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Clarifying the relationship between metformin, acute kidney injury and lactic acidosis

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We read, with interest, the News & Views article by C. Rhee and K. Kalantar-Zadeh (Diabetes mellitus: Complex interplay between metformin, AKI and lactic acidosis. *Nat. Rev. Nephrol.* **13**, 521–522 (2017))[1], which discusses our recent work looking at the relationship between metformin, acute kidney injury (AKI) and lactic acidosis[2,3]. In response to this discussion of some of our findings, we would like to highlight several points.

First, Connelly *et al.* demonstrated that 80% of lactic acidosis within the study cohort occurred in the presence of AKI[3]. In view of the effectiveness of treatment and increasing evidence of the beneficial cardiovascular effects of metformin, we feel that metformin should be only temporarily discontinued in patients with a condition that predisposes them to acute AKI; this advice is similar to the advice given for angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers.

Second, although we acknowledge the difficulties of accurately identifying metformin-associated lactic acidosis (MALA) cases in observational studies, we do not agree that the crude incidence rate of lactic acidosis observed in the study by Connelly *et al.* is biased because it differs from rates reported by others. Instead, we would like to emphasize that crude incidence rates disregard the structure of the population. Thus, comparing crude incidence rates alone can be misleading before standardization is carried out to remove the effect of differential structures in populations under comparison.

Third, it was also suggested that the absence of a 'new-user' design in the study by Bell *et al.*[2] may not have accounted for patients who stopped using metformin or died due to its adverse effects before study entry, biasing results towards a protective effect. Our study population comprised 63% incident users over a long period, making survivor bias a less likely explanation of our findings.

Fourth, the elevated risk of developing AKI that is associated with 'ever' having been on or currently being on metformin is due to within and between-person allocation bias, where being prescribed metformin is a marker for other comorbidities that make the patient more vulnerable to AKI. The fact that AKI incidence is not elevated in patients during periods on the drug versus periods off the drug suggests that the drug itself is not increasing the risk of AKI.

Finally, we do not agree with the recommendation made by C. Rhee and K. Kalantar-Zadeh that the use of metformin should be restricted in patients with chronic kidney disease (CKD), particularly in view of the increasing evidence base that supports metformin safety in patients with CKD[4,5]. We eagerly await further pharmacokinetic studies on the safety and efficacy of metformin in these patients.

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Competing interests statement
The authors declare no competing interests.