The current burden and pathogenesis of diabetic kidney disease

How prevalent is diabetic kidney disease and what are the consequences?

As Professor Mark Cooper (Monash University, Melbourne, VIC, Australia) explained, it is vital to appreciate the global explosion in the prevalence of diabetes and how common DKD is in patients with diabetes. The consequences of DKD for patients and society are profound. On a societal level, DKD is a substantial burden to healthcare systems; the annual cost of treating a person with stage 5 kidney dysfunction is €80 000. Screening to detect early signs of DKD (albuminuria with or without reduced estimated glomerular filtration rate [eGFR]) is therefore vital, because these patients are often asymptomatic. On an individual level, the presence of DKD has been shown to increase the 10-year risk of death by approximately 47% compared with people without diabetes or DKD, and by 43% compared with those with diabetes but without DKD. In both men and women with DKD, this equates to a loss of approximately 15 years of life compared with those without DKD, early chronic kidney disease (CKD) or diabetes. Similarly, data from the ACCORD study indicate that the risk of all-cause death or cardiovascular (CV) death is twofold greater in patients with both type 2 diabetes (T2D) and DKD than in those with T2D alone. Moreover, there is an exponential relationship between an increasing albumin–creatinine ratio and the risk of CV death or all-cause death, particularly in patients with T2D. Similarly, the risk of both CV death and all-cause death dramatically increases as the eGFR declines. So, why is there a close relationship between kidney function and CV health? The kidney and the heart act in tandem to regulate blood pressure, vascular tone, diuresis and natriuresis; as such, if one of the pathways that is known to lead to dysfunction in one organ is activated, this can also cause dysfunction in the other. This provides us with an opportunity, because a treatment that acts on the underlying pathways affecting this connection may have beneficial effects for both organs. Ultimately, understanding the shared pathways between the heart and the kidney is critical to the development of effective treatments for DKD that reduce the morbidity and mortality burdens.
What are the pathophysiological mechanisms underlying cardiorenal disease in diabetes?

Following directly on, Professor Richard Gilbert (University of Toronto, Toronto, ON, Canada) was tasked with guiding the audience through the key pathways that underlie the link between CV disease and kidney disease, with a specific focus on heart failure (HF) and kidney failure. It is known that the risk of hospitalization for HF increases dramatically as kidney function worsens. Looking under the microscope, there is a shared cause, with the presence of fibrosis and fibrotic scar tissue being readily evident in both renal and cardiac tissues. In fact, a linear relationship exists between the degree of fibrosis and the degree of impairment in both the kidney and the heart, irrespective of whether the cardiac ejection fraction is reduced (rEF) or preserved (pEF). A study in Zeeland in the Netherlands suggested that up to 22% of people with T2D also had undiagnosed HFpEF. So, why do many endocrinologists have the feeling that they don’t really see patients with HF? This may be because HF is not presenting in a way that we are familiar with; HFpEF in patients with diabetes may not present as acute pulmonary oedema but, rather, as a slow reduction in exercise capacity over several years. This creates a feedback cycle in which the underlying subclinical HFpEF reduces exercise capacity, leading to increasing weight that worsens glycaemic control and causes further cardiac damage.

The steroidal mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone are familiar treatments for HFrEF. The RALES study showed a 30% increase in survival rates in patients with severe HFrEF who had been treated with spironolactone. Although we cannot conduct biopsies in large clinical trials, measurements of biomarkers, such as the procollagen type-III N-peptide (PIIINP) produced during collagen metabolism, reveal a very interesting finding. Patients in the RALES study with high PIIINP levels at baseline had a higher risk of death than those with low PIIINP levels, and use of spironolactone reduced the levels of PIIINP and risk of death in this group by 50%. When we think about the mineralocorticoid receptor (MR), we only focus on its expression in the distal convoluted tubule of the kidney and its role in the regulation of blood pressure and serum potassium levels. However, the MR is actually expressed much more widely, including in myocytes and fibroblasts in the heart; in the distal and proximal tubules, glomerulus, podocytes and interstitium of the kidney; and in the endothelium, retina, vascular smooth muscle and mononuclear cells. So, just like missing HF in our endocrinology teaching, there is a whole world of MR activity beyond the kidney. In the podocytes, MR overexpression stimulates apoptosis, leading to proteinuria; a small open-label study has suggested that this proteinuria can be reduced using steroidal MRAs. However, there are limitations with these molecules. Spironolactone is very potent but not very specific for the MR; it also shows significant activity at the glucocorticoid, androgen and progesterone receptors, resulting in off-target effects such as gynaecomastia and menstrual irregularities. Eplerenone is more specific for the MR, but also approximately 20-fold less potent than spironolactone. Moreover, both agents increase the risk of hyperkalaemia approximately twofold. The challenge is therefore to develop a new MRA that maintains efficacy and potency, with high selectivity for the MR, but without the hyperkalaemia seen with steroidal MRAs.

