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Emerging paradigms of treating diabetic nephropathy

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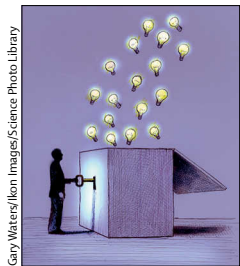
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## Emerging paradigms of treating diabetic nephropathy



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Type 2 diabetes is the leading cause of chronic kidney disease, including end-stage renal disease, worldwide. Few effective therapeutic strategies exist for the prevention and treatment of diabetic kidney disease; the main strategy is modulation of the renin-angiotensin-aldosterone system by angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). These drugs have renal protective effects beyond their traditional effects on blood pressure.<sup>1,2</sup> Angiotensin-pathway modulators and low-protein diet have been shown to have a synergistic effect on intraglomerular pressure, with the former relaxing the efferent arteriole and the latter contracting the afferent arteriole, leading to amelioration of glomerular hyperfiltration and reduced proteinuria.<sup>3</sup> However, even after maximising dietary and pharmacological interventions, proteinuria might continue in some patients with diabetic kidney disease,<sup>4</sup> and combining ARBs and ACE inhibitors or adding aliskiren<sup>5,6</sup> have not been shown to provide additional benefits.

Over the past decade, several clinical trials have investigated the potential added benefit of using novel pharmacotherapeutic drugs to improve proteinuria and renal outcomes in patients with diabetic kidney disease. Trials of the antioxidant bardoxolone methyl (NCT01351675), the endothelin-receptor antagonist avosentan (NCT00120328), and the anticoagulant sulodexide (NCT00130312) were terminated early because of an increased risk of adverse events or lack of efficacy. In another trial,<sup>7</sup> empagliflozin (an antihyperglycaemic drug targeting sodium-glucose co-transporter-2 [SGLT2]) provided both cardiac and renal protection in patients with type 2 diabetes, although there was no significant difference between empagliflozin and placebo groups in the proportion of patients who had incident albuminuria. However, the proportion of patients who progressed to macroalbuminuria in that trial<sup>7</sup> was lower in the empagliflozin group than in the placebo group. Canagliflozin, another SGLT2 inhibitor, yielded similar results.<sup>8</sup> Epigenetic pathway modulation might also emerge as a potential therapeutic strategy for chronic kidney disease; apabetalone, a novel inhibitor of bromodomain and extra-terminal proteins, reduced the incidence of major adverse cardiac events in

phase 2 trials,<sup>9,10</sup> slowing the decline in the estimated glomerular filtration rate (eGFR) at the end of 6 months of treatment and lowering serum concentrations of alkaline phosphatase, a surrogate marker for adverse cardiovascular outcomes.<sup>10</sup>

In *The Lancet Diabetes & Endocrinology*, Dick de Zeeuw and colleagues<sup>11</sup> report the results of the ALBUM trial, a randomised, double-blind, placebo-controlled, multicentre, phase 2 study examining the efficacy of a vascular adhesion protein-1 (VAP-1) inhibitor, ASP8232, in reducing albuminuria when added to ACE inhibitors or ARBs for patients with type 2 diabetes and chronic kidney disease. VAP-1 is a member of the semicarbazide-sensitive amine oxidase enzyme family, which is involved in the production of byproducts of oxidative stress, such as aldehyde, hydrogen peroxide, and ammonia.<sup>12</sup> This enzyme is expressed in vascular endothelial cells where it mediates adhesion and transmigration of leucocytes to areas of inflammation. VAP-1 enhanced neutrophil infiltration in the kidneys of a rat model of renal ischaemia-reperfusion injury, and elevated VAP-1 activity has been detected in patients with atherosclerosis, obesity, diabetes, or hypertension.<sup>12,13</sup> Epidemiological studies<sup>14,15</sup> suggest that elevated VAP-1 concentrations are associated with albuminuria and decreased eGFR, and that the VAP-1 concentration independently predicts cardiovascular mortality and risk of progression of chronic kidney disease to end-stage renal disease in patients with diabetes.

In the study by de Zeeuw and colleagues,<sup>11</sup> 125 patients with type 2 diabetes and albuminuria were recruited from 64 sites in ten European countries and randomly assigned to receive ASP8232 40 mg (n=64) or placebo (n=61) once a day for 12 weeks. Participants were followed up for an additional 24 weeks after treatment cessation. The primary endpoint was mean change from baseline to 12 weeks in log-transformed urinary albumin-to-creatinine ratio (UACR), with change in 24-h albuminuria assessed as a secondary endpoint. The study showed that, compared with placebo, ASP8232 significantly reduced UACR at 12 weeks (treatment difference -19.5%, 95% CI -34.0 to -1.8; p=0.033), whereas 24-h albuminuria was not significantly decreased at this timepoint

(−20%, −38.5 to 4.0;  $p=0.094$ ). The effect of ASP8232 on UACR was sustained until the last follow-up visit 24 weeks after discontinuation of ASP8232. The drug was well tolerated, with no drug-related serious adverse event reported in either group. However, there was an acute reduction in eGFR in the ASP8232 group, which returned to normal after the end of treatment. This finding suggests a transient haemodynamic effect of the drug, which might be favourable over longer treatment durations, similar to what is observed for angiotensin-pathway modulators and low-protein diet. Overall, there was no difference in eGFR between groups by the end of follow-up.

The study is well designed and provides important evidence of a renoprotective effect of VAP-1 inhibition in patients with diabetic nephropathy. The main strength of the study is that both treatment and placebo groups received ACE inhibitors or ARBs as the standard of care, allowing an additive effect to be confirmed. However, possible interactions with dietary protein intake were not analysed. There was no change in blood pressure between the two groups, suggesting that the reduction in albuminuria with ASP8232 was independent of any effect on blood pressure. Nevertheless, although reduction in albuminuria might be associated with improved cardiovascular outcomes, the effect of this endpoint on progression of chronic kidney disease has yet to be ascertained. Larger trials with longer follow-up are needed to assess the decline in eGFR during the 12-week treatment period in the ASP8232 group, as are phase 3 trials to assess the long-term renal, cardiovascular, and metabolic effects of this promising drug. Preclinical studies of ASP8232 in appropriate models of diabetic and non-diabetic kidney disease are also needed to better understand the underlying mechanisms of VAP-1 inhibitors.

Although further studies are needed to assess the efficacy and safety of this innovative therapy in patients with diabetic kidney disease when added to standard interventions, the findings of this study are a cause for cautious optimism that targeting this novel pathway might provide meaningful renal and cardiac benefits that compliment currently available therapies for chronic kidney disease.

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