A huge unmet need exists for new pharmacological approaches to prevent the onset and progression of diabetic nephropathy (DN), which remains the primary cause of chronic kidney disease and need for renal replacement therapy worldwide. Two new classes of glucose-lowering agents with putative glucose-independent renoprotective properties have been developed for patients with type 2 diabetes mellitus (T2DM): sodium–glucose cotransporter 2 (SGLT2) inhibitors and the incretin-based therapies, glucagon-like peptide 1 receptor (GLP1R) agonists and dipeptidyl peptidase 4 (DPP4) inhibitors. New data from the LEADER trial show that the glucagon-like peptide 1 receptor agonist liraglutide protects against diabetic nephropathy in patients with type 2 diabetes mellitus. The renoprotective efficacy of liraglutide is not, however, as great as that reported for the sodium–glucose cotransporter 2 inhibitor empagliflozin in the EMPA-REG OUTCOME trial.


The effects of SGLT2 inhibitors on tubuloglomerular feedback are probably more important than blood pressure lowering in determining their renoprotective effects. Under conditions of hyperglycaemia, reabsorption of glucose and sodium is increased in the proximal tubule, resulting in decreased delivery of sodium to the juxtaglomerular apparatus. The resulting increase in the local generation of renin and angiotensin in the juxtaglomerular apparatus leads to the constriction of efferent arterioles and dilation of the afferent renal arterioles, which is mediated by factors such as prostanoids, nitric oxide and adenosine. The combination of efferent renal arteriolar vasoconstriction and afferent renal arteriolar vasodilation causes an increase in intraglomerular pressure, resulting in glomerular hyperfiltration and damage to the glomerulus in the long term. By blocking the transport of sodium and glucose in the proximal tubule, SGLT2 inhibition increases sodium delivery to the juxtaglomerular apparatus, leading to afferent arteriolar vasoconstriction and a decrease in intraglomerular pressure, which is likely a key renoprotective mechanism. GLP1R agonists might also affect glomerular pressure by altering glomerular haemodynamics; however, these effects likely vary depending on specific conditions such as disease stage and glycaemia. These varying haemodynamic effects might help to explain why liraglutide therapy did not reduce the incidence of doubling of creatinine levels and the occurrence of ESRD in patients with T2DM.

Remarkably, in both the LEADER and EMPA-REG OUTCOME trials, as well as in the landmark RENAAAL and IDNT studies of angiotensin II receptor blockers (ARBs) for the treatment of DN, the effects of the intervention on progression of DN were independent of the glucose-lowering effects. Comparing data from these studies, ARBs showed similar efficacy to empagliflozin and natriuresis most likely involves inhibition of sodium/hydrogen exchanger 3 (NHE3) in the proximal tubule. GLP1R agonists increase the generation of cAMP, activation of protein kinase A (PKA) and phosphorylation of NHE3 at the PKA consensus sites Ser552 and Ser605, thus decreasing NHE3 activity. However, the net effect of GLP1R agonists on blood pressure seems to be less pronounced than that of SGLT2 inhibitors.
greater efficacy than liraglutide in terms of effects on urinary albumin and protein excretion, doubling of serum creatinine levels and need for renal replacement therapy478 [TABLE 1]. They also reduced all-cause mortality similarly to the SGLT2 inhibitor when given in a blood pressure-lowering dose. Liraglutide reduces all-cause mortality as well; however, in contrast to the SGLT2 inhibitor the effect of liraglutide on all-cause mortality is most likely not due to its moderate beneficial effects on the kidney. Rather, its non-renal effects seem to be more important. The study size necessary to demonstrate superiority to standard of care was, however, much smaller in the ARB studies than in the EMPA-REG OUTCOME and LEADER trials. This difference reflects the fact that RAAS blockade is the current standard of care, and showing an additional benefit on top of this therapy is much harder than with previous standard of care therapies for DN. If SGLT2 inhibitors or GLP1R agonists had been developed before RAAS inhibitors, we would most likely face the same challenge in showing an additional benefit of RAAS inhibition.

The efficacy of GLP1R agonists and SGLT2 inhibitors for the treatment of DN needs to be confirmed in outcome trials with primary renal end points, and robust safety data need to be generated. In addition, why liraglutide showed convincing effects on reduction of persistent macroalbuminuria, but failed to demonstrate clinically important effects on doubling of serum creatinine levels and progression to ESRD, remains to be determined. Importantly, evidence suggests that incretin-based therapies8 and targeting the tubuloglomerular feedback mechanism9 will likely also be effective in non-diabetic CKD. The success of GLP1R agonists and in particular SGLT2 inhibitors in diabetic kidney disease might stimulate the design of appropriate phase II proof-of-concept studies in nondiabetic patients with CKD.

