# Nephropathy

## SGLT2 inhibitors and the kidney: A new approach to nephropathy treatment

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Each human kidney comprises around 1 million filtering units, or nephrons. The filtration organelle of the nephron is the glomerulus, which comprises a meshwork of interconnecting capillaries fed by an afferent arteriole and drained by an efferent arteriole. These two vessels control the pressure within the glomerular capillaries and this, in turn, drives filtration (Mogensen et al, 1990)

In type 1 diabetes, afferent arteriolar dilatation and relative efferent arteriolar constriction occurs, leading to an increase in capillary pressure and glomerular filtration rate (GFR), known as hyperfiltration (Magee et al, 2009). This afferent arteriolar dilatation is probably caused by decreased sodium and chloride content in the filtrate that reaches the distal tubule as a result of increased proximal absorption due to sodium–glucose co-transporter 2 (SGLT2) activity. This increase in intraglomerular capillary pressure (IGCP) is thought by many to cause pathophysiological changes in the glomerulus that result in nephropathy and progressive loss of filtration (O'Bryan and Hostetter, 1997). Hyperfiltration is more common in people with poor glycaemic control and is reversible by improving glycaemic control, which has been shown to reduce IGCP in animal models (Thomson et al, 2012). The evidence for the effects of hyperfiltration in type 2 diabetes is less strong but consistent with observations in type 1 diabetes (Ruggenenti et al, 2012).

Renin–angiotensin system (RAS)-blocking agents reduce IGCP by dilating the efferent arteriole, and it is this property that is thought to be nephroprotective in diabetes (O'Bryan and Hostetter, 1997). However, these agents do not completely prevent nephropathy, so there is a need to explore other methods of reducing IGCP. In the article summarised alongside, Cherney and colleagues have beautifully demonstrated a novel method of reducing hyperfiltration in type 1 diabetes in a series of carefully controlled clinical experiments in people with type 1 diabetes receiving SGLT2 inhibitors. These agents reduce proximal tubular reabsorption of glucose (and, as a result, sodium and chloride), thus restoring normal filtrate composition in the distal tubule and reversing afferent arteriolar dilatation, in turn reducing GFR. However, the most interesting finding was that this reduction was only seen in participants with hyperfiltration at baseline, who would, therefore, have an increased risk of later development of nephropathy. These agents thus provide a completely novel way of correcting ICGP and, perhaps, subsequent loss of GFR.

As a result of these findings, a large, long-term study is underway in people with type 2 diabetes and increased albuminuria using a combination of SGLT2 inhibitors and RAS inhibitors, and with a mixture of both cardiovascular and renal endpoints (ClinicalTrials.gov identifier NCT02065791). However, it is possible that SGLT2 inhibitors may be less effective once nephropathy is established because other non-haemodynamic mechanisms may be operating. Moreover, the role of hyperfiltration in progressive type 2 diabetes-related nephropathy is not well established, partly because people with this complication tend to be older and have a reduced GFR due to ageing and non-diabetic renal disease. The ideal study would, in my view, involve people with type 1 diabetes who are hyperfiltering at baseline, and would assess whether we can primarily prevent the development of nephropathy. Such a study would, of course, take a long time and the financial rewards would be limited, which is one of the problems in relying on pharmaceutical funding for clinical research. Nonetheless, the findings of Cherney and colleagues open new avenues of therapy for nephropathy, and the results of the ongoing clinical trials are keenly awaited. There is clearly a great deal more to SGLT2 inhibitors than lowering blood glucose levels alone. ■

**References on next page**

## Circulation

### Empagliflozin reduces renal hyperfiltration in people with T1D

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| **Readability** | ✓✓✓✓✓ |
| **Applicability to practice** | ✓✓✓✓ |
| **WOW! Factor** | ✓✓✓✓✓ |

1 The aim of this first-in-class, 8-week, open-label study was to determine the effects of empagliflozin, a sodium–glucose co-transporter 2 (SGLT2) inhibitor, on renal hyperfiltration in people with T1D.

2 Of 40 participants, 13 had normofiltration (glomerular filtration rate [GFR], 90–134 mL/min/1.73 $m^2$) and 27 had hyperfiltration (GFR, ≥135 mL/min/1.73 $m^2$). All were assessed under euglycaemic and then hyperglycaemic clamp conditions before and after 8 weeks of treatment with empagliflozin.

3 Treatment resulted in a reduction in renal hyperfiltration in both euglycaemic (change in GFR, –33 mL/min/1.73 $m^2$) and hyperglycaemic (–44 mL/min/1.73 $m^2$) conditions. The final GFRs were close to the upper limit of normal. GFR was largely unaffected in those with normofiltration at baseline.

4 Changes in weight, $HbA_{1c}$, metabolic parameters and dietary factors were similar between the normofiltration and hyperfiltration groups; therefore, the authors conclude that the baseline differences in renal function were a result of increased proximal tubular sodium–glucose co-transport, and that SGLT2 inhibition negated this.

5 Empagliflozin increased urinary volume and 24-hour urinary glucose excretion significantly more in the hyperfiltration group, which suggests that the renal haemodynamic response was related to increased sodium chloride delivery to the distal tubule.

