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## Metformin in chronic kidney disease: more harm than help?

Drug regulatory agencies in countries around the world have issued specific warnings and restrictions pertaining to the use of metformin in patients with chronic kidney disease (CKD). An increased risk of hypoglycaemia and impaired lactate metabolism has been reported in patients taking metformin, which could lead to profound metabolic acidosis, adverse outcomes, and death in individuals with kidney dysfunction.<sup>1</sup> One prominent example of such prohibitory warnings is the US Food and Drug Administration (FDA)'s recommendation against metformin use in men with serum creatinine concentrations above 133  $\mu\text{mol/L}$  and in women with serum creatinine concentrations above 124  $\mu\text{mol/L}$ .

Unlike classic lactic acidosis, which is caused by impaired tissue perfusion, metformin-induced lactic acidosis is characterised by increased lactate generation and

accumulation resulting from diminished gluconeogenesis and glycogenolysis, inhibition of oxygen consumption, and impaired mitochondrial function.<sup>2</sup> In addition to a build-up of lactate, pancreatitis and hypoglycaemia might occur more frequently in patients with impaired renal function.<sup>3</sup>

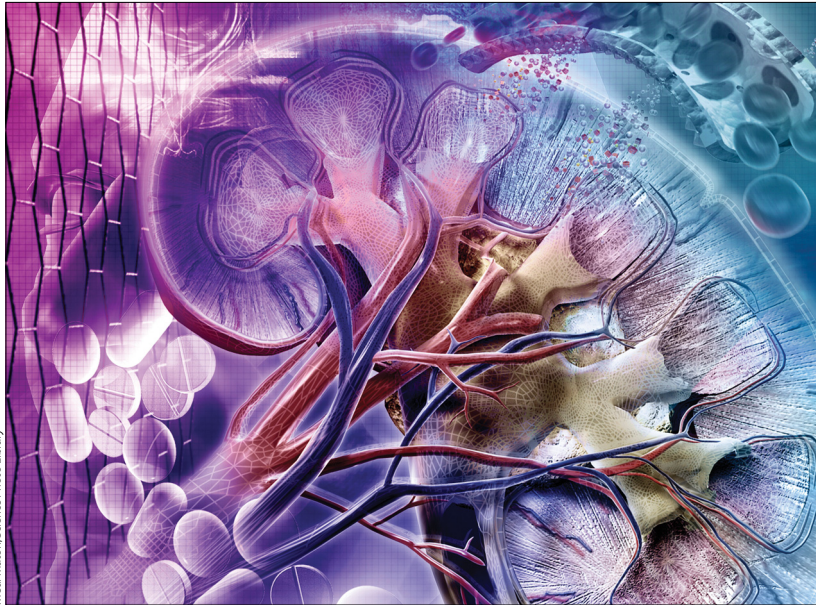
Because of unacceptably high rates of harmful events, including fatal cases of metabolic acidosis, two biguanide drugs—phenformin and buformin—were removed from the market many years ago. Metformin, however, is still commonly prescribed. Adverse effects of this drug are reported less frequently than they were with phenformin and buformin, which could be attributable to inherent biochemical differences between metformin and other biguanides or to a direct result of the regulations that have recommended against use

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of metformin in patients with CKD. In view of the very rare but fatal nature of metformin-associated adverse effects, and the highly selective and conservative nature of clinical trials of metformin, in which patients with CKD have typically been excluded, investigation of real-world scenarios involving liberal and frequent administration of metformin to individuals with advanced CKD are urgently needed, particularly because expansion of metformin use in this population has been advocated.<sup>4</sup>

In *The Lancet Diabetes & Endocrinology*, Szu-Chun Hung and colleagues<sup>5</sup> present historical data from Taiwan, one of very few nations where, until recently, metformin administration was allowed for all patients with type 2 diabetes and CKD, irrespective of the severity of renal impairment. This study analysed a contemporary cohort of 12 350 patients from Taiwan's national health insurance research database with type 2 diabetes and advanced CKD. Patients with approximately stage 5 disease were identified on the basis of prescriptions for erythropoiesis-stimulating agents, which are used in patients with CKD who have serum creatinine concentrations greater than 530  $\mu\text{mol/L}$ . After propensity matching 813 metformin users in a 1:3 ratio to 2439 non-users, adjusted mortality in metformin users was 35% (20–51) higher than non-users over a median of 2.1 (range 0.3–9.8) years, with robust consistency across all subgroups. Moreover, the authors reported a dose-dependent effect in the association between metformin use and death. The incidence of

metabolic acidosis was 30% higher in metformin users than in non-users, but this difference was not significant (adjusted hazard ratio 1.30, 95% CI 0.88–1.93;  $p=0.19$ ).

Notwithstanding the inherent limitations of this cohort study, including restriction of CKD severity to very advanced stages of kidney impairment and scant data for events other than mortality, the study by Hung and colleagues has important strengths. These include its nationwide representativeness, a high proportion of deaths in metformin non-users (41%) and users (53%), which confers statistical robustness, and granular ascertainment of drugs and comorbidity over a follow-up period of up to 9.8 years.

The findings of Hung and colleagues<sup>5</sup> give us little doubt that metformin use leads to excess deaths in patients with type 2 diabetes and advanced CKD. However, an argument could be made that not giving metformin to patients with CKD deprives millions of individuals with type 2 diabetes a standard of care. Would discontinuation of metformin on worsening of kidney function result in poor glycaemic control and accelerated complications of diabetes? Would avoidance of metformin in patients with CKD lead to use of other agents with worse side-effect profiles than metformin, in turn resulting in greater harm? Are the well-intentioned recommendations against metformin use in patients with CKD arbitrary and outdated, and should they be withheld or reinforced? The present study data,<sup>5</sup> together with case reports describing the gravity of metformin-related adverse events<sup>1</sup> and historical data showing the toxic effects of other biguanide agents, suggest that regulations restricting metformin use have probably protected many patients from lactic acidosis, hypoglycaemia, and pancreatitis, and saved thousands of lives every year. Indeed, progressive CKD is typically associated with decreased concentrations of lipids, glucose, and  $\text{HbA}_{1c}$ , along with seemingly counterintuitive improvements in metabolic and glycaemic burden.<sup>6</sup> These changes might result from prolonged insulin half-life in advanced CKD to the point that so-called burnt-out diabetes emerges, in which all hypoglycaemic agents are discontinued because of frequent hypoglycaemia.<sup>7</sup> Worsening uraemia in patients with CKD also leads to accumulation of lactate and uraemic toxins, including guanidino compounds that are closely related in structure to biguanides, which might negate the need for metformin in view of the potential harms of the expanding pool of guanidino compounds in the system.<sup>8</sup>

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. History should never forget the courageous stance of a lone researcher—in the face of immense pressures from the medical community and powerful industry lobbyists—who stood against approval of thalidomide in the USA. The lessons learned from Frances Oldham Kelsey's story should motivate us to uphold the "never again" motto when it comes to safety considerations surrounding commonly used yet potentially harmful drugs such as metformin.<sup>9</sup>

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