Dipeptidyl Peptidase-4 Inhibitors

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New Directions in Diabetic Kidney Disease Trials

By Vlado Perkovic

The outlook for people diagnosed with type 2 diabetes and chronic kidney disease today is more hopeful than it has ever been. A broad array of treatments are available, and the last decade has seen an explosion of evidence from high-quality, properly powered, randomized trials that have defined the benefits and risks of many of these treatment options.

The 2008 decision by the U.S. Food and Drug Administration (FDA) and other regulatory agencies to require the conduct of cardiovascular safety trials for all new diabetes medications (1) has directly led to the generation of evidence that can guide treatment. We now know which agents reduce the risk of cardiovascular disease, kidney disease, or both, as well as lowering glucose levels. These trials have also taught us much about the effects of these agents on both common and uncommon adverse events, and have driven new areas of basic research, as we try to understand the mechanisms underpinning the clinical effects observed. The decision to mandate these trials will allow more effective and efficient use of glucose-lowering treatments, and has directly improved outcomes for people with diabetes.

Over the coming years, a number of additional placebo-controlled outcome trials of novel glucose-lowering therapies will report (Table 1), providing further richness to the available evidence. But a number of factors suggest that the landscape of trials going into the next decade are likely to look quite different from those completed over the past 10 years.

One reason for this is that the proven benefits of existing treatments must be taken into account in designing new trials. Previous trials looking at clinical renal outcomes in diabetes and CKD have required most or all participants to be receiving renin-angiotensin system blockade. Clear benefit for canagliflozin was demonstrated in people with diabetes and very high albuminuria in the CREDENCE trial (2), and there is growing evidence of renal benefits for SGLT-2 inhibitors across the spectrum of diabetes and kidney disease (3). Rapid increases in the use of these agents by nephrologists and other practitioners is therefore appropriate and will need to be taken into account for future trial design. While it would be ideal to test future treatments on top of SGLT inhibitors, many people may not have access to them for financial reasons, or be able to tolerate SGLT-2 inhibitors. So some degree of pragmatism will be required, particularly as uptake is (unfortunately) likely to take some time.

Slower kidney function loss in diabetes with proven new treatments is obviously a great outcome. But it may also make it more difficult to demonstrate benefits on existing renal outcomes. Event rates will be lower in treated participants, so that larger sample sizes will be required to demonstrate realistic effects on these outcomes. In this light, the recent initiatives by the National Kidney Foundation, the U.S. FDA, and the European Medicines

Table 1. Ongoing renal and cardiovascular outcome trials in Type 2 Diabetes

Trial Name	Treatment	Number of participants	Primary Outcome	Planned completion date
VERTIS CV	Ertugliflozin	8000	Cardiovascular	2019
Dapa HF	Dapagliflozin	4744	Heart Failure	2019
FIDELIO-DKD	Finerinone	5734	**Renal**	2020
Dapa_CKD	Dapagliflozin	4000	**Renal**	2020
EMPOROR	Empagliflozin	8850	Heart Failure	2020
DELIVER	Dapagliflozin	4700	Heart Failure	2021
FIGARO	Finerinone	7437	Cardiovascular	2021
SCORED	Sotagliflozin	10,500	Cardiovascular	2022
EMPA-Kidney	Empagliflozin	5000	**Renal**	2022
SOUL	Semaglutide	9642	Cardiovascular	2024
FLOW	Semaglutide	3160	**Renal**	2024

Abbreviations: VERTIS CV = eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial; Dapa HF = Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure; FIDELIO-DKD = Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease; Dapa CKD = Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; EMPOROR = EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; DELIVER = Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; FIGARO = Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease; SCORED = Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; EMPA-Kidney = Study of Heart and Kidney Protection With Empagliflozin; SOUL = Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes; FLOW = Semaglutide versus Placebo in People With Type 2 Diabetes and Chronic Kidney Disease.

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 collecting adequate 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 in 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 disease.

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. ■

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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), 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 managing diabetic kidney disease and growing attention to the significant cardiovascular, kidney, and survival benefits of sodium glucose cotransporter 2 inhibitors, the important role of metformin should not be forgotten (1, 3, 4).

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 antiglycemic agent by European and U.S. guidelines (Figure 1) (5, 6). Metformin is a biguanide recognized for its important role in improving glycemic control through mechanisms distinctly different from those of insulin, sulfonylureas, glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, and sodium glucose co-transporter 2 inhibitors. Our understanding of the mechanisms of action of metformin remains incomplete, although its antiglycemic effects occur primarily through enhanced insulin sensitivity and decreased gluconeogenesis by mitochondrial inhibition and increased activation of AMP-kinase (7, 8).

Bolstered by evidence regarding the long-term cardiovascular, diabetes-related, and survival benefits of metformin therapy, the American Diabetes Association (ADA) 2019 guidelines recommend consideration of metformin for the prevention of type 2 diabetes in individuals with prediabetes, especially in those older than 60 years, those with body mass index >35, and women with a history of gestational diabetes (9). Moreover, metformin continues to be the ADA's preferred initial agent for the treatment of type 2 diabetes as long as it is well tolerated and not contraindicated.

When metformin is used as a single agent, the average hemoglobin A1c reduction associated with it ranges from 1% to 1.5%. In addition, important longer-term benefits of metformin in reducing cardiovascular risk date back to compelling data from the UK Prospective Diabetes Study (UKPDS) (8). Metformin significantly reduced the risk for any diabetes-related endpoint, diabetes-related mortality, and all-cause mortality in obese individuals with newly diagnosed type 2 diabetes when it was compared with conventional therapy (with dietary control) alone (8). Although additional studies are needed to 1) understand the effects of metformin in combination with sulfonylureas and 2) better understand the impact of metformin in 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 concerns regarding a relatively uncommon but dreaded complication: metformin-associated lactic acidosis (MALA) (1).

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 lipophilic 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 hypoperfusion 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 comparison 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 metformin 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 ($p < 0.001$, $I2 = 89.8\%$).

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 hypoglycemia 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

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