Cherney DZ, Perkins BA, Soleymanlou N et al (2014) Renal hemodynamic effect of sodium–glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* **129**: 587–97

## Diabetes Care

### Effects of blood and pulse pressure on renal outcomes in T2D

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| Readability | ✓✓✓✓ |
| Applicability to practice | ✓✓✓✓ |
| WOW! Factor | ✓✓✓ |

1 In people with T2D, the optimal levels of systolic blood pressure (SBP), diastolic BP and pulse pressure (PP) to protect renal function have not been fully elucidated.

2 In this *post hoc* analysis of the VADT (Veterans Affairs Diabetes Trial), the authors examined the effects of these variables on renal outcomes in terms of albumin:creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR).

3 Among the 1791 participants with T2D, compared with an SBP of 105–129 mmHg, the risk of worsening ACR increased with SBPs of 130–139 mmHg (hazard ratio [HR], 1.88) and ≥140 mmHg (HR, 2.51).

4 Compared with a PP of 40–49 mmHg, the risk of worse ACR reduced with a PP of <40 mmHg (HR, 0.36) but increased with a PP of ≥60 mmHg (HR, 2.38).

5 There was an interaction between SBP ≥140 mmHg and $HbA_{1c}$, such that people with this level of SBP were 15% more likely than those with a lower SBP to experience eGFR worsening for each 1% (11-mmol/mol) increase in $HbA_{1c}$.

6 The authors conclude that an SBP of ≥130 mmHg and a PP of ≥60 mmHg were associated with worsening renal function. They advocate more rigorous treatment of hypertension to reduce renal risk, particularly in people with an SBP of ≥140 mmHg.

7 Improving glycaemic control may have a particularly significant renoprotective effect in people with an SBP ≥140 mmHg.

Anderson RJ, Bahn GD, Emanuele NV et al (2014) Blood pressure and pulse pressure effects on renal outcomes in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Care* **37**: 2782–8

## JAMA

### eGFR decline and risk of ESRD

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| Readability | ✓✓✓ |
| Applicability to practice | ✓✓✓✓ |
| WOW! Factor | ✓✓✓✓ |

1 Clinical trials in chronic kidney disease (CKD) typically use an endpoint of end-stage renal disease (ESRD) or reduction in estimated glomerular filtration rate (eGFR) of ≥57%; however, these are late events that occur over a long follow-up of around 5 years.

2 In this meta-analysis of 1.7 million participants with CKD, the effect of changes in eGFR over 1–3 years on ESRD and mortality was evaluated.

3 Among people with a baseline eGFR of <60 mL/min/1.73 $m^2$, a ≥57% reduction was more strongly associated with ESRD than a ≥30% reduction (hazard ratio, 32.1 vs 5.4); however, the smaller reduction was 10-times more common and thus had a higher population attributable risk (44% vs 10%). Associations with death were weaker but qualitatively similar.

4 Thus, lower eGFR declines could be valid endpoints in shorter (2–3-year) clinical trials.

Coresh J, Turin TC, Matsushita K et al (2014) Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* **311**: 2518–31

## Diabetologia

### Effect of long-term normoglycaemia on kidney graft function and structure in T1D

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| Readability | ✓✓✓✓ |
| Applicability to practice | ✓✓✓ |
| WOW! Factor | ✓✓✓ |

1 The authors determined whether long-term normoglycaemia, achieved by simultaneous pancreas and kidney (SPK) transplant, improved 10-year kidney graft survival compared with hyperglycaemia (kidney transplant alone) in 42 people with T1D.

2 Mean $HbA_{1c}$ was 37 mmol/mol (5.5%) in the SPK group and 68 mmol/mol (8.3%) in the kidney group.

3 Compared with the SPK group, the kidney group had a greater mean glomerular basement membrane width and mesangial volume fraction, and a reduced slope of estimated glomerular filtration rate reduction per year.

4 These findings suggest that pancreatic transplantation reduces the long-term risk of diabetic glomerulopathy in transplanted kidneys.

Lindahl JP, Reinholt FP, Eide IA et al (2014) In patients with type 1 diabetes simultaneous pancreas and kidney transplantation preserves long-term kidney graft ultrastructure and function better than transplantation of kidney alone. *Diabetologia* **57**: 2357–65

## J Diabetes Complications

### Diabetic retinopathy associated with renal outcomes in T2D

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| Readability | ✓✓✓✓ |
| Applicability to practice | ✓✓✓✓ |
| WOW! Factor | ✓✓✓✓ |

1 In this subanalysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, the authors evaluated the association between diabetic retinopathy (DR) and renal and cardiovascular (CV) outcomes in 3210 people with T2D.

2 Participants were stratified according to absent or mild ($n$=2215) and moderate or severe ($n$=995) DR.

3 Compared with those with no/mild DR, people with moderate/severe DR had an unadjusted hazard ratio for incident macroalbuminuria, doubling of serum creatinine level and non-fatal CV events of 2.58, 2.31 and 1.98, respectively.

4 Within the two DR strata, there was no difference in the incidence of renal or CV endpoints. Further study of the specificity of DR for renal and CV risk in other populations is warranted.

Mottl AK, Pajewski N, Fonseca V et al (2014) The degree of retinopathy is equally predictive for renal and macrovascular outcomes in the ACCORD Trial. *J Diabetes Complications* 12 Jul [Epub ahead of print]

> *"The authors conclude that a systolic blood pressure of ≥130 mmHg and a pulse pressure of ≥60 mmHg were associated with worsening renal function."*

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