used with caution in those with CKD stage 3. The recommendation to avoid metformin in CKD stages 4 and 5 remained (1). In 2016, the European Medicines Agency and the U.S. Food and Drug Administration removed the contraindications to the use of metformin in stages 3A and 3B (eGFR 45 to 59 and 30 to 44 mL/min/1.73 m^2, respectively) (26,27) and recommended not starting the medication if the eGFR is less than 45 mL/min/1.73 m^2 and to stop the medication at <30 mL/min/1.73 m^2. However, patients taking metformin and having eGFRs between 30 and 45 mL/min/1.73 m^2 may continue to take the medication at a daily dose of 1,000 mg/day given in 2 divided doses after assessment of the benefits and risks of continued treatment.

There have also been changes in the recommendations for patients receiving metformin and iodinated contrast imaging. Rather than routinely stopping metformin for 48 h for all patients receiving iodinated contrast imaging, the 2017 American College of Radiology Manual on Contrast Media now recommends that metformin needs to be held only for those with acute kidney injury or CKD (stage 4 or stage 5; i.e. eGFR <30 mL/min/1.73 m^2) and those who are undergoing arterial catheter studies that might result in emboli (atheromatous or other) to the renal arteries because of the higher risk in this population. Patients with eGFRs above 30 mL/min/1.73 m^2 may continue taking the medication (28).

A New Study Looks at Metformin in CKD Stages 3A, 3B and 4

In the January 2018 issue of *Diabetes Care*, Lalau and colleagues published 3 complementary studies of the use of metformin in people with CKD stages 3A, 3B or 4—a dose-finding study, a chronic metformin treatment study and a pharmacokinetic study (Figure 2). In the first dose-finding study, 69 participants with diabetes at any CKD stage underwent 3 1-week blocks of metformin treatment at increasing doses, with a 1 week washout after each block. Plasma and erythrocyte metformin concentrations were

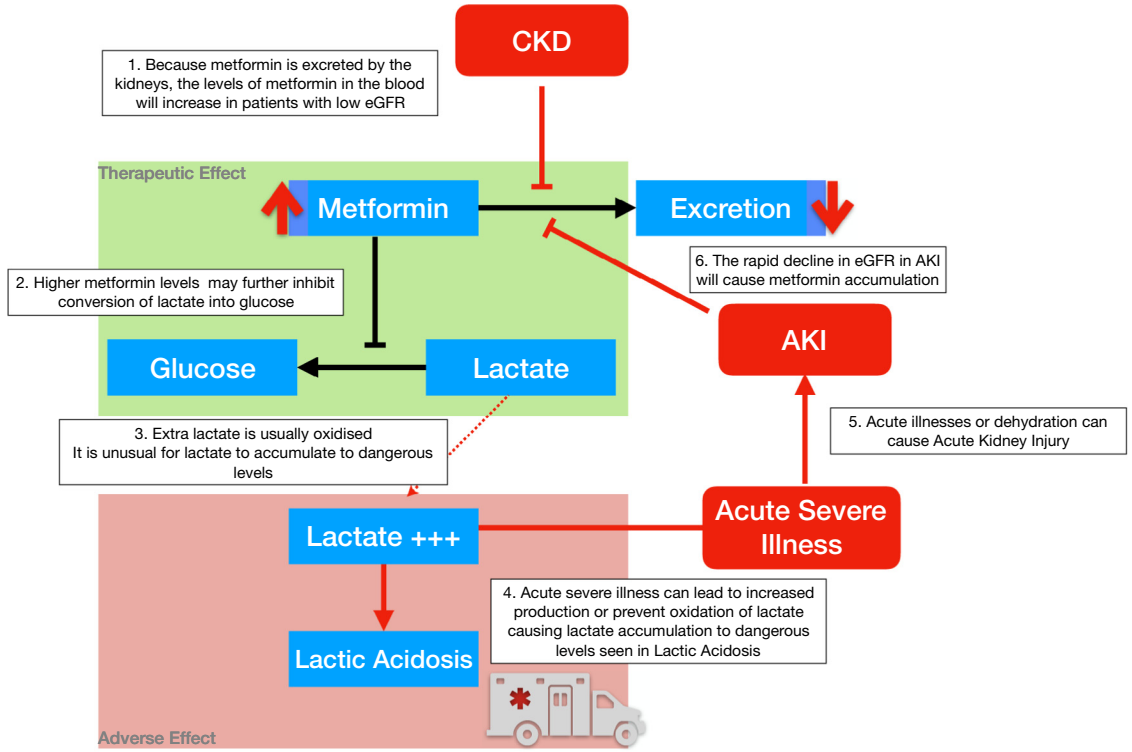

Figure 1. Proposed mechanisms describing the impact of acute and chronic changes in glomerular filtration rates on the pharmacology of metformin and its potential association with lactic acidosis. *AKI,* acute kidney injury; *CKD,* chronic kidney disease; *eGFR,* estimated glomerular filtration rate.

