LETTERS TO THE EDITOR

Restricting Metformin in CKD: Continued Caution Warranted

To the Editor:

Given the low observed incidence of metformin-associated lactic acidosis (MALA) in a systematic review of diabetic patients with and without CKD,[1] a commentary by Stanton[2] recommends liberalizing metformin use in CKD, namely, continuation at a reduced dose over an eGFR range of 30-60 mL/min/1.73 m^2. The FDA black box warning and NKF-KDOQI recommendations advise against metformin with Scr levels ≥ 1.4 mg/dL and ≥1.5 mg/dL in men and women, respectively (Table 1).[3,4] We are concerned about relaxing restrictions for 3 primary reasons.

First, MALA fatality is high (45%-48%).[5,6] The multitude of alternative diabetic pharmacotherapies calls into question whether a small risk for death justifies any benefit of metformin.[7,8]

Second, MALA incidence may be underestimated. Randomized trials of metformin are not generalizable to real-life scenarios given their strict inclusion/exclusion criteria and monitoring. While large observational studies may better reflect real-life practices, MALA event capture may be poor.

Third, patients with CKD are susceptible to AKI.[9] The metformin package insert advises against use in conditions leading to AKI, including "cardiovascular collapse (shock), acute myocardial infarction, and septicemia." Such complications are common in CKD, substantially increasing MALA risk.[9]

No trials have evaluated the safety and effectiveness of metformin specifically in CKD. New data show that metformin users had higher mortality compared with nonusers among patients with Scr > 6 mg/dL in Taiwan, where until recently there were no metformin restrictions in CKD.[10] While studies are needed to granularly determine the eGFR threshold above which metformin is safe, we recommend a conservative approach: metformin use should be reviewed with eGFRs of 45 to 60 mL/min/1.73 m^2 and discontinued with eGFRs < 45 mL/min/1.73 m^2, and treatment should be interrupted with any illness heightening AKI risk regardless of eGFR.

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Table 1. Clinical Practice Guidelines Regarding Metformin Use and Kidney Function

Clinical Practice Guideline (Year)	Recommendations
US Food and Drug Administration (1994)	Metformin use contraindicated at Scr ≥ 1.4 mg/dL in men and ≥1.5 mg/dL in women
NKF-KDOQI (2012)	Metformin use contraindicated at Scr ≥ 1.4 mg/dL in men and ≥1.5 mg/dL in women
American Diabetes Association and European Association for Study of Diabetes (2012)	Metformin dose reduction if eGFR < 45 mL/min/1.73 m^2 Metformin use contraindicated if eGFR < 30 mL/min/1.73 m^2
KDIGO (2012)	Metformin use reviewed if eGFR of 30-44 mL/min/1.73 m^2 Metformin use contraindicated if eGFR < 30 mL/min/1.73 m^2 Metformin temporarily discontinued if eGFR < 60 mL/min/1.73 m^2 with a concurrent serious illness increasing the risk for AKI
National Institute for Health and Clinical Excellence (2009)	Metformin use reviewed if Scr > 1.5 mg/dL or eGFR < 45 mL/min/1.73 m^2 Metformin use contraindicated if Scr > 1.7 mg/dL or eGFR < 30 mL/min/1.73 m^2
Canadian Diabetes Association (2013)	Metformin use cautioned if eGFR < 60 mL/min/1.73 m^2 Metformin use contraindicated if eGFR < 30 mL/min/1.73 m^2
Royal Australian College of General Practitioners (2014-2015)	Metformin use cautioned and dose reduction advised if eGFR 30-45 mL/min/1.73 m^2 Metformin use contraindicated if eGFR < 30 mL/min/1.73 m^2
Japanese Society of Nephrology (2012)	Metformin use re-evaluated if eGFR < 45 mL/min/1.73 m^2 Metformin use contraindicated if eGFR < 30 mL/min/1.73 m^2

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NKF-KDOQI, National Kidney Foundation–Kidney Disease Outcomes Quality Initiative; Scr, serum creatinine.

national, retrospective, observational, cohort study. *Lancet Diabetes Endocrinol*. 2015;3(8):605-614.

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In Reply to 'Restricting Metformin in CKD: Continued Caution Warranted'

I appreciate the comments from Drs Rhee and Kalantar-Zadah.[1] Certainly caution is always warranted when using metformin in patients with CKD and the dose should be adjusted or held, as noted in my commentary.[2] In response to the first point raised by Drs Rhee and Kalantar-Zadeh, there are new alternatives to metformin, but the long-term safety of these medications is unknown in the CKD and non-CKD populations. For example, recently, diabetic ketoacidosis has been associated with SGLT2 inhibitors,[3] and severe disabling joint pain, with DPP4 inhibitors.[4] Major diabetes organizations select metformin as the first choice because of its proven efficacy and overall safety record.[5,6] Regarding their second concern, I agree that randomized studies of metformin may underestimate the incidence of MALA, but the study by Inzucchi et al[7] and others are reports from large observational databases and randomized studies. The large sizes of these databases likely provide a reasonable estimate of MALA. With respect to their final point, patients with CKD are certainly more susceptible to AKI, but most of these situations are predictable. The authors cite a just-published article from Hung et al[8] showing increased death rates in patients with CKD using metformin who have an Scr > 6 mg/dL. Nobody is suggesting using metformin at CKD stage 4 or 5. Hung et al note that "metformin provides clinical benefits in patients with mild-to-moderate chronic kidney disease (eGFR 30–60 mL/min per 1.73 m^2)."[8(p611)] Certainly surveillance and good judgment by the physician will help our patients both achieve excellent management of their diabetes and minimize risk from metformin.

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Methodological Concerns About a Systematic Review and Meta-analysis of the Mortality Risk of Darbepoetin Alfa Versus Epoetin Alfa

To the Editor:

We read the recent article from Wilhelm-Leen and Winkelmayer[1] with great interest and appreciate the authors' efforts to summarize the effects of 2 kinds of erythropoiesis-stimulating agents. However, we would like to point out 4 concerns regarding this work.

First, the authors used free-text terms only in their search strategy. To retrieve as many relevant studies as possible, it is important to use a combination of subject terms selected from a controlled vocabulary and free-text terms. Using free-text terms only may reduce search quality.[2]

Second, searching international trial registries (eg, the ClinicalTrials.gov registries) is necessary to avoid publication bias, especially when conducting systematic reviews of interventions.

Third, the study was performed only partially in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines in that it was not registered in PROSPERO (International Prospective Register of Systematic Reviews). PROSPERO registration is important to avoid unintentional duplication of effort in preparing systematic reviews.[3]

Last, it is essential for any summary estimate in a meta-analysis to have an associated quality assessment table that evaluates each study in the analysis. Without such a table, the reliability of the data included in the meta-analysis is unknown.

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Wilhelm-Leen et al declined to respond.

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