Title

Metformin in chronic kidney disease: a strong dose of caution

Journal

Kidney International, 98(5)

ISSN

0085-2538

Authors

Hanna, Ramy M
Rhee, Connie M
Kalantar-Zadeh, Kamyar

Publication Date

2020-11-01

DOI

10.1016/j.kint.2020.04.060

renal function: a cohort study from the Swedish National Diabetes Register. *BMJ Open*. 2012;2:e001076.
7. Eppenga WL, Lalmohamed A, Geerts AF, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care*. 2014;37:2218–2224.
8. Inzucchi SE, Lipska KJ, Mayo H, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA*. 2014;312:2668–2675.
9. Hung SC, Chang YK, Liu JS, et al. Metformin use and mortality in patients with advanced chronic kidney disease: national, retrospective, observational, cohort study. *Lancet Diabetes Endocrinol*. 2015;3:605–614.
10. Kwon S, Kim YC1, Park JY, et al. The long-term effects of metformin on patients with type 2 diabetic kidney disease. *Diabetes Care*. 2020;43:948–955.
11. Lin CX, Li Y, Liang S, Liang S, Tao J, et al. Metformin attenuates cyclosporine A-induced renal fibrosis in rats. *Transplantation*. 2019;103:e285–e296.
12. Satriano J, Sharma K, Blantz RC, et al. Induction of AMPK activity corrects early pathophysiological alterations in the subtotal nephrectomy model of chronic kidney disease. *Am J Physiol Renal Physiol*. 2013;305:F727–F733.
13. Hardie DG. AMPK: positive and negative regulation, and its role in whole-body energy homeostasis. *Curr Opin Cell Biol*. 2015;33:1–7.
14. Rajani R, Pastor-Soler NM, Hallows KR. Role of AMP-activated protein kinase in kidney tubular transport, metabolism, and disease. *Curr Opin Nephrol Hypertens*. 2017;26:375–383.
15. Lee M, Katerelos M, Gleich K, et al. Phosphorylation of acetyl-CoA carboxylase by AMPK enhances anaerobic metabolism reduces renal fibrosis and is essential for the anti-fibrotic effect of metformin. *J Am Soc Nephrol*. 2018;29:2326–2336.
16. Neven E, Vervaet B, Brand K, et al. Metformin prevents the development of severe chronic kidney disease and its associated mineral and bone disorder. *Kidney Int*. 2018;94:102–113.
17. Cao X, Li H, Tao H, et al. Metformin inhibits vascular calcification in female rat aortic smooth muscle cells via the AMPK-eNOS-NO pathway. *Endocrinology*. 2013;154:3680–3689.
18. Komaba H. Energy sensor as a new regulator of FGF23 synthesis. *Kidney Int*. 2018;94:453–455.
19. Glosse P, Feger M, Mutig K, et al. AMP-activated kinase is a regulator of fibroblast growth factor 23 production. *Kidney Int*. 2018;94:491–501.
20. Lalau JD, Arnouts P, Sharif A, et al. Metformin and other antidiabetic agents in renal failure patients. *Kidney Int*. 2015;87:308–322.
21. Hung AM, Roumie CL, Greevy RA, et al. Kidney function decline in metformin versus sulfonylurea initiators: assessment of time-dependent contribution of weight, blood pressure, and glycemic control. *Pharmacoepidemiol Drug Saf*. 2013;22:623–631.
22. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in enhances anaerobic metabolism populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. *Ann Intern Med*. 2017;166:191–200.
23. Stephen J, Anderson-Haag TL, Gustafson S, et al. Metformin use in kidney transplant recipients in the United States: an observational study. *Am J Nephrol*. 2014;40:546–553.
24. Charytan DM, Solomon SD, Ivanovich P, et al. Metformin use and cardiovascular events in patients with type 2 diabetes and chronic kidney disease. *Diab Obes Metab*. 2019;21:1199–1206.
25. Levin A, Tonelli M, Bonventre J, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet*. 2017;390:1888–1937.
26. Lalau JD, Farshad K, Youssef B, et al. Rationale for the prescription of metformin in patients with CKD 3A, 3B, and 4. *Diabetes Care*. 2018;41:547–555.