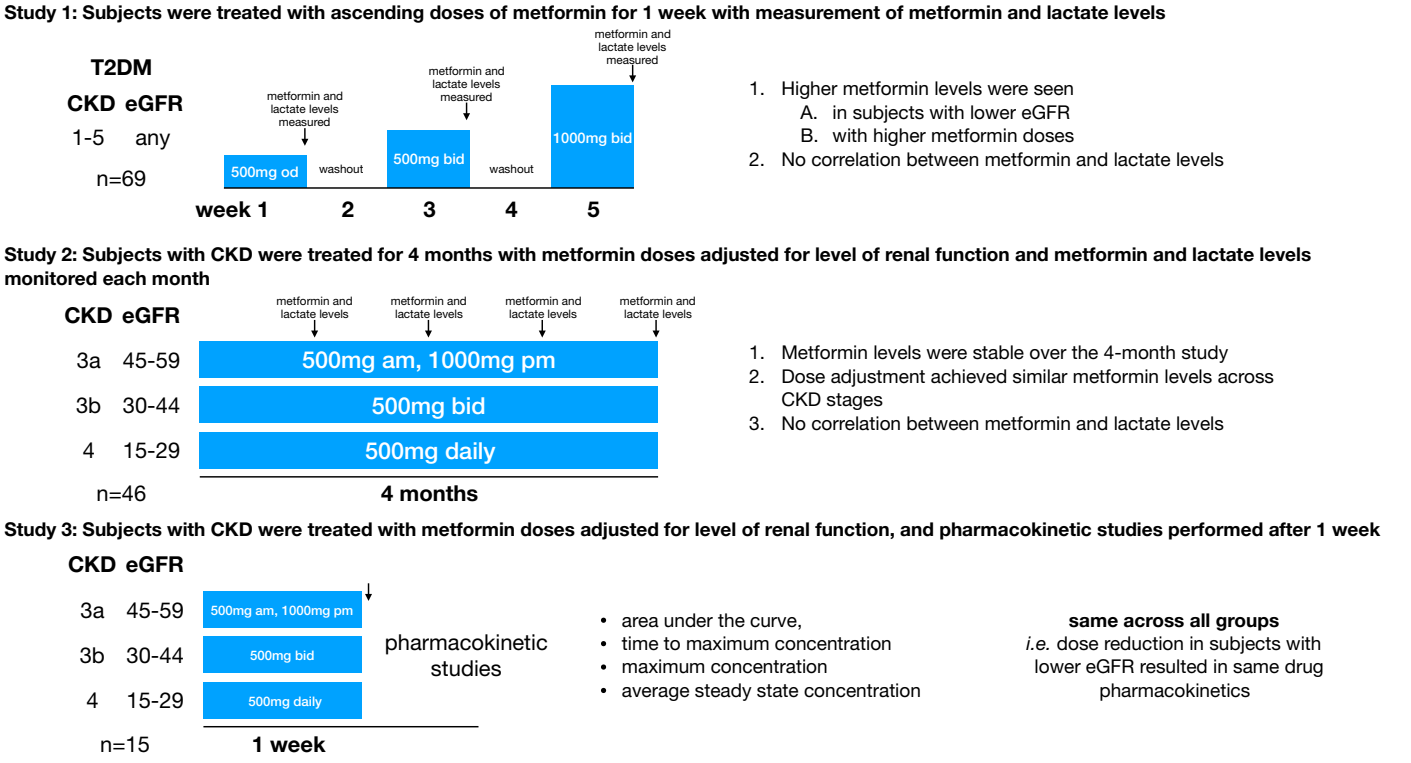

Figure 2. Visual summary of the design and key results of 3 complementary studies examining the impact of renal impairment on the pharmacology of metformin. *AKI,* acute kidney injury; *CKD,* chronic kidney disease; *eGFR,* estimated glomerular filtration rate; *T2DM,* type 2 diabetes.

