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de Borst, Martin H

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A new era in cardio-renal risk management: overview of landmark papers published in *NDT* in 2021

Martin H. de Borst

Department of Internal Medicine, Division of Nephrology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands

Correspondence to: Martin H. de Borst; E-mail: m.h.de.borst@umcg.nl

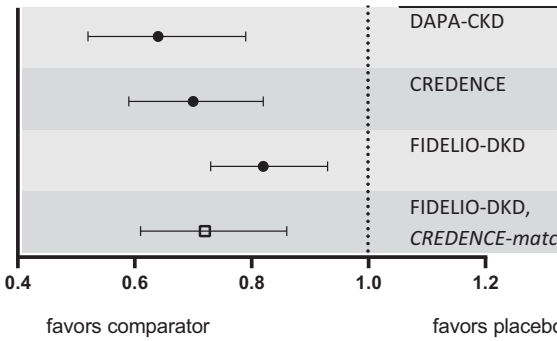
The World Health Organization Global Action Plan for the Prevention and Control of Non-Communicable Diseases (NCDs) aims to reduce mortality from cardiovascular diseases, cancers, diabetes and chronic respiratory diseases among individuals aged 30–70 years by 25% between 2010 and 2025 [1]. Although some progress has been made over the past decade, focussing on just these four groups of NCDs may not be sufficient. A recent study analysed premature deaths caused by NCDs that could be prevented through effective public policies and health interventions at global, regional and national levels. Although an overall global reduction in premature avertable mortality from NCDs was observed, the number of premature avertable deaths from chronic kidney disease (CKD) and acute glomerulonephritis increased in many countries and regions [2]. While alarming, recent developments in the field of nephrology raise hope that this trend will change soon. Several novel therapies have become available or are currently under development to better manage cardiovascular complications, the main cause of death in CKD. This editorial will address emerging strategies and therapies that may contribute to improving cardiovascular outcomes in CKD, with a specific focus on five landmark articles published in *Nephrology Dialysis Transplantation* (*NDT*) in 2021.

AVOIDANCE OF RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM BLOCKADE DISCONTINUATION

Since the 1990s, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) have demonstrated efficacy to reduce the risk of kidney failure and mortality in patients with CKD and form the cornerstone therapy for these patients. Yet, for various reasons including acute deterioration of kidney function, hyperkalaemia or hypotension, ACEi or ARB treatment may be discontinued. A recent *NDT* study in a large cohort of US veterans with CKD showed that ACEi/ARB discontinuation was associated with a 1.7–2.3 times increased risk of death [3]. Remarkably, this association was already evident if ACEi/ARB was interrupted for a short period (14–30 days). The observational nature of this and similar studies published previously precludes firm conclusions on causality, but given trial data that ACEi treatment reduces the risk of mortality or kidney failure also in advanced CKD [4], there seems a strong basis to further explore interventions that could facilitate its continuation. Recently, novel potassium binders patiromer and sodium zirconium cyclosilicate (SZC) have become available, theoretically making it possible to overcome hyperkalaemia as a reason for ACEi/ARB discontinuation in some patients. Several studies with both compounds have demonstrated their efficacy for long-term normalization of potassium levels in patients with CKD. Roger *et al.* addressed whether SZC had similar efficacy in patients with worse kidney function [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2], compared with those with mildly impaired or normal kidney function (eGFR ≥30 mL/min/1.73 m^2) [5]. The main finding was that proportions of patients with normokalaemia were similar among both eGFR strata (82% and 90% at 1 year, respectively), although greater proportions of patients with baseline eGFR <30 mL/min/1.73 m^2 experienced adverse events (83% versus 54%, respectively). Whether continuation, or even uptitration, of ACEi/ARB treatment facilitated by patiromer or SZC leads to clinical benefits remains to be demonstrated.

SGLT2 INHIBITORS AND FINERENONE

Decades after the landmark ACEi and ARB trials, several promising new therapies have recently emerged. Large randomized controlled trials with sodium-glucose cotransporter 2 inhibitors (SGLT2i) including the Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) [6] and Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) [7] studies have demonstrated further



Trial name	N	Eligibility criteria	Primary endpoint	Ref
DAPA-CKD	4304	eGFR 25-75 mL/min/1.73 m^2 ACR 200-5000 mg/g	Kidney failure, ≥50% eGFR reduction, renal/CV death	(6)
CREDENCE	4401	eGFR 30-90 mL/min/1.73 m^2 ACR 300-5000 mg/g	Kidney failure, ≥57% eGFR reduction, renal/CV death	(7)
FIDELIO-DKD	5674	eGFR 25-75 mL/min/1.73 m^2 ACR 30-5000 mg/g	Kidney failure, ≥40% eGFR reduction, renal death	(8)
FIDELIO-DKD, *CREDENCE-matched*	4619	eGFR 30-75 mL/min/1.73 m^2 ACR 300-5000 mg/g	Kidney failure, ≥57% eGFR reduction, renal/CV death	(10)