Professor Gilbert concluded by summarizing the development of finerenone: the first non-steroidal MRA to be specifically developed for patients with DKD. It had been shown in vitro that dihydropyridine calcium-channel blockers could act as MRAs. Subsequent high-throughput screening of related molecules and modification of the initial chemical scaffold led to the development of finerenone. Compared with steroidal MRAs, finerenone has a different three-dimensional interaction with the MR, a more equal distribution between the kidney and the heart, and greater selectivity for, and comparable potency at, the MR. This results in differential effects on cofactor recruitment and gene expression. In an animal model, finerenone reduced proteinuria and cardiac collagen synthesis; furthermore, in the ARTS-DN phase 2 trial, administration of finerenone 20 mg once daily was associated with significant reductions in UACR and a favourable safety profile (e.g. incidence of hyperkalaemia, worsening renal function).
The cardiorenal connection: how do nephrologists and cardiologists see the current data?

Filtering the facts: the nephrologist’s view of the cardiorenal connection

After the excellent pathophysiological overview from Professor Gilbert, Professor David Cherney (University of Toronto, Toronto, ON, Canada) switched gears slightly to give the delegates an insight into a nephrologist’s view of the cardiorenal connection and the current status of treatment for patients with DKD. Various studies have suggested some therapies currently used to manage T2D may also demonstrate efficacy in terms of renal outcomes. Professor Cherney guided the delegates through the evidence for each class in turn and provided some indications of how the treatment landscape might be evolving.

The sodium–glucose co-transporter-2 inhibitors (SGLT-2is) have been hypothesized to provide renal benefits through various mechanisms, including reducing solute resorption in the proximal tubule and increasing both erythropoietin production and vascular endothelial growth factor A expression, with the effect of reducing hypoxia and renal ischaemia. From a haemodynamic viewpoint, SGLT-2is are thought to increase afferent arteriole constriction, thereby reversing hyperfiltration. Further experimental hypotheses include the effect of SGLT-2is on reduction of inflammation and fibrosis. However, although the exact relevance of these mechanisms is still to be elucidated, renoprotective effects of SGLT-2is have been suggested by clinical trials. In the EMPA-REG CV outcome trial (CVOT), treatment of patients with empagliflozin led to a 39% reduction in the secondary composite outcome of albuminuria, was also seen with canagliflozin compared with placebo in the CANVAS programme. Results are highly anticipated from the CREDENCE trial in patients with DKD, which was recently halted for meeting its primary endpoint, and from the DECLARE-TIMI 58 trial, which included a slightly different patient population, while further trials, such as Dapa-CKD and EMPA-KIDNEY, are ongoing.

The incretin therapies dipeptidyl peptidase-4 inhibitors (DPP-4is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are hypothesized to exert their renoprotective effects predominantly through natriuretic mechanisms. In the major CVOTs TECOS (sitagliptin), EXAMINE (alogliptin) and SAVOR-TIMI 53 (saxagliptin), which recruited patients with T2D at high risk of CV outcomes (20% of whom also had DKD), and also in the MARLINA-T2D trial, only neutral or minor effects on albuminuria progression were observed with DPP-4is, and there was no impact on eGFR change. As shown in animal models, this is because DPP-4is upregulate the chemokine stromal cell-derived factor-1, which acts too far downstream (in the distal tubule) to affect the eGFR and has too modest an effect to reduce blood pressure. Combining SGLT-2is and DPP-4is may provide more benefits than using each agent in isolation in terms of decreasing albuminuria levels, reducing inflammation and increasing natriuresis.