[1]*Department of Medicine, Division of Nephrology, University of California Irvine Medical Center, Irvine, California, USA;* [2]*Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology, Hypertension and Kidney Transplantation, Department of Medicine, University of California Irvine School of Medicine, Orange, California, USA;* [3]*Nephrology Section, Department of Medicine, Veterans Affairs Long Beach Healthcare System, Long Beach, California, USA; and* [4]*Lundquist Institute at Harbor–UCLA Medical Center, Torrance, California, USA*

Correspondence: *Kamyar Kalantar-Zadeh, Division of Nephrology, Hypertension and Kidney Transplantation, University of California Irvine, 101 The City Drive South, Orange, California 92868, USA. E-mail: kkz@uci.edu*

counterpoint

Metformin in chronic kidney disease: a strong dose of caution

Ramy M. Hanna[1,2], Connie M. Rhee[1,2,3] and Kamyar Kalantar-Zadeh[1,2,3,4]

Kidney International (2020) **98,** 1101–1105; https://doi.org/10.1016/j.kint.2020.04.060

Metformin is a biguanide anti-hyperglycemic that inhibits hepatic gluconeogenesis, decreases enterocyte intake of glucose, and attunes cells for peripheral glucose uptake.[1] It has become a nearly universally used first-line agent in the treatment of diabetes mellitus and impaired glucose tolerance.[2] Metformin is a historic treatment for diabetes mellitus, with lilac goat's rue used in French herbal therapy in the Middle Ages.[1] The active ingredients, guanidino compounds, were identified and chemically isolated in the 1920s.[1] These compounds do have a potentially hazardous side because they are also uremic toxins, which can result in hypoglycemia as their concentrations rise in acute kidney injury and chronic kidney disease (CKD). It is in the context of this background that we discuss a derivative of these compounds, metformin, which was officially approved by the US Food and Drug Administration in 1995.

The benefits of metformin in improving insulin sensitivity, promoting weight loss, and improving hepatic steatosis have been useful, and millions of patients have been exposed to this agent worldwide. Cardiovascular benefits have been reported,[2] although these positive findings are not unique to biguanides and are increasingly being duplicated and surpassed in studies of patients receiving sodium glucose cotransporter (SGLT2) inhibitors.[3] The trade-off has been the development of life-threatening metformin-associated lactic acidosis (MALA) in patients with impaired estimated glomerular filtration rate (eGFR),

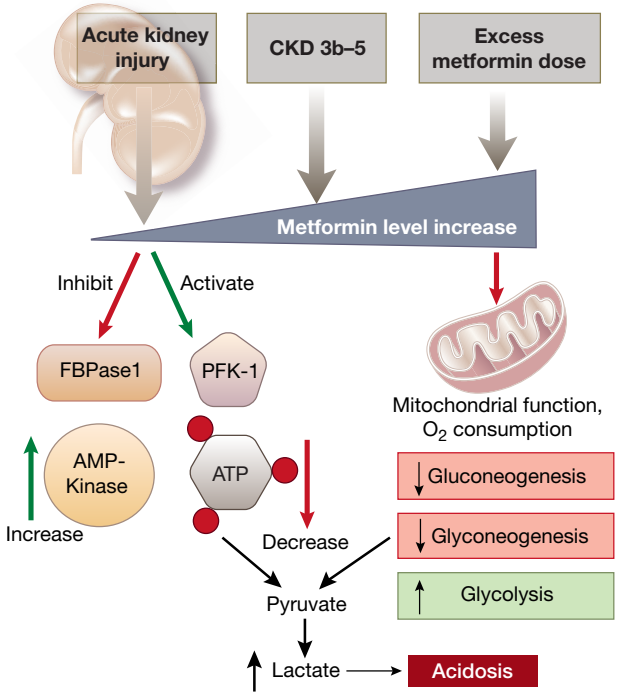

Figure 1 | Pathways to lactic acidosis from metformin use. AMP-kinase, adenosine monophosphate–activated protein kinase; ATP, adenosine triphosphate; CKD, chronic kidney disease; FBPase 1, fructose 1,6 bisphosphatase (1); GFR, glomerular filtration rate; O_2, oxygen; PKF, phosphofructokinase-1.

