SGLT-2 INHIBITORS IN TYPE 2 DIABETES

Protecting the Kidney (and Heart) beyond glucose control

Background

Longstanding diabetes is associated with both macrovascular (myocardial infarction, stroke and peripheral vascular disease) and microvascular disease (retinopathy, nephropathy and neuropathy). Nephropathy affects approximately 40% of patients with diabetes and follows a long natural history (Figure 1), initially manifesting with an elevated glomerular filtration rate (GFR) due to poor glucose control. In time there is a progressive and inexorable decline in renal function to end-stage renal disease. However, because many diabetics remain undiagnosed for many years, chronic kidney disease (CKD) may be present at diagnosis.

Nephropathy is predicted by small amounts of albumin in the urine (below dipsticks detection) or microalbuminuria that progressively increases to overt albuminuria associated with loss of kidney function. In the United Kingdom Prospective Diabetes Study (UKPDS) the progression rate from normoalbuminuria to microalbuminuria was 2% per year, microalbuminuria to macroalbuminuria 2.8%, and macroalbuminuria to elevated serum creatinine 2.3%. If nephropathy develops at age 30 years, life expectancy is reduced by 14.8 years in men and 16.9 years in woman. The reasons for the increased CV risk are complex and involve both traditional risk factors, especially worsening of hypertension, and non-traditional risk factors like vascular calcification, which is beyond the scope of this article.

Secondly, DKD is now the commonest cause of end-stage CKD in most countries in the world and South Africa is no exception. Currently 47.2% of dialysis patients in the private sector are diabetics and the vast majority type 2. In the state sector the figure is 11.2% and the implication of this is that the majority of diabetics in the public sector are sent home to die of end-stage CKD. The cost of dialysis in the private sector is in excess of R200 000 per annum per patient and accounts for one of the single biggest expenditures by medical aids in South Africa.

It is abundantly clear that CV disease and DKD are inextricably linked, and both need to be addressed to reduce the burden of kidney and associated CV disease.

Current knowledge of prevention and treatment of DKD

There are many challenges in the treatment of DKD. Firstly, it is silent and insidious with signs and symptoms only developing in CKD stages 4 and 5; so late diagnosis is common. There is lack of public awareness and failure to implement regular screening. The major modifiable risk factors for DKD are the presence of microalbuminuria (or incipient nephropathy), hypertension, smoking, obesity, dyslipidaemia and dietary factors.

It is also critical to understand that...
small improvements in the trajectory of GFR can translate into long-term benefits. For example, by changing the trajectory of loss of GFR from 3ml/min/year to 2ml/min/year, the time to end-stage CKD can be increased by up to 10 years or more.6

All diabetics should have their creatinine, estimated GFR, urine dipsticks, and urine albumin/creatinine ratio performed at diagnosis and annually. If abnormal, these need to be performed more regularly. Dipsticks positive for albumin, macroalbuminuria, and/or eGFR <60ml/min are very suggestive of DKD. Microalbuminuria signifies incipient nephropathy and a very elevated eGFR >120ml/min is also a risk factor because of the long-term harmful effects of hyperfiltration.

Correct performance and interpretation of urinary albumin/creatinine ratio is essential. Firstly, the urine should be a first overnight-voided specimen to standardise testing. Spot urines significantly overestimate the presence of albuminuria. Ideally three specimens need to be obtained, but in practice testing is usually performed using only one. Normoalbuminuria is an albumin creatinine ratio <3mg/mmol, microalbuminuria 3-30mg/mmol and macroalbuminuria >30mg/mmol (Table 1). Unfortunately several laboratories report in gm of albumin to gm of creatinine, which results in problems with interpretation. To obtain ranges for gm/gm multiply the above ranges by 10.