FIGURE 1: Comparison of the effect sizes of three large randomized controlled trials: DAPA-CKD (dapagliflozin), CREDENCE (canagliflozin) and FIDELIO-DKD (finerenone), and a subgroup of FIDELIO-DKD that matches the CREDENCE population and endpoints. From the original publications, it may seem that the effect size of renoprotection by finerenone is smaller compared with the two SGLT2i trials. However, Agarwal *et al.* [10] performed a *post hoc* analysis accounting for differences in eligibility criteria and endpoints (FIDELIO-DKD, CREDENCE matched population). The result is presented in the lowest row (open square symbol) and shows that the effect size of finerenone in a similar population with a similar (cardio-renal) endpoint is in line with DAPA-CKD and CREDENCE. Data derived from referenced studies. CV, cardiovascular.

cardio-renal risk reduction in patients with CKD on top of ACEi/ARB. Furthermore, two recent large trials [Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD)] reported cardio-renal protection by the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone in patients with type 2 diabetes and CKD who already received ACEi or ARB treatment at the maximum tolerated dose [8, 9]. In CREDENCE, DAPA-CKD and FIDELIO-DKD, the relative risks of the primary outcomes were reduced by 30% (95% confidence interval 18–41%), 39% (28–49%) and 18% (7–27%), respectively. It may therefore seem that finerenone had a smaller magnitude of effect than the SGLT2i canagliflozin and dapagliflozin (Figure 1). However, just comparing the primary results of these trials does not take into account that there were considerable differences in the design of the trials, their patient populations and primary endpoints. In a recent *NDT* paper by a group of FIDELIO-DKD investigators [10], these differences were (partly) accounted for by selecting a subpopulation of FIDELIO-DKD participants with inclusion criteria largely overlapping with the CREDENCE population ('CREDENCE-matched', Figure 1). The investigators also accounted for differences in heart failure prevalence at baseline and analysed a modified primary endpoint corresponding as closely as possible with CREDENCE. Interestingly, the main result of this *post hoc* analysis of the FIDELIO-DKD was that cardio-renal protective effects of finerenone were of a similar magnitude to those of canagliflozin in the CREDENCE trial. Therefore, both finerenone and the SGLT2i canagliflozin and dapagliflozin are novel therapies with similar potential to improve the prognosis of patients with CKD. A subsequent question may be whether the combination of SGLT2i and MRA, on top of an optimally dosed ACEi or ARB, might further enhance cardio-renal protection. On one hand, this might seem feasible since side-effects of one drug might be counteracted by the other (e.g. hyperkalaemia, a common side effect of MRA, may be avoided or tempered by concomitant SGLT2i use [11]). On the other hand, other side effects such as an acute decrease in kidney function have been observed for both classes of drugs and may be more pronounced if combined. A secondary analysis of the DAPA-HF trial showed similar efficacy and safety of dapagliflozin in 3370 patients with heart failure who were on MRA treatment [12]. In CKD patients, prior studies with ACEi, ARB and direct renin inhibitors have shown that their combined use is only indicated under specific circumstances. Whether or not the combination of SGLT2 and MRA may be safe and (more) effective in CKD remains to be addressed in dedicated clinical trials. At the same time, further strategies should be explored to target additional pathways deregulated in (advanced) CKD that further improve cardiovascular outcomes.

BONE AND MINERAL DISEASE

Vascular calcification is a hallmark of advanced CKD and the presence and extent of vascular calcification are associated with cardiovascular morbidity and mortality. Deregulations in mineral metabolism, including hyperphosphatemia and hyperparathyroidism, are considered to drive vascular calcification in advanced CKD. The phosphaturia-inducing hormone fibroblast growth factor 23 (FGF23) is one of the earliest hallmarks of CKD-metabolic bone disorder (CKD-MBD) and a higher FGF23 level has been consistently associated with cardiovascular outcomes and mortality across stages of CKD. Interestingly, several studies have demonstrated bilateral cross-talk between aldosterone and FGF23 [13]. Aldosterone and angiotensin II induce expression of FGF23 in bone cells, the main source of FGF23 in the body, as well as in other cells including cardiomyocytes. Conversely, FGF23 can induce angiotensinogen expression and may increase angiotensin II formation, in turn leading to higher aldosterone levels [13]. Also, several studies have shown that MRA can reduce FGF23 levels in animals and patients. Whether the cardiovascular benefits of MRA treatment including finerenone are at least in part mediated by a reduction in FGF23 remains to be addressed.

In addition to efforts aiming to reduce FGF23, other interventions targeting CKD-MBD with the aim to improve cardiovascular outcomes include phosphate binders and vitamin K supplementation. Although phosphate binders are widely used to correct hyperphosphatemia in advanced CKD and kidney failure, evidence that these compounds can reduce cardiovascular morbidity and mortality is limited. Recently, it was demonstrated that phosphate binders can also bind vitamin K, a major inhibitor of vascular calcification. In a recent preclinical study published in *NDT*, Neradova *et al.* showed that combining phosphate binder treatment with high-dose vitamin K2 supplementation attenuated vascular calcification [14]. While these findings require prospective confirmation in humans, this could imply that combination therapy is needed to overcome progressive vascular calcification in patients with kidney failure.

CONCLUSION

New treatments have emerged that will undoubtedly improve the renal and cardiovascular prognosis of patients with CKD. Increasing our knowledge about the optimal positioning of SGLT2i and MRA and their mechanisms of cardio-renal protection may further advance patients' outcomes in the coming years. *NDT* will continue to publish cutting-edge original articles and review papers in this area to further contribute to these exciting developments.

CONFLICT OF INTEREST STATEMENT

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