hepatic insufficiency, and congestive heart failure.[1,4] The rate of lactic acidosis has been reported as 2.2 events per 100,000 patients in patients without renal dysfunction but 7.4 per 100,000 patients in the CKD population. Although the event rate is small, the fatality rate is exceedingly high, with an astounding mortality rate of 50%.[1,2] The mechanism of lactic acidosis in metformin administration is lactic acid production, accumulation, and decreased clearance of lactic acid.[1] Figure 1 demonstrates how metformin administration results in lactic acidosis.[5]

Metformin was actually not the first biguanide compound used in the treatment of diabetes mellitus. In 1970, phenformin and buformin were used extensively and were removed from the market due to reports of multiple cases of lactic acidosis.[4] Metformin was more readily cleared and so presented less of a risk of lactic acidosis in patients with normal kidney function.[1] Metformin levels rise 75% when the eGFR drops to the equivalent of Kidney Disease Improving Global Outcomes stage 3a–b kidney disease (eGFR 30–59).[6] The mechanism of lactic acidosis is clearly the inhibition of gluconeogenesis, the same mechanism responsible for the agent's antihyperglycemic effect.[1] Large-scale studies were held to examine the rate of development of MALA. Connelly *et al.* used a case-control design and looked at development of anion gap metabolic acidosis with a serum bicarbonate of 18 meq/l and a lactic acid level >5 meq/l.[7] The study used the Genetics of Diabetes Audit and Research Tayside (GoDART) and involved 846 individuals. The relative risk of a patient developing MALA was 2.3 times higher in the metformin arm. The risk of lactic acidosis increased with degree of CKD and eGFR decline.[7]

Bell *et al.* conducted an even larger-scale study of 25,148 patients with type II diabetes that attempted to use acute kidney injury as a proxy for lactic acidosis.[8] Although this was not significant, there was a 1.3-fold higher risk of lactic acidosis in patients who had used metformin at any time previously.[8] This is important in discerning that acute kidney injury is not the cause of MALA; rather, it is eGFR decline that predicts metformin buildup and direct toxicity from the agent's action against mitochondria. Given the aforementioned historical data with other biguanides and the 2 prior studies, the original recommendations for metformin suggested using a serum creatinine

of 1.4 mg/dl in males and 1.3 mg/dl in females.[2] In many cases, this corresponded to stage 3a CKD (eGFR 45–60 ml/min); but the inaccuracy of GFR estimating equations meant that this creatinine covered a wide range of actual GFRs. Ekstrom *et al.* studied 51,675 and suggested an inflection point toward increased cardiovascular, mortality, and infection risks at an estimated GFR of 45 ml/min.[9]

Outside of the United States, restrictions on metformin use were even more liberal than the creatinine criteria. Taiwanese data from before 2009 is instructive; at that time, patients with CKD 4 and 5 and end-stage renal disease were prescribed metformin.[4,10] Hung *et al.* followed mortality data on patients receiving erythropoietin stimulating agents,[11] which are restricted in Taiwan in patients with creatinine >6 mg/dl, corresponding to CKD 5 and end-stage renal disease. Of the 1005 metformin users in this database, 813 were matched using propensity scores to 2395 patients who were not taking metformin. A statistically significant increased mortality risk (hazard ratio = 1.35) was noted, with a dose response observed with increasing doses of metformin. A higher risk of metformin-induced lactic acidosis was found in metformin users versus nonusers, but the difference was not statistically significant despite a hazard ratio of 1.3.[11]

The US Food and Drug Administration guidelines for metformin prescription were changed in 2016 to allow prescribing this agent in patients with an eGFR ≥30 ml/min.[6] Although the use of eGFR is prudent and more specific than the use of serum creatinine, there is some evidence that at the 30 to 45 ml/min eGFR that metformin buildup can contribute to morbidity and mortality generally, and to MALA specifically.[6] It is important also to call to mind that GFR estimations, are at best, estimations, and calculated eGFR can vary between creatinine and cystatin C. Measures that are closer to a gold standard include nuclear medicine renal scintalligraphy and the accurate but cumbersome and rarely used inulin clearance. This error in estimating renal clearance is also confounded by the dynamic and often progressive nature of CKD and diabetic kidney disease.[4]

