Agency to explore the role of changes in kidney function (eGFR slope) as an outcome for future trials may be critical (4). Slope-based outcomes are likely to make reliable demonstration of benefit easier, but separate attention to collect high-quality safety data will also be required. Slope-based outcomes may also facilitate the development of more efficient approaches to the conduct of trials, using platform approaches and adaptive methodologies (5), particularly as new targets are identified through modern ‘omics’ approaches.

Another difference will be a growing need to understand the absolute and relative effects of combinations of therapy. Incomplete uptake of SGLT-2 inhibitors in future trials will allow assessment of effects of people with and without this treatment. As more renoprotective therapies (hopefully) are identified, the assessment of different combinations is likely to become more important.

Perhaps most important, the development of a growing number of proven renoprotective therapies poses a new challenge. Use of RAS blockade among people in whom it is indicated is still likely to be suboptimal, almost two decades after the benefits were proven. Vast numbers of people who could have benefited from this treatment are likely to have reached kidney failure prematurely as a result of implementation failure. The challenge for us going forward will be to make the development and testing of implementation strategies a research focus, so that we can translate research findings much faster, for the benefit of people with kidney approaches.

We have achieved much in diabetic kidney disease, and the rich tapestry of ongoing research suggests we are likely to achieve much more over the coming years. But we will need to adapt our questions, our approaches, and our goals if we want to achieve the best possible outcomes for our patients into the future.

Vlado Perkovic, MBBS, PhD, is Executive Director of The George Institute, Australia, Professor of Medicine at UNSW Sydney, and a staff specialist in nephrology at the Royal North Shore Hospital.

References

Metformin: The Forgotten Agent

By Clarissa Diamantidis

Effective, safe glycemic control is a global priority because uncontrolled diabetes contributes to a substantial burden of morbidity and mortality related to chronic kidney disease (CKD), end-stage kidney disease (ESKD), and cardiovascular disease (CVD) (1, 2). However, achieving this goal in patients with advanced kidney disease is complicated by evolving safety recommendations and contraindications to several existing antihyperglycemic medications when kidney function is substantially impaired (2). Amid robust evidence for inhibition of the renin-angiotensin system as the mainstay of management and increased activation of AMP-kinase (7, 8), the therapeutic efficacy of metformin, its 60-plus-years history of use, and its relatively strong safety profile, low cost, and weight neutrality render it a first-line agent in combination with conventional therapy (with dietary control) alone (8). Although additional studies are needed to understand the effects of metformin in combination with saxagliptin and 2) better understand the impact of metformin on non-U.S. and European populations, the long-term effects of metformin are robust. For example, the 10-year follow-up of the metformin group in UKPDS showed that significant reductions persisted for diabetes-related endpoints, death of any cause, and myocardial infarction (10). Finally, metformin continues to be studied for its potential pleiotropic benefits, including antineoplastic effects mediated by AMP-kinase-dependent and independent inhibition of mTOR, treatment of polycystic ovary syndrome, attenuated atherosclerosis and vascular senescence as demonstrated in mouse models, and lipid-lowering and anti-inflammatory effects (2, 11).

Before 2016: the legacy of phenformin

Despite abundant evidence regarding its benefits, the U.S. Food and Drug Administration (FDA) regulations before 2016 restricted the use of metformin in several groups because of concern regarding a relatively uncommon but dreaded complication: metformin-associated lactic acidosis (MALA) (11). Concerns regarding metformin date back to the use of phenformin, the predecessor of metformin, which was withdrawn in 1977 because of concerns about lactic acidosis (12). Phenformin alters hepatic oxidative phosphorylation and thus leads to increased lactate production. It is distinguished from metformin because of its more lipo- philic nature and its slower renal excretion: half-life 7 to 15 hours versus an estimated 6.5 hours for metformin (3, 12). Metformin, unlike phenformin, has been shown to be maintained closer to therapeutic and safe ranges, even in mild to moderate CKD (eGFR >30). In sum, there is no consistent association between metformin and lactic acidosis, and the overall number of cases is small (1 per 23,000 to 30,000 person-years among metformin users compared with approximately 1 per 18,000 to 21,000 person-years among patients with type 2 diabetes using other agents) (12).

A landmark publication in 2014 by Inzucchi et al. (12) suggested expanding the use of metformin to previously ineligible populations (e.g., individuals with mild to moderate CKD). Furthermore, the study suggested that avoiding MALA and its sequelae requires understanding the unique risk factors for MALA, including less common situations in which systemic hyperperfusion and hypoxia result in excess lactic acidosis production (3, 12).

2016: expansion of FDA guidance

These findings are reflected in the revised 2016 FDA guidance, which states that metformin is contraindicated in patients with an eGFR <30, which is in line with the report by Hung et al. (4) suggesting that metformin may be an independent risk factor for death in comparisons with propensity-matched non-metformin users among individuals with stage 5 CKD. The FDA guidelines further suggest careful eGFR monitoring in a patient using metformin, reassessment of the risks and benefits when eGFR is 45, avoiding initiation of new metformin therapy when eGFR is <45, and temporary discontinuation before and during iodinated contrast imaging procedures in patients with eGFR 30 to 60.

Beyond 2016: metformin use in contraindicated conditions

An important 2017 systematic review and meta-analysis by Crowley et al. (1), released after the 2016 FDA labeling changes, evaluated metformin use in individuals with type 2 diabetes and moderate to severe CKD, congestive heart failure (CHF), or chronic liver disease with impaired hepatic function. Four retrospective cohort studies, one prospective cohort study, and one nested case-control study were evaluated, and follow-up in these studies ranged from 1 to 3.9 years. Among these studies, which included 33,442 individuals and examined all-cause mortality, the relative chance of death was 22% lower for individuals using versus not using metformin (p = 0.001, 12 = 89.8%).

The authors found associations of metformin use with reduced all-cause mortality in all three groups for which metformin had been previously contraindicated. Metformin use was also noted in two separate studies to be 1) significantly associated with lower risk of CHF readmissions and 2) not significantly associated with a difference in major adverse cardiovascular events among individuals with GFR 40 to <60 compared with those with GFR 30 to <45. Supporting its overall safety profile, metformin was associated with less glycaemia than were glyburide and insulin among individuals with GFR <30 and <45. In spite of limitations in this meta-analysis, including the use of observational studies with moderate risk of bias and low strength of evidence overall, the authors suggest that metformin may be associated with important mortality benefits and other benefits in individuals with moderate CKD. They also corroborate the evidence from a similar systematic review suggesting that metformin is associated with reduced mortality in CHF; a condition often comorbid in patients with CKD (13).

Given these findings, additional studies focused on the
Metformin

Continued from page 21

safety and benefits of metformin use in individuals with eGFR 30 to 45 and <30 are warranted to guide nuanced clinical decision-making. In the meantime, nephrologists and other clinicians who care for individuals with mild to moderate CKD should remember metformin as a critical part of the antiglycemic pharmacologic repertoire, using clinical equipoise and FDA guidelines to guide an individualized approach to prescribing and to patient education.

Clarissa Jonas Diamantidis, MD, is a nephrologist affiliated with Duke University School of Medicine.

References

Figure 1. An abbreviated history of metformin. Adapted with permission from Bailey (6).