assayed 12 h after the last dose of metformin, and lactate concentrations were measured for those with CKD stages 3 through 5. For each dosage level, there was a significant inverse relationship between eGFR and the plasma and erythrocyte metformin concentration. However, no relationship was observed between metformin and plasma lactate. The patients with the highest metformin levels did not display elevated lactate levels, and true hyperlactatemia (>5 mmol/L) was never observed. In the second

study, 46 patients with type 2 diabetes and CKD stage 3A, 3B or 4 underwent 4 months of metformin treatment at fixed dosages adjusted for CKD stage. Again, plasma and erythrocyte metformin levels were measured at the end of each month 12 h after the last dose of metformin (or 24 h after the last dose in CKD stage 4). Overall, the plasma and erythrocyte metformin concentrations remained stable; and, similar to the first study, no relationship was observed between metformin levels and plasma lactate. Although 6 patients had lactate levels >2.5 mmol/L, there was no statistically significant relationship between lactate concentrations and plasma or erythrocyte metformin levels. Only 1 patient had a level >5 mmol/L in the context of a myocardial infarction. In the final pharmacokinetic study, patients with CKD stage 3A, 3B or 4 (n=5 per group) who received 1 month of treatment using the same adjusted-dosage regimen based on CKD stage used in the second study had various metformin parameters measured, including peak plasma concentration (Cmax), time to Cmax and trough; then Lalau and colleagues calculated the area under the plasma drug concentration-time curve, the elimination-rate constant, the terminal half-life and the average steady state (29). There were no significant differences for the pharmacokinetic parameters across the 3 CKD stages, providing validation for the chosen dosage regimens. Based on their results, the authors recommend a dosage of 1.5 g daily (500 mg in the morning and 1 g in the evening) for CKD stage 3A and 1 g daily (500 mg bid) in CKD stage 3B. The US Food & Drug Administration and the European Medicines Agency do not provide different dosage recommendations for CKD stage 3A and 3B and recommend 500 mg twice daily in both groups. However, this recommendation was made before this new evidence was available. Although there was no increase in the risk for elevated lactate levels, the authors did not make any recommendation for the use of metformin in CKD stage 4, and the number of participants was relatively small. These pharmacologic studies provide a rationale for testing the safety and effectiveness of metformin 500 mg once daily in a larger, long-term prospective study in people with CKD stage 4.

Conclusions

Metformin is an effective and widely used drug. Serious adverse effects such as MALA are extremely rare and usually occur in patients with underlying causes (5,21,22). The study by Lalau has demonstrated that although an inverse relationship between eGFR and metformin levels was noted, no relationship was observed between metformin levels and plasma lactate levels. Consensus guidelines suggest that metformin can be used safely in those with eGFRs as low as 30 mL/min/1.73 m^2. We now have important data providing robust evidence for rational dosage adjustments for patients with eGFRs between 30 and 60 mL/min/1.73 m^2, specifically 1.5 g daily for CKD stage 3A and 1 g daily for CKD stage 3B. Furthermore, this study suggests that low-dosage metformin (500 mg once daily) may be safe in patients with eGFRs between 15 and 30 mL/min/1.73 m^2. Dosage adjustment of metformin should be recommended for people with CKD so as to maximize the benefits and minimize the risks of this effective medication. Further minimizing the risk for MALA will require effective dissemination of sick-day management recommendations to patients and providers so as to avoid metformin use when there is a risk for lactic acidosis, acute kidney injury or hypoxia.

Author Disclosures

Dr. MacCallum reports personal fees from Janssen and Novo Nordisk outside the submitted work. Dr. Senior reports personal fees from Abbott, Boehringer Ingelheim, Eli Lilly, Janssen, and Merck; grants and personal fees from Novo Nordisk, Sanofi, and AstraZeneca; and grants from Prometic and Viacyte, outside the submitted work.

Author Contributions

Both authors contributed equally to all aspects of the manuscript from concept, drafting and critically revising the manuscript and preparing illustrations.