Treatment and prevention of DKD and CV events require a multifaceted approach. Healthy lifestyle remains crucial. For example, in early DKD physical inactivity increases mortality by 50%, smoking by 40%, excess alcohol by 21% and obesity by 68%.4 Blood pressure (BP) should be targeted to <140/90mmHg and ideally <130/80mmHg if well tolerated. All patients with micro- and macroalbuminuria must receive an ACE inhibitor or angiotensin receptor antagonist, even if normotensive, as this prevents progression of microalbuminuria to macroalbuminuria, the doubling of serum creatinine and reduces end-stage CKD.7 All patients should receive statin treatment almost regardless of serum cholesterol,8 but aspirin is not routinely indicated unless for secondary prevention of CV disease. In the early phases, tight glucose control is recommended (HBA, <6.5mmol/l) as it prevents the onset of early DKD and other microvascular complications.9 In late DKD, tight glucose control has little impact and may be harmful because of the risk of hypoglycaemia.

In the STENO-2 study this type of multifaceted approach resulted in a 46% risk reduction in death, 59% in CV events, 61% in nephropathy and 58% in retinopathy. Importantly, these benefits only accrued after five years of treatment.10

Importance of Na⁺-glucose co-transport (SGLT) in the kidney

The normal kidney filters 180 litres of plasma, approximately 24 000mmol of Na⁺ and 180g or 1000mmol of glucose. The sodium-glucose co-transporters (SGLT-1 and -2) completely reabsorb glucose linked to Na⁺ in the proximal tubule. Glucose is reabsorbed one-to-one with Na⁺ by SGLT-2 and one-to-two by SGLT-1. SGLT-2 is responsible for 90% and SGLT-1 10% of reabsorption.11 Any defect in SGLT-2 results in renal glycosuria that has no long-term harmful effects on the kidney. In diabetes, particularly if it is suboptimally controlled, the filtration of glucose increases and the SGLT is upregulated to counteract the increased filtration.12 However, once its threshold is exceeded glycosuria occurs causing an osmotic diuresis, resulting in the typical manifestations of uncontrolled diabetes, namely polyuria and polydipsia.
SGLT-2 inhibitors

Highly specific inhibitors of SGLT-2 have been developed by several pharmaceutical companies. The best known are empagliflozin, dapagliflozin and canagliflozin. Briefly, inhibition of the co-transporter results in glucose wasting through the kidney, resulting in insulin-independent improvement in HBA1C similar to that seen with metformin, sustained weight loss due to calorie loss and significant reduction in BP due to natriuresis. These drugs are now widely registered in many countries for the treatment of type 2 diabetes. In the kidney, SGLT-2 inhibitors increase natriuresis by blocking glucose-mediated Na+ uptake in the proximal tubule. The resultant increased Na+ delivery to the juxta glomerular apparatus brings about constriction of the afferent arteriole through TGF resulting in restoration of renal autoregulation and reduction in hyperfiltration. These effects reduce the GFR in the short term by 2-3ml/min but are likely to protect the kidney in the long term in a manner similar to the effects of RAS inhibitors. Addition of SGLT-2 inhibitors to RAS inhibitors is likely to fully restore renal autoregulation (Figure 2).

Relationship between heart failure and DKD

These changes have a profound effect on renal autoregulation that potentially lies at the heart of the pathophysiology of DKD and heart failure (HF). (Many physicians are not aware that HF is more common than myocardial infarction in longstanding type 2 diabetics.) Because the SGLT is upregulated by the increased glucose load in diabetics there is both increased Na+ (and glucose) reabsorption. The resultant reduction in Na+ delivery to the juxta glomerular apparatus results in tubular glomerular feedback (TGF) and activation of the intrarenal renin-angiotensin system (RAS). The net result is a dilated afferent and constricted efferent arteriole causing increased intraglomerular pressure, hyperfiltration and loss of autoregulation (Figure 2). The position is compounded by the increased systemic Na+ reabsorption that stimulates atrial natriuretic peptides, which increases renal blood flow further exacerbating the hyperfiltration. The glomerulus is particularly sensitive to the effects of glomerular hypertension, hyperfiltration and loss of autoregulation, and is seen as a fundamental pathophysiological mechanism for the development of nephropathy and the raised GFR seen in early diabetes (Figure 1). It also exposes the glomerulus to systemic BP, and it is for this reason that both BP control and RAS inhibitors are renoprotective. RAS inhibitors, in addition to lowering BP, dilate the efferent arteriole and reduce glomerular pressure, but do not fully restore autoregulation as the afferent remains dilated (Figure 2). Longstanding increased Na+ reabsorption by the kidney may also be plausibly linked to development of HF due to Na+ overload and exacerbation of hypertension.

