

## CHRONIC KIDNEY DISEASE

# Metformin increases risk of mortality in patients with advanced chronic kidney disease

**T**he use of metformin in patients with type 2 diabetes mellitus (T2DM) and advanced chronic kidney disease (CKD) confers a 35% increased risk of all-cause mortality compared to those not treated with metformin, according to new findings published in *The Lancet Diabetes & Endocrinology*. The researchers say their observational cohort study is the first of its kind to study the association between metformin and clinical outcomes in this patient population.

Metformin is recommended as a first-line therapy for T2DM, but until recently had been contraindicated in patients with both T2DM and CKD owing to a perceived risk of lactic acidosis. Accumulating data, however, has shown that the overall incidence of lactic acidosis with metformin use is almost indistinguishable from the background rate in the overall diabetes population, and has led to more relaxed clinical guidelines to permit metformin use in patients with mild-to-moderate CKD. “There is an ongoing debate as to whether metformin can be prescribed more widely to patients with advanced CKD, but until now, no studies had evaluated the risks and benefits of metformin use in these patients,” explains researcher Der-Cherng Tarn. “Here we aimed to assess the safety of metformin in patients with T2DM and advanced CKD.”

The investigators used Taiwan’s National Health Insurance Research Database (NHIRD) to assess the safety of metformin in patients with T2DM and serum

creatinine levels  $>530 \mu\text{mol/l}$  (stage 5 CKD). Data were obtained for patients enrolled between 2001 and 2009, before Taiwan’s prescribing guidelines for metformin contraindicated its use in men and women with serum creatinine levels  $\geq 133$  and  $\geq 124 \mu\text{mol/l}$ , respectively. Baseline data for serum creatinine and estimated glomerular filtration rate were not available in the NHIRD; therefore, the selection of patients with advanced CKD was inferred based on the national health insurance regulation for prescription of an erythropoietin-stimulating agent in patients with serum creatinine level  $>530 \mu\text{mol/l}$ . The primary outcome of all-cause mortality and the number of admissions for metabolic acidosis was assessed.

A total of 12,350 patients were identified with T2DM and stage 5 CKD from the NHIRD during the study period. In this cohort, 1,005 individuals were users and 11,345 were non-users of metformin. The patients were matched in a 1:3 ratio according to propensity score, resulting in 813 metformin users matched to 2,439 non-users. The two cohorts were similar with respect to their baseline characteristics.

In the matched cohort, 53% of the metformin population died during follow-up, compared to 41% in the non-user population. Further analyses indicated that metformin use was associated with a higher risk of admission for cardiovascular disease before death, compared to those not prescribed metformin. After multivariate adjustment, metformin use remained a significant independent risk factor for mortality, imposing a 35% increased risk of death in patients with T2DM and advanced CKD. The increased risk of mortality due to

metformin was dose-dependent—patients who were prescribed 501–1,000 mg daily had a nonsignificant increased risk of death, whereas those who were prescribed  $>1,000$  mg daily had the greatest risk ( $P=0.048$  for trend). Metformin use was also associated with a higher, but insignificant risk of metabolic acidosis.

In their accompanying editorial, Kamyar Kalantar-Zadeh and Connie Rhee say “...the study by Hung and colleagues has important strengths, [including] its nationwide representativeness...statistical robustness, and granular ascertainment of drugs and comorbidity over a follow-up period of up to 9.8 years. Notwithstanding ongoing pressures from the endocrinology and nephrology communities to liberalise use of metformin in patients with CKD, the restrictions should be maintained, bearing in mind the utmost priority of practicing safe and conservative medicine.”

The investigators note that although randomized controlled studies are required to confirm or refute these findings, it might not be feasible to perform clinical trials to test the safety of metformin in patients with T2DM and advanced CKD. “Our results further corroborate previous observations in the literature by showing that there is no significant link between metformin and lactic acidosis, even in stage 5 CKD,” says Tarn. “Further study is required, however, to understand the exact mechanisms of increased risk of death associated with metformin use in these patients.”

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**Original article** Hung, S. C. *et al.* Metformin use and mortality in patients with advanced chronic kidney disease: national, retrospective, observational, cohort study. *Lancet Diabetes Endocrinol.* doi:10.1016/S2213-8587(15)00123-0

**Further reading** Kalantar-Zadeh, H. & Rhee, C. M. Metformin in chronic kidney disease: more harm than help? *Lancet Diabetes Endocrinol.* doi:10.1016/S2213-8587(15)00133-3

