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EDITORIAL

The era of combination of nephroprotective agents in CKD is there

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In the 1980s, Barry Brenner hypothesized that maladaptive glomerular hemodynamic changes exert a major influence on the factors that initiate and perpetuate kidney disease progression. This concept of hyperfiltration triggered experimental studies with enalapril, which mitigated the relentless progression of kidney disease in various models [1]. Clinical trials with ACE-Inhibitors (ACE-I) confirmed the validity of this concept in patients with type 1 diabetes [2], then in patients with heavily albuminuric non-diabetic CKD [3]. Angiotensin-receptor blockers (ARB) subsequently were shown to delay the progression of CKD in participants with type 2 diabetes [4, 5]. Yet, the range of nephroprotective drugs for the general management of CKD remained limited to ACE-I or ARB [6]. Multiple studies then tested their combination to enhance nephroprotection but success was not at the end of the road: all three major trials (one of them using a direct renin inhibitor, aliskiren) showed increased risk of AKI and hyperkalemia with the combination of two agents blocking the RAS system, without clear evidence of additional nephroprotection compared with a single agent [7–9].

Fortunately, the field has recently experienced a welcome burst of additional effective nephroprotective agents, effective both in participants with type 2 diabetes (TD2) and other causes of CKD. These include SGLT2-inhibitors in both indications, and the nonsteroidal mineralocorticoid receptor antagonist finerenone in T2D only so far. This has now been included in recent guidelines [10, 11]. Even more recently, the publication of the FLOW trial results with the glucagon-like peptide 1 receptor agonist semaglutide in T2D with CKD [12] adds another agent to the armamentarium, of course awaiting regulatory approval for the CKD and T2D indication for semaglutide and position in guidelines. These encouraging results have led to the concept of four pillars of therapy for CKD as the agents may work on different additive mechanisms [13].

The good news is that this flurry of new drugs is likely to expand further, with multiple additional phase 3 trials now starting or underway. These include the indication of finerenone for albuminuric non-diabetic CKD, currently tested in the FIND-CKD trial and albuminuric CKD in type 1 diabetes tested in the FINE-ONE trial, the development of aldosterone synthase inhibitors, whose promising results in phase 2 [14] prompted phase 3 trials in CKD with or without diabetes, and the renewal of interest for endothelin-receptor antagonists in combination with SGLT2-i, again after encouraging phase 2 results [15].

In this Supplement of *Nephrology Dialysis Transplantation*, top experts highlight key aspects of the implications of this ongoing revolution in the management of CKD.

Jaisser and Barrera-Chimal review the preclinical evidence showing new mechanisms by which mineralocorticoid receptor inhibition results in beneficial effects against cardiorenal damage in non-diabetic kidney disease. Moreover, they summarize the clinical trials testing the safety and efficacy of steroidal and non-steroidal MRAs in patients with advanced non-diabetic CKD.

Carsten Wagner reviews the relevance of some major proximal tubule transport systems as drug targets in individuals with CKD. Indeed, in addition to SGLT2 inhibitors, carbonic anhydrase inhibitors and uricosuric drugs are already available. Inhibition of phosphate and amino acid transporters has been recently proposed to remove excess phosphate or to protect the proximal tubule metabolically, respectively. In addition, organic cation and anion transporters involved in drug and toxin excretion may serve as targets of new drugs. He discusses the advantages and challenges associated with (novel) drugs targeting proximal tubule transport.

Zhu *et al.* from the Oxford Clinical Trial Center discuss, in the current era, the implications of the revolution of combination therapies to manage risk of CKD progression for trial design (in terms of sample size, study design, adherence to study interventions a.o.). They also review recent innovations in trial design.

Moedt *et al.* discuss the use of selective endothelin-receptor antagonists (ERA) as a viable therapeutic option in CKD. Indeed, whereas the use of ERA was fraught with the risk of fluid retention, the concomitant use of SGLT2 inhibitors mitigates this risk.

Nardone *et al.* highlight the clinical evidence supporting emerging therapies for CKD, including glucagon-like peptide-1 receptor agonists and other incretin-based therapies, aldosterone synthase inhibitors, ERA, soluble guanylate cyclase agonists, and anti-inflammatory drugs.

Alicic *et al.* discuss the available evidence supporting combination therapy in CKD with diabetes and additionally discuss ongoing and future trials evaluating the efficacy and safety of combination therapies for CKD with or without diabetes.

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Finally, Neuen *et al.* review the rationale for combination therapy with evidence-based kidney therapies for diabetic and non-diabetic CKD. They further outline the randomized evidence supporting a combination therapy approach, safety considerations, and potential frameworks for implementation to reduce long-term risk of kidney failure and other associated complications.

We do hope that the readers of this Supplement issue of *Nephrology Dialysis Transplantation* will enjoy these insightful contributions, which collectively highlight the current fast progress and paradigm shift in nephroprotection.

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REFERENCES

1. Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 1986;**77**:1993–2000. https://doi.org/10.1172/JCI112528
2. Lewis EJ, Hunsicker LG, Bain RP *et al.* The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;**329**:1456–62. https://doi.org/10.1056/NEJM199311113292004
3. GISEN Group. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997;**349**:1857–63.
4. Brenner BM, Cooper ME, de Zeeuw D *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–9. https://doi.org/10.1056/NEJMoa011161
5. Lewis EJ, Hunsicker LG, Clarke WR *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851–60. https://doi.org/10.1056/NEJMoa011303
6. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney IntSuppl* 2013;**3**:1–150.
7. Parving HH, Brenner BM, McMurray JJ *et al.* Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;**367**:2204–13. https://doi.org/10.1056/NEJMoa1208799
8. Fried LF, Emanuele N, Zhang JH *et al.* Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**:1892–903. https://doi.org/10.1056/NEJMoa1303154
9. Mann JFE, Schmieder RE, McQueen M *et al.* Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;**372**:547–53. https://doi.org/10.1016/S0140-6736(08)61236-2
10. Kidney Disease: Improving Global Outcomes diabetes work G. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2022;**102**:S1–S127. https://doi.org/10.1016/j.kint.2022.06.008
11. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2024;**105**:S117–s314. https://doi.org/10.1016/j.kint.2023.10.018
12. Perkovic V, Tuttle KR, Rossing P *et al.* Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med* 2024;**391**:109–21. https://doi.org/10.1056/NEJMoa2403347
13. Naaman SC, Bakris GL. Diabetic nephropathy: update on pillars of therapy slowing progression. *Diabetes Care* 2023;**46**:1574–86. https://doi.org/10.2337/dci23-0030
14. Tuttle KR, Hauske SJ, Canziani ME *et al.* Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, phase 2 trial. *Lancet* 2024;**403**:379–90. https://doi.org/10.1016/S0140-6736(23)02408-X
15. Heerspink HJL, Kiyosue A, Wheeler DC *et al.* Zibotentan in combination with dapagliflozin compared with dapagliflozin in patients with chronic kidney disease (ZENITH-CKD): a multicentre, randomised, active-controlled, phase 2b, clinical trial. *Lancet* 2023;**402**:2004–17. https://doi.org/10.1016/S0140-6736(23)02230-4

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