Berthold Hocher is at the Key Laboratory of Study and Discovery of Small Targeted Molecules of Hunan Province, School of Medicine, Hunan Normal University, Changsha 410013, China.
Oleg Tsuprykov is at the Institute of Nutritional Science, University of Potsdam, 14558 Nuthetal-Potsdam, Germany.

Correspondence to B.H. hocher@uni-potsdam.de
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Competing interests statement
B.H. is a consultant for Boehringer Ingelheim on the development of dipetidyl peptidase 4 (DPP4) inhibitors and has received research funding from this company for investigation of the renal effects of the DPP4 inhibitor linagliptin. O.T. declares no competing interests.

### Table 1 | Comparison of key studies of the treatment of diabetic nephropathy in patients with T2DM

<table>
<thead>
<tr>
<th>Trial (drug)</th>
<th>Population</th>
<th>Baseline characteristics*</th>
<th>Duration (years)</th>
<th>Outcomes (drug/placebo)</th>
<th>Need for RRT</th>
<th>All-cause mortality</th>
<th>BP lowering</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1R agonist</td>
<td>LEADER (liraglutide)</td>
<td>9,340 (64%/75.5%)</td>
<td>Age 64.3 years; SBP 135.9 mmHg; eGFR 80.4 ml/min/1.73 m²; macroalbuminuria present in 11.3%; HbA1c 8.7%</td>
<td>3.8</td>
<td>New-onset persistent macroalbuminuria: 3.4%/4.6% (HR 0.74, 95% CI 0.60–0.91, P = 0.004)</td>
<td>1.8%/2.08% (HR 0.89, 95% CI 0.67–1.19, P = 0.43)</td>
<td>1.7%/1.4% (HR 0.87, 95% CI 0.61–1.24, P = 0.44)</td>
<td>8.2%/9.6% (HR 0.82, 95% CI 0.74–0.97, P = 0.02)</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>EMPA-REG OUTCOME (empagliflozin)</td>
<td>7,020 (72%/72%)</td>
<td>Age 63.1 years; SBP 135.4 mmHg; eGFR 65.1 ml/min/1.73 m²; HbA1c 8.1%</td>
<td>3.1</td>
<td>New-onset persistent macroalbuminuria: 11.2%/16.2% (HR 0.54–0.72, P &lt; 0.001)</td>
<td>1.5%/2.6% (HR 0.56, 95% CI 0.39–0.79, P &lt; 0.001)</td>
<td>0.3%/0.6% (HR 0.45, 95% CI 0.21–0.97, P = 0.04)</td>
<td>5.7%/8.3% (HR 0.68, 95% CI 0.57–1.23, P &lt; 0.001)</td>
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<tr>
<td>Angiotensin II receptor blockers</td>
<td>IDNT (irbesartan)</td>
<td>1,715 (66.5%/72.4%)</td>
<td>Age 58.9 years; SBP 159.0 mmHg; urinary protein excretion 2.9 g per 24 h; HbA1c 8.2%</td>
<td>2.6</td>
<td>Reduction in proteinuria: –33% (P &lt; 0.001)/–10% (P = NA)</td>
<td>16.9%/23.7% (HR 0.67, 95% CI 0.52–0.87, P &lt; 0.003)</td>
<td>14.2%/17.8% (HR 0.77, 95% CI 0.57–1.03, P = 0.07)</td>
<td>15.0%/16.3% (HR 0.92, 95% CI 0.69–1.23, P = 0.57)</td>
</tr>
<tr>
<td>RENAAI (losartan)</td>
<td>1,513 (63.5%/48.6%)</td>
<td>Age 60 years; SBP 152.5 mmHg; median ACR 1.24 g/g; HbA1c 8.5%</td>
<td>3.4</td>
<td>Proteinuria reduction: –35%/18% (P &lt; 0.001)</td>
<td>21.6%/26.0% (HR 0.89, 95% CI 0.69–0.95, P = 0.02)</td>
<td>19.6%/25.5% (HR 0.85, 95% CI 0.68–1.08, P = 0.10)</td>
<td>21.0%/20.3% (HR 0.88, 95% CI 0.72–1.09, P = 0.15)</td>
<td>Mean arterial BP: –0.4 mmHg (P = NS)</td>
</tr>
</tbody>
</table>

The investigated drugs were given in addition to the current standard of care therapy. ACR, albumin:creatinine ratio; BP, blood pressure; eGFR, estimated glomerular filtration rate; GLP1, glucagon-like peptide 1; HbA1c, haemoglobin A1c; NA, not available; NS, not significant; RRT, renal replacement therapy; SBP, systolic blood pressure; SGLT2, sodium–glucose cotransporter 2; T2DM, type 2 diabetes mellitus. *Data are means unless otherwise specified. †A composite outcome comprising doubling of serum creatinine levels accompanied by eGFR ≤45 ml/min/1.73 m².

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