So, what about GLP-1RAs? The expression of glucagon-like peptide-1 at the afferent arteriole causes a direct vasodilatory effect on endothelial cells but, unlike SGLT-2is, the clinical effect of GLP-1RAs on renal function seems to be neutral. In the LEADER trial, there was a 22% reduction in the secondary composite renal endpoint; however, in contrast to what was seen with the SGLT-2is, this was driven by a reduction in the risk of albuminuria alone. There was no effect of GLP-1RA treatment on the other outcomes, such as change in the eGFR, compared with placebo. Significant effects of GLP-1RAs on the eGFR were only seen in patients with a baseline eGFR of 30–59 mL/min/1.73 m². Similar results were seen with semaglutide and dulaglutide in the SUSTAIN-6 trial and in the AWARD-7 trial, respectively, suggesting that there may be a small renoprotective effect over time, although the mechanisms are currently unknown. Combining SGLT-2is and GLP-1RAs as a treatment option has an additive effect in terms of lowering weight, reducing CV events and increasing renoprotection.

Professor Cherney briefly recap the how the development of non-steroidal MRAs may provide an additional renoprotective treatment option in the future. In the phase 2 ARTS-DN trial in patients with DKD, finerenone in combination with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers resulted in a dose-dependent reduction in albuminuria levels with a favourable safety profile (e.g. incidence of hyperkalaemia, worsening of renal function). In his summary to the delegates, Professor Cherney highlighted how important it will be to take an integrated cardiorenal–metabolic approach to treatment moving forward.
The cardiorenal connection: how do nephrologists and cardiologists see the current data?

Getting to the heart of the matter: a cardiologist’s view of the cardiorenal connection

Having heard a nephrologist’s viewpoint, Professor Mikhail Kosiborod (University of Missouri, Kansas City, MO, USA) shared his cardiologist’s view of the cardiorenal connection, highlighting the need to reduce the burden of CV events aggressively in patients with DKD. He walked us through the many strategies (some more effective than others) that have been tested or are being investigated to improve CV outcomes in patients with DKD.

The KEEP study demonstrated that the combination of low eGFR and high albuminuria is associated with a steep increase in mortality and progression to end-stage renal disease (ESRD) compared with either a low eGFR or high albuminuria levels alone. Furthermore, the ALTITUDE study indicated that HF was the most common cause of hospitalization and death among patients with DKD, followed by myocardial infarction (MI), stroke and ESRD.

We know that lipid-lowering agents (SHARP study), blood-pressure-lowering agents (ACCORD study) and renin–angiotensin–aldosterone system (RAAS) inhibitors (HOPE trial, RENAAL trial) are all efficacious in reducing CV events and in improving survival in patients who are at risk. Moreover, steroidal MRAs, such as spironolactone and eplerenone, have been associated with improved CV outcomes in patients with HFREF (RALES trial, EMPHASIS trial) or post-MI HF (EPHESUS trial). Conversely, dual RAAS inhibition (ONTARGET), intensive glucose-lowering therapy and specific glucose-lowering agents such as thiazolidinediones have all shown signs of being potentially harmful.

It is clear, therefore, that there is a critical need for additional therapies. Encouraging results have been seen with SGLT-2is. Use of the SGLT-2is canagliflozin (CANVAS programme) and empagliflozin (EMPA-REG) was associated with reductions in CV mortality and hospitalizations for HF in patients with T2D. In contrast, DPP-4is showed neutral CV effects. GLP-1RAs, although efficacious in reducing CV mortality, were neutral with respect to hospitalizations for HF. Another class of therapeutic agent showing promising results is the non-steroidal MRAs. One such molecule, finerenone, was shown in the ARTS-HF trial to be associated with a reduction in all-cause death and CV hospitalization in patients with worsening chronic HF, T2D and/or CKD when compared with eplerenone. No dose-dependent effects of finerenone were observed on hyperkalaemia and the eGFR. The effects of finerenone on both renal and CV outcomes are currently being investigated in two phase 3 clinical trials (FIDELIO-DKD, FIGARO-DKD).

Looking to the future

Professor Cooper wrapped up the presentations with an overview of the trials in patients with DKD that are ongoing, including CREDENCE (canagliflozin, terminated prematurely at an interim analysis), FIDELIO-DKD (finerenone), FIGARO-DKD (finerenone), Dapa-CKD (dapagliflozin) and EMPA-KIDNEY (empagliflozin), and highlighted their similarities and differences in terms of endpoints and how representative the study populations are of patients with DKD or CKD. The results of these studies are highly anticipated and will help us to understand better how to treat patients with DKD optimally.