“All patients with micro- and macroalbuminuria must receive an ACE inhibitor or angiotensin receptor antagonist.”
CV and kidney outcome studies with SGLT-2 inhibitors

Historically, although improving glycaemic control is associated with reduction in microvascular events, the effects on improving CV outcomes have generally been inconclusive. It also became apparent that some hypoglycaemia, for example rosiglitazone, may be associated with CV harm. For this reason in 2008 the FDA required companies to demonstrate empirically that a developmental drug for diabetes does not appear to increase the rate of CV disease. As a result, a plethora of CV outcome studies were launched. Most notably the DPP-4 inhibitors lowered glucose, but did not improve CV outcomes.

This nihilism regarding prevention of CV outcomes was dramatically changed when the EMPA-REG OUTCOME study was presented at the European Association for the Study of Diabetes congress in Stockholm in 2015. Empagliflozin 10 and 25mg was compared to placebo in patients with uncontrolled diabetes in patients with established CV disease or at very high risk for CV disease, treated with standard of care. Both doses of empagliflozin lowered HBA1C and body weight, and improved BP control, but more importantly there was a 38% reduction in CV death (p<0.0001) and a 35% reduction in hospitalisation for HF (p=0.0017). From the kidney perspective, there was a 39% reduction in new or worsening nephropathy (p<0.001) and 46% in hard renal end-points namely doubling in serum creatinine, initiation of renal-replacement therapy and death from end-stage CKD (p<0.001). The benefits were also seen in patients where the estimated GFR was <45ml/min where there was a 44% reduction in doubling of serum creatinine (p=0.0009) (Figure 3).

There was strong support that benefits accrued primarily due to the underlying mechanism of action of empagliflozin and not through glucose-lowering per se. Hospitalisation for HF separated very early suggesting that increased natriuresis was the primary reason. Kidney benefit appeared after six months of treatment and analysis of the estimated GFR showed early reduction in GFR in both empagliflozin arms followed by a stable trend thereafter. In the placebo arm, there was no initial drop in estimated GFR, but this was followed by inexorable decline with the lines crossing at about 52 weeks. This supports the concept that reducing hyperfiltration as described above is the primary mechanism for renal protection with reduction in BP having a lesser role.

The CANVAS programme using canagliflozin compared to placebo reported similar reductions in CV and kidney events. More recently a dedicated trial (CREDENCE) using canagliflozin vs placebo in patients with DKD was stopped prematurely due to the superior effects of canagliflozin on kidney end-points (https://www.jnj.com/). This study is not published and further details are awaited.

Figure 2. Nephron changes in Diabetes and after administration of RAS Inhibitor + SGLT2 Inhibitor

“These effects reduce the GFR in the short term by 2-3 ml/min but are likely to protect the kidney in the long term in a manner similar to the effects of RAS inhibitors...”
Outcomes studies with dapagliflozin have not been reported to date. Although the place of SGLT-2 inhibitors in the treatment of type 2 diabetes is not formally established, they should undoubtedly be used in overweight patients with established CV or at high risk of CV disease based on the EMPA-REG OUTCOME study and the CANVAS programme, provided there are no contraindications, and taking into account the side effect profile of the SGLT-2 inhibitors.