References

1. Booth G, Lipscombe L, Butalia S, et al. Diabetes Canada 2016 clinical practice guidelines for the prevention and management of diabetes in Canada: Pharmacologic management of type 2 diabetes: 2016 Interim Update. Can J Diabetes 2016;40:484–6.
2. American Diabetes Association. Pharmacologic approaches to glycemic treatment. Sec. 8. In Standards of Medical Care in Diabetes–2017. Diabetes Care 2017;40(Suppl. 1):S64–74.
3. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015;58:429–42.
4. International Diabetes Federation. IDF clinical practice recommendations for managing type 2 diabetes in primary care: Initial pharmacologic treatment. 2017. www.idf.org/managing-type2-diabetes. Accessed February 8, 2018.
5. 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;36:733–46.
6. Lalau J-D, Arnouts P, Sharif A, et al. Metformin and other antidiabetic agents in renal failure patients. Kidney Int 2015;87:308–22.
7. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34:1431–7.
8. Bakris GL, Molitch ME. Should restrictions be relaxed for metformin use in chronic kidney disease? Yes, they should be relaxed! What's the fuss? Diabetes Care 2016;39:1287–91.
9. Canadian Institute for Health Information. Canadian Organ Replacement Register Annual Report: Treatment of end-stage organ failure in Canada, 2004 to 2013. 2015. https://secure.cihi.ca/free_products/2015_CORR_AnnualReport_ENweb.pdf. Accessed February 9, 2018.
10. Warram JH, Gearin G, Laffel L, et al. Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. J Am Soc Nephrol 1996;7:930–7.
11. Reenders K, de Nobel E, van den Hoogen HJ, et al. Diabetes and its long-term complications in general practice: a survey in a well-defined population. Fam Pract 1993;10:169–72.
12. Weir MR. Albuminuria predicting outcome in diabetes: Incidence of microalbuminuria in Asia-Pacific Rim. Kidney Int 2004;66:S38–9.
13. Brier ME, Bays H, Sloan R, et al. Pharmacokinetics of oral glyburide in subjects with non-insulin-dependent diabetes mellitus and renal failure. Am J Kidney Dis 1997;29:907–11.
14. Jonsson A, Rydberg T, Ekberg G, et al. Slow elimination of glyburide in NIDDM subjects. Diabetes Care 1994;17:142–5.
15. Krepinsky J, Ingram AJ, Clase CM. Prolonged sulfonylurea-induced hypoglycemia in diabetic patients with end-stage renal disease. Am J Kidney Dis 2000;35:500–5.
16. Rachmani R, Slavachevski I, Levi Z, et al. Metformin in patients with type 2 diabetes mellitus: Reconsideration of traditional contraindications. Eur J Intern Med 2002;13:428–33.
17. Assan R, Heuclin C, Girard JR, et al. Phenformin-induced lactic acidosis in diabetic patients. Diabetes 1975;24:791–800.
18. Sambol NC, Chiang J, Lin ET, et al. Kidney function and age are both predictors of pharmacokinetics of metformin. J Clin Pharmacol 1995;35:1094–102.
19. Bolen S, Feldman L, Vassy J, et al. Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007;147:386–99.
20. Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010;(40):CD002967.
21. Lalau JD, Lacroix C, Compagnon P, et al. Role of metformin accumulation in metformin-associated lactic acidosis. Diabetes Care 1995;18:779–84.
22. Schrier RW, Wang W, Poole B, et al. Acute renal failure: Definitions, diagnosis, pathogenesis, and therapy. J Clin Invest 2004;114:5–14.
23. Lu WR, Defilippi J, Braun A. Unleash metformin: Reconsideration of the contraindication in patients with renal impairment. Ann Pharmacother 2013;47:1488–97.
24. U.S. Department of Health and Human Services. Guidance for industry: Pharmacokinetics in patients with impaired renal function: Study design, data analysis, and impact on dosing and labelling. 2010. https://www.fda.gov/downloads/drugs/guidances/ucm204959.pdf. Accessed February 8, 2018.

25. European Medicines Agency. Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. 2004. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003123.pdf. Accessed February 8, 2018.
26. U.S. Food and Drug Adminstration. FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. 2016. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf. Accessed February 8, 2018.
27. European Medicines Agency. Use of metformin to treat diabetes now expanded to patients with moderately reduced kidney function: Recommendations for patients with kidney impairment updated in product information. 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Metformin_31/WC500214235.pdf. Accessed February 8, 2018.
28. American College of Radiology. ACR Manual on Contrast Media Version 10.3. 2017. https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed February 9, 2018.
29. Lalau J-D, Kajbaf F, Bennis Y, et al. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B, or 4. Diabetes Care 2018;dc172231.