The data supporting an inflection point where the risks of lactic acidosis due to metformin use rise are from population studies showing increased MALA risk below various eGFR thresholds of <45 or <60 ml/min per 1.73 m^2.[10,12,13] Because the precise eGFR threshold for metformin toxicity remains uncertain and the risks of overestimation of renal function remain a possibility, the recommendation of the US Food and Drug Administration to drop the eGFR threshold for caution to 30 ml/min comes into question. The current recommendation to give metformin freely in eGFR >60 ml/min, with careful review if use and dose reduction between eGFR or 45 ml/min to 60 ml/min makes sense. The effect of a medication in which levels build up compounds the problem.[14] Various newer studies cite concerns about use of metformin in CKD.[7,10–12,15–18] These studies include Gosmanova *et al.*, showing higher lactate levels in elderly patients[17]; Corchia *et al.*, quoting 23% mortality rate of MALA as worse than the 7% mortality rate of metformin-*induced* lactic acidosis[16]; Angioi *et al.*, showing 21.4% mortality in patients with MALA despite being treated with slow low efficiency dialysis[15]; and Mariano *et al.*, who found a rate of 12.04 per 100,000 cases of MALA among metformin-treated diabetics.[18] Table 1 includes these results and systematic reviews, along with other trials showing more positive data regarding risk of developing MALA, for the sake of a balanced presentation.[7–13,15–21]

The SGLT2 inhibitors vetted by CREDENCE trials demonstrate even greater cardioprotective potential than biguanides. Their renal risks, although initially a concern, have been shown to also be very low likelihood events.[3] Risk of cardiovascular death has decreased by 2% absolute risk and 33% relative risk in trials of SGLT2 blockade.[3] This suggests that biguanides are not irreplaceable agents, and SGLT2 inhibitors will likely overtake them and have a superior safety margin in CKD patients. Nevertheless, the makers of SGLT2 inhibitors wisely recommend careful monitoring with an eGFR <45 ml/min.[3] We would do well to recall Dr Frances Oldham Kelsey's principled crusade against the dangers of thalidomide during pregnancy. She proclaimed that the US Food and Drug Administration should "never again" compromise safety, despite dogged proindustry lobbyists using every effort to obscure the truth. It is our responsibility as physicians to advocate for our patients, without compromise. This high calling is particularly aimed at physician thought leaders at the crossroads of endocrinology and nephrology.

Developments in hematology may also aid in making metformin safer for patients in the

Table 1 | Studies and meta-analyses regarding metformin use

Study	Findings	N taking Metformin	Year	Reference
Connelly *et al.*[a]	Clear association was found between metformin and lactic accumulation and lactic acidosis	1746	2017	7
Bell *et al.*[a]	No evidence of acute kidney injury on metformin	25,148	2017	8
Ekstrom *et al.*[a]	Worsening safety of metformin at an eGFR of ≤45 ml/min with risk for serious infection, CVD, and AC mortality	51,675	2012	9
Yeh *et al.*[a]	Lactic acid level in MILA correlated with mortality rate	253	2017	10
Hung *et al.*[a]	Hazard ratio of 1.35 for mortality among metformin users Dose response: higher mortality risk with higher dose	831	2015	11
Eppenga *et al.*[a]	Risk of lactic acidosis 7.4/100,000 person years in metformin users vs. 2.2/100,000 person years in nonusers	223,968	2014	12
Richy *et al.*[a]	No difference in lactic acidosis across range of renal function	77,601	2014	13
Angioi *et al.*[a]	MALA mortality rate with slow low efficiency dialysis as 21.4%	28	2018	15
Corchia *et al.*[a]	MILA mortality rate of 7% and MALA mortality rate of 23%	173	2019	16
Gosmonava *et al.*[a]	Higher lactate level in elderly patients	92	2020	17
Mariano *et al.*[a]	Rate of MALA 12.04/100,000	141,174	2017	18
Chartyan *et al.*[b]	Metformin safe for use in CKD 3 and lower risk of cardiovascular events	591	2019	19
Kwon *et al.*[b]	No increased risk of MALA	10,426[c]	2020	20
Lalau *et al.*[b]	If properly dose adjusted, metformin Is safe in CKD 3–4, without high levels of metformin in blood	69	2018	21