In addition, they should be considered in patients with signs of CKD (albuminuria and/or reduced eGFR but not below 30ml/min), although this not a registered indication in South Africa. There is also no reason, except for immediate drug costs, why these drugs should not also be considered as second line after metformin in the diabetic algorithm of care; they can also be combined with most other antidiabetic medications, including insulin.

The future of these drugs looks very exciting as further CV and kidney outcomes studies are nearing completion. Additionally, studies are being extended to CV and kidney protection in non-diabetic subjects. In patients with CKD, there is increased single-nephron GFR due to increased glomerular pressure and hyperfiltration to compensate for loss of GFR, which in the long term is deleterious to the kidney. SGLT-2 inhibitors may indeed benefit patients with non-diabetic CKD by reducing glomerular pressure and hyperfiltration.

**Cautions and side effects of SGLT-2 inhibitors**

The prescriber should refer to the full package insert before selecting a SGLT-2 inhibitor for treatment of type 2 diabetes, but there are a few important contraindications and cautions to be considered. Firstly it should not be given to type 1 diabetics due to risk of ‘normoglycaemic’ ketoacidosis and used with caution in thin type 2 diabetics as they may potentially be mislabelled and have type 1 diabetes. Normoglycaemic ketoacidosis can occur very rarely in type 2 diabetics, usually during periods of prolonged fasting. The SGLT-2 inhibitor should be stopped in these circumstances or carefully monitored. They should also be avoided in patient >75 years, where risks of dehydration may outweigh benefits.

**Figure 3. Risk compression for seven renal outcomes.**

From EMPA-REG OUTCOME renal trial

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**Table:**

<table>
<thead>
<tr>
<th>Renal Outcome Measure</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy or cardiovascular death</td>
<td>675/4170 (16.2)</td>
<td>497/2101 (23.6)</td>
<td>0.61 (0.55–0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>525/4124 (12.7)</td>
<td>388/2061 (18.8)</td>
<td>0.61 (0.53–0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to macroalbuminuria</td>
<td>459/4091 (11.2)</td>
<td>330/2033 (16.2)</td>
<td>0.62 (0.54–0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45ml/min/1.73m²</td>
<td>70/4645 (1.5)</td>
<td>60/2323 (2.6)</td>
<td>0.56 (0.39–0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initiation of renal-replacement therapy</td>
<td>13/4687 (0.3)</td>
<td>14/2333 (0.6)</td>
<td>0.45 (0.21–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45ml/min/1.73m², initiation of renal-replacement therapy, or death from renal disease</td>
<td>81/4645 (1.7)</td>
<td>71/2323 (3.1)</td>
<td>0.54 (0.40–0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident albuminuria in patients with a normal albumin level at baseline</td>
<td>1430/2779 (51.5)</td>
<td>703/1374 (51.2)</td>
<td>0.95 (0.87–1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

All the analyses shown were performed with the use of Cox regression in patients who received at least one dose of either empagliflozin or placebo. All the analyses were prespecified except for the composite outcome of a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease. The abbreviation eGFR denotes estimated glomerular filtration rate.
The most common side effect is genital candidiasis due to glucosuria, and is mainly seen in females. This is easily treated with local antifungal creams and seldom recurs. There may be a slight increase in urinary tract infection, but this is seldom severe.

Initial reports suggested a possible increase in fracture risk with SGLT-2 inhibitors, but this was not borne out by a recent meta-analysis. Initial reports suggested an association between bladder cancer and dapagliflozin, but further analysis suggested these cases were pre-existing. Canagliflozin was linked to increased risk of amputation in the CANVAS programme, and further study is required to establish if this is a causal link.

Conclusions

The publication of the EMPA-REG OUTCOME study in 2015 was a major milestone in development of safer and more effective drugs for type 2 diabetes. It broke the nihilism expressed by many in relation to prevention of CV disease in type 2 diabetics. For the first time in decades an antidiabetic drug was found to safely lower blood glucose and show unequivocal evidence for prevention of CV and renal disease that can be explained by the underlying mechanism of action.

References