Slowing Progression in CKD
DAPA CKD and Beyond

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Introduction

There is a recognized large global burden of CKD (1). With the projected rise in prevalence of diabetes in coming years, that burden may indeed increase. Thus, the need for therapies to slow the progression of CKD, and its attendant comorbidities, is critical. The goal to reduce the human and financial costs associated with CKD is ambitious, but essential. Despite 2 decades of work, CKD remains underdiagnosed, with suboptimal screening in high-risk groups and inappropriate medication use (2). Until recently, there has been a paucity of large, significant clinical trials aimed at delaying CKD progression and associated comorbidities, in contrast to other chronic diseases and conditions. Our armory for slowing CKD progression has been limited, with evidence for use of ACE inhibitors and ARBs on the basis of trials performed 20 years ago, predominantly in people with type 2 diabetes and proteinuria (3,4). Despite a robust evidence base, these agents are still prescribed in only 21% of patients with CKD in the United States (2).

Evidence demonstrating favorable effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors on kidney and cardiovascular outcomes in patients with type 2 diabetes has been growing over the last 5 years (5). The CREDENCE trial, the first study specifically designed to address kidney outcomes in high-risk patients with diabetes, impaired kidney function, and proteinuria, demonstrated substantial reductions in risk for kidney failure and cardiovascular events in those treated with canagliflozin (6). The profound benefits of these agents, in all studies, seem to be independent of glucose lowering. Thus, additional studies in those without diabetes have been conducted. The DAPA-CKD trial enrolled 4304 people with diabetic and nondiabetic CKD and proteinuria to determine whether an SGLT2 inhibitor, dapagliflozin, would benefit these patients as compared with placebo (7). Consistent with previous SGLT2i studies, the study demonstrated benefit for kidney and cardiovascular outcomes in those with diabetes (36% RRR) and extended the findings to those without diabetes (50% RRR). Note that dapagliflozin was added to best current therapy, which included RAAS blockade. The etiologies of CKD were diverse and included a substantial number of patients with IgA nephropathy. The SCORED study reported benefit of sotagliflozin versus placebo for cardiovascular and heart failure events in over 10,000 people randomized with diabetes, CKD, and cardiovascular risk, irrespective of albuminuria (8).

Of note, all of the SGLT2i studies have used fixed doses of drug without targeting specific parameters, such as blood glucose or BP, nor reduction in proteinuria.

In addition to SLT2i agents, the role of mineralocorticoid receptor antagonists in slowing CKD progression has been of interest. The FIDELIO-DKD trial, designed to establish whether finerenone slowed CKD progression and reduced cardiovascular mortality among patients with type 2 diabetes and CKD, demonstrated a 20% reduction in progression to kidney failure end points (9).

Where We Are Now

We have increasing knowledge of different mechanisms by which progression of CKD occurs. We have tested and confirmed that interfering with these mechanisms with specific medications results in delay of kidney disease progression and cardiovascular events. We have been successful in completing large, international, randomized control trials with different agents.

We know that SGLT2 inhibitors have multiple mechanisms of action. These include reduced intraglomerular pressure and proteinuria, interference with proximal glucose reabsorption, and proximal sodium reabsorption, which results in natriuresis. These agents reduce effective circulating volume, have BP-lowering effects, and induce some weight loss (9). Additionally, SGLT2 inhibitors modify factors that promote inflammation and fibrosis, may reduce kidney hypoxia, and alter mitochondrial metabolism in cardiac and kidney tissue (9).

The mineralocorticoid receptor antagonists (MRAs) prevent binding of aldosterone to mineralocorticoid receptors and, thus, prevent sodium retention and potassium loss. Finerenone, with its nonsteroidal structure, binds to the MR with higher affinity than steroidal MRAs and inhibits recruitment of transcriptional coactivators involved in expression of hypertrophic and profibrotic genes. The use of steroidal MRAs (*e.g.*, spironolactone and eplerenone) has been limited by side effects (hyperkalemia and gynecomastia). The new compound finerenone seems

to offer an alternative with lower risks and more benefits than earlier agents (10).