AC, all cause; CKD, chronic kidney disease; CVD, cardiovascular disease; MALA, metformin-associated lactic acidosis; MILA, metformin-induced lactic acidosis.
[a]Studies showing deleterious metformin safety profile in CKD.
[b]Studies showing favorable safety results of metformin in CKD.
[c]Metformin and sulfonylurea groups.

intermediate zone of risk (CKD 3b–4, with eGFR of 30–45 ml/min). Recent studies found that coadministration of metformin with prolyl hydroxylase inhibitors–hypoxia-inducing factor stabilizers may decrease risk of MALA. Sugahara *et al.*[22] and Oyaizu-Toramaru *et al.*[23] both present an attractive although expensive therapeutic option to decrease lactic acidosis in patients with moderate CKD while improving hemoglobin levels. However, many patients with diabetic kidney disease who receive metformin may not have anemia and thus not require concurrent therapy with these agents. Thus, the clinical utility of this approach under real-world scenarios may be questionable. We believe that metformin is a drug that was prematurely deemed safe in advanced CKD,[6,24,25] and past guidelines of prominent organization remind us of earlier trepidation of its use in CKD.[25] Clearly, a stark accounting of the benefits and risks are in order. Without magnifying risk or minimizing gain, a reasonable recommendation of reserving metformin use for patients with an estimated GFR of 60 ml/min, with review of use below this and down to 45 ml/min, can be made. The SGLT2 inhibitors show great potential and a potential improvement in risk-factor profile in patients with CKD 3a–b. These heartening new trial results give hope for a superior agent that will be available to combat diabetes, cardiovascular disease, and even diabetic kidney disease. Ultimately, we can provide metformin to our patients with mild and moderate CKD—but with a strong dose of caution.

DISCLOSURE

RMH is part of the Alexion Speaker's Bureau for Eculizumab and Ravulizumab. CMR has received honoraria and/or support from Astra-Zeneca, Fresenius, Ostuka, Reata, and Roche. KK-Z has received honoraria or support from Abbott, Abbvie, Alexion, Amgen, Astra-Zeneca, Aveo, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Novartis, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZS-Pharma.

ACKNOWLEDGMENTS

KK-Z is supported by the National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) grant K24-DK091419 and by philanthropist grants from Mr. Harold Simmons, Mr. Louis Chang, Dr. Joseph Lee, and AVEO. CMR is supported by research grants from the NIH/NIDDK grants K23-DK102903, R03-DK114642, and R01-DK122767 and by philanthropist grants from Dr. Joseph Lee.

REFERENCES

1. Rhee CM, Kalantar-Zadeh K. Diabetes mellitus: complex interplay between metformin, AKI and lactic acidosis. *Nat Rev Nephrol*. 2017;13:521–522.

2. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care*. 2014;37:2864–2883.
3. Neumiller JJ, Rhee CM, Kalantar-Zadeh K. Will canagliflozin lend credence to the potential effects of sodium-glucose co-transporter 2 inhibitors on renal endpoints in diabetic nephropathy. *Am J Nephrol*. 2017;46:459–461.
4. Rhee CM, Kovesdy CP, Kalantar-Zadeh K. Risks of metformin in Type 2 diabetes and chronic kidney disease: lessons learned from Taiwanese data. *Nephron*. 2017;135:147–153.
5. Kalantar-Zadeh K, Uppot RN, Lewandrowski KB. Case records of the Massachusetts General Hospital. Case 23-2013. A 54-year-old woman with abdominal pain, vomiting, and confusion. *N Engl J Med*. 2013;369:374–382.
6. Kalantar-Zadeh K, Rhee CM. Metformin in chronic kidney disease: more harm than help? *Lancet Diabetes Endocrinol*. 2015;3:579–581.
7. Connelly PJ, Lonergan M, Soto-Pedre E, et al. Acute kidney injury, plasma lactate concentrations and lactic acidosis in metformin users: a GoDarts study. *Diabetes Obes Metab*. 2017;19:1579–1586.
8. Bell S, Farran B, McGurnaghan S, et al. Risk of acute kidney injury and survival in patients treated with metformin: an observational cohort study. *BMC Nephrol*. 2017;18:163.
9. Ekstrom N, Schioler L, Svensson AM, 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.
10. Yeh HC, Ting IW, Tsai CW, et al. Serum lactate level and mortality in metformin-associated lactic acidosis requiring renal replacement therapy: a systematic review of case reports and case series. *BMC Nephrol*. 2017;18:229.
11. Hung S, Chang Y, Liu J, et al. Metofrmin use and mortaity in patients with advanced chronic kidney disease: national, retropsective, observational, cohort study. *Lancet Diabetes Endocrinol*. 2015;3:605–614.
12. Eppenga WL, Lalmohamed A, Geerts AF, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care*. 2014;37:2218–2224.
13. Richy FF, Sabido-Espin M, Guedes S, et al. Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: a retrospective cohort study. *Diabetes Care*. 2014;37:2291–2295.
14. Kalantar-Zadeh K, Derose SF, Nicholas S, et al. Burnt-out diabetes: impact of chronic kidney disease progression on the natural course of diabetes mellitus. *J Ren Nutr*. 2009;19:33–37.
15. Angioi A, Cabiddu G, Conti M, et al. Metformin associated lactic acidosis: a case series of 28 patients treated with sustained low-efficiency dialysis (SLED) and long-term follow-up. *BMC Nephrol*. 2018;19:77.
16. Corchia A, Wynckel A, Journet J, et al. Metformin-related lactic acidosis with acute kidney injury: results of a French observational multicenter study. *Clin Toxicol (Phila)*. 2020;58:575–582.
17. Gosmanova EO, Shahzad SR, Sumida K, et al. Metformin is associated with increase in lactate level in elderly patients with type 2 diabetes and CKD stage 3: a case-control study. *J Diabetes Complications*. 2020;34:107474.
18. Mariano F, Pozzato M, Inguaggiato P, et al. Metformin-associated lactic acidosis undergoing renal replacement therapy in intensive care units: a five-million population-based study in the north-west of Italy. *Blood Purif*. 2017;44:198–205.
19. Charytan DM, Solomon SD, Ivanovich P, et al. Metformin use and cardiovascular events in patients with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab*. 2019;21:1199–1208.
20. Kwon S, Kim YC, Park JY, et al. The long-term effects of metformin on patients with type 2 diabetic kidney disease. *Diabetes Care*. 2020;43:948–955.
21. Lalau JD, 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;41:547–553.
22. Sugahara M, Tanaka T, Nangaku M. Prolyl hydroxylase domain inhibitors as a novel therapeutic approach against anemia in chronic kidney disease. *Kidney Int*. 2017;92:306–312.
23. Oyaizu-Toramaru T, Suhara T, Hayakawa N, et al. Targeting oxygen-sensing prolyl hydroxylase for metformin-associated lactic acidosis treatment. *Mol Cell Biol*. 2017;37:e00248-17.
24. Kalantar-Zadeh K, Kovesdy CP. Should restrictions be relaxed for metformin use in chronic kidney disease? No, we should never again compromise safety!. *Diabetes Care*. 2016;39:1281–1286.
25. Rhee CM, Kalantar-Zadeh K. Restricting metformin in CKD: continued caution warranted. *Am J Kidney Dis*. 2015;66:1101–1102.

from the editor

Metformin—to use or not to use . . . is that the question?

Kidney International (2020) **98,** 1105–1107; https://doi.org/10.1016/j.kint.2020.07.021

Metformin improves insulin sensitivity, reduces body weight, and improves cardiovascular events. Although recent clinical trials have provided strong evidence of improvement of cardiovascular and kidney outcomes by sodium glucose cotransporter (SGLT2) inhibitors,[1] it is an overstatement to say that metformin had been the only drug with firm evidence of improvement of hard endpoints among a variety of antidiabetic agents before the SGLT2 inhibitor era.

Several studies have shown beneficial effects of metformin that are independent of glucose control. Hypoxia is a final common pathway to end-stage kidney disease and plays a crucial role in the pathogenesis of diabetic kidney disease (DKD). Systemic metabolic disorders such as hyperglycemia cause alterations of kidney metabolism, and pharmacologic activation of hypoxia-inducible factor, a master regulator of defense against hypoxia,