The totality of studies with SGLT2i in those with diabetes, and the DAPA-CKD study in those with and without diabetes, in addition to the FIDELIO-DKD study, heralds a significant change in the current care paradigm for people with CKD. DAPA CKD demonstrated that use of fixed dose dapagliflozin in patients with CKD, with or without diabetes, resulted in a significant reduction in risk of decline in GFR, kidney failure, and death from kidney or cardiovascular causes. It confirmed the benefit of SGLT2 inhibitor use across a wide spectrum of etiologies of CKD and with a lower GFR (25 versus 30 ml/min per 1.73 m^2) in comparison with previous studies in patients with diabetes mellitus and CKD to variable degrees. Finerenone use within the FIDELIO-DKD trial was well tolerated and significantly reduced the risk of CKD progression in patients with type 2 diabetes.

The SGLT2 inhibitors do lower BP, as compared with the nonsteroidal MRAs, but both medications appear to have a similar effect on reducing albuminuria. Finerenone does not lower weight or blood glucose and exhibits anti-inflammatory and antifibrotic effects. Experimental models suggest that SGLT2 inhibitors may also modify factors that promote inflammation and fibrosis (9). It is not known if the potential overlap in mechanisms is beneficial. In DAPA CKD, 5% of participants were receiving MRA at baseline (eplerenone or spironolactone); within FIDELIO-DKD, 5% of patients were on SGLT2 inhibitors. The effect of dapaglifozin was not attenuated nor enhanced by MRA use as regards kidney composite outcomes, nor were there differences in rates of adverse events or discontinuation of medications in that subgroup. Similarly, within the FIDELIO-DKD study, there were no differences in outcomes in the group that was on both MRA and SGLT2i. Although the numbers remain small, we are unable to conclude whether there are additive effects of the two agents. As both compounds have an effect on kidney and cardiovascular outcomes and there is a known complex interaction by which progression of one can affect progression of the other, these findings are exciting. The reduction in cardiovascular outcomes and, in particular, heart failure admission and visits, is of particular value to patients and health care systems and should be highlighted.

Where We Want to Be

We know more now about mechanisms of kidney disease and interactions with cardiovascular disease, and now, we have medications targeted at these mechanisms. With increasing emphasis on precision medicine and increasing appreciation of the value of biopsies for those with CKD, through the Kidney Precision Medicine Project, we are further poised to improve and extend our knowledge of mechanisms and identify new targets.

We have demonstrated an ability to complete large-scale international trials, with both diabetic and nondiabetic populations with varying degrees of kidney function and proteinuria, and that delay of CKD progression and reduction of cardiac events are possible. It is critical that we ensure the uptake of these strategies into clinical practice and avoid clinical inertia, as has been the case with RAAS inhibitors, despite 20 years of accumulated data.

Looking forward, we should aim to change the culture in nephrology to embrace this new era of disease-modifying medications while gaining further definitive answers for additional populations in which these therapies may be effective. The EMPA-KIDNEY study (11) will add information about the use of SGLT2 inhibitors in nondiabetic kidney disease, in those with lower GFR, and in those without albuminuria.

Ultimately, we need to embrace precision polypharmacy for individuals on the basis of evidence of benefit. We need to test the value of different combinations of medications at different stages of CKD, and for different etiologies, to maximize benefits and reduce risks for individuals. The identification of subgroups who will benefit from specific combinations of interventions will foster a true personalized medicine approach.

It is an immensely exciting time for patients and nephrologists to have and to offer hope of improved outcomes. As a community, we must continue to work together to complete important clinical trials and to implement the results in practice. We need to continue the exponential progress we have made to date.

Disclosures

K. Larmour reports employment with the University of British Columbia. A. Levin reports employment with BC Provincial Renal Agency and the University of British Columbia; consultancy agreements with Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Johnson and Johnson/Jansen, Reata, and Retrophin; receiving research funding from AstraZeneca, Boehringer-Ingelheim, the Canadian Institute of Health Research, Janssen, Johnson and Johnson, the Kidney Foundation of Canada, Merck, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institutes of Health (NIH), Ortho Biotech, Otsuka, and Oxford Clinical Trials; and serving as a scientific advisor or member of AstraZeneca, Bayer, Boehringer-Ingelheim, *Canadian Journal of Kidney Health and Disease*, Certa, Chinook Therapeutics, Canadian Institute of Health Research, The George Institute, Johnson and Johnson, the Kidney Foundation of Canada, NIH NIDDK, Otsuka, Reata, and Retrophin.

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