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## **A step forward towards a new treatment paradigm in the cardiorenal continuum**

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Chronic kidney disease (CKD), mostly defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73m<sup>2</sup>, is a highly prevalent condition in patients with acute and chronic heart failure (HF), while it is associated with dismal clinical outcomes in these patients. CKD and HF are intertwined conditions sharing common cardiovascular (CV) risk factors and disease pathways, which contribute to cardiorenal syndromes- the latter referring to the interactions between chronic or acute HF and CKD or acute kidney injury. Patients with these diseases or risk factors share common pathophysiological pathways that fall along a cardiorenal syndrome continuum. We therefore proposed that they be grouped under a single cardiorenal syndrome umbrella (1). Cardiorenal syndrome could then encompass concomitant cardiovascular and renal disorders that result from systemic diseases and their related neurohormonal, inflammatory, immunologic, and fibrotic consequences. These common pathophysiological pathways have varying clinical expression in the heart (e.g. left ventricular hypertrophy, diastolic dysfunction, HF with preserved (HFpEF), or reduced (HFrEF) ejection fraction) and in the kidney (CKD (w/wo proteinuria) or acute injury) (1). Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) were universally acknowledged across guidelines during the last two decades to improve CV and renal outcomes throughout the cardiorenal continuum. ACEI (or ARB) should be prescribed to all patients with either HFrEF or CKD or both unless contra-indicated. The recent demonstration that sodium –glucose cotransporter 2 Inhibitors (SGLT2is) dapagliflozin and empagliflozin improve CV outcomes in patients with HFrEF when added to all appropriate treatments for HF— is also of paramount importance as a game-changer, while they have also been shown to reduce the progression of CKD in this setting (2). Furthermore, the SGLT2i empagliflozin was recently shown to reduce the combined risk of cardiovascular death or hospitalization for HF (primary outcome) in 5988 patients with HFpEF (50% with an eGFR <60 ml/min/1.73 m<sup>2</sup> at baseline; 81% of the patients treated with an ACEI, ARB, or

angiotensin receptor neprilysin inhibitor; 37% treated with a mineralocorticoid receptor antagonist (MRA) at baseline), regardless of the presence or absence of diabetes. The rate of decline in the eGFR (the second secondary outcome, assigned an alpha level of 0.001) was slower in the empagliflozin group than in the placebo group (−1.25 vs. −2.62 ml per minute per 1.73 m<sup>2</sup> per year; P<0.001) (3). Of note, the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial (NCT03619213) results will be available shortly.

In 4401 patients with proteinuric diabetic nephropathy (as defined by eGFR of 30 to < 90 ml/min/1.73m<sup>2</sup>), and elevated albuminuria (as defined by a urinary albumin:creatinine ratio, >300-5000 mg/g) while on a stable dose of an ACEI or ARB for at least 4 weeks prior to randomization, a post hoc analysis of the Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation (CREDENCE) showed that, compared with placebo, canagliflozin safely reduced renal and cardiovascular events with consistent effects in patients with and without a prior history of HF (all efficacy P interaction >.150)(4).

In this issue of JACC Heart Failure(5), McMurray et al. aimed to extend these findings to 4304 patients with and without a history of HF at baseline, and proteinuric (with a urinary albumin-to-creatinine ratio between 200 and 5000 mg/g) CKD (with an eGFR between 25 and 75 ml/min/1.73 m<sup>2</sup>), with and without type 2 diabetes, all prescribed an ACEI or ARB in a stable dose for at least 4 weeks before screening unless intolerant, in a prespecified analysis of the Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease trial (DAPA-CKD). Irrespective of randomized treatment assignment, the primary composite outcome of sustained decline in eGFR of at least 50%, end-stage kidney disease or death from cardiovascular disease or kidney failure, occurred at a rate of 8.7 (95% CI 6.9-10.8) per 100 person-years in the patients with a history of HF, compared with a rate of 5.7 (5.1-6.2) per

100 person-years in patients without a history of HF, hazard ratio (HR) 1.48; 95%CI 1.17-1.88; P=0.0019). Dapagliflozin reduced the risk of the primary outcome equally in patients with (HR, 0.58 [95% CI, 0.37–0.91]) and without (0.62, 0.51–0.75) HF (P-interaction=0.59). The proportional risk reductions were similar in patients with/without HF for the cardiovascular death/HF hospitalization composite (0.68, 0.44–1.05 versus 0.70, 0.51–0.97, respectively, P interaction= 0.90), and all-cause death (0.56, 0.34–0.93 versus 0.73, 0.54–0.97, respectively, P-interaction=0.39). Adverse event rates were low overall and generally similar among patients with/without HF. Importantly, these analyses were wisely stratified by randomization stratification factors (type 2 diabetes, urinary albumin-to-creatinine ratio), and adjusting for baseline eGFR, which further strengthens the relevance of these findings.

The authors rightly conclude that “Dapagliflozin was equally efficacious in reducing the risk of kidney failure, the composite outcome of hospitalization for HF or cardiovascular death, and death from any cause, irrespective of history of HF at baseline. These findings highlight the crucial value of SGLT2is in the primary and secondary prevention of HF in patients with CKD, irrespective of history of diabetes (and the value of this class of therapy in slowing progression of CKD, irrespective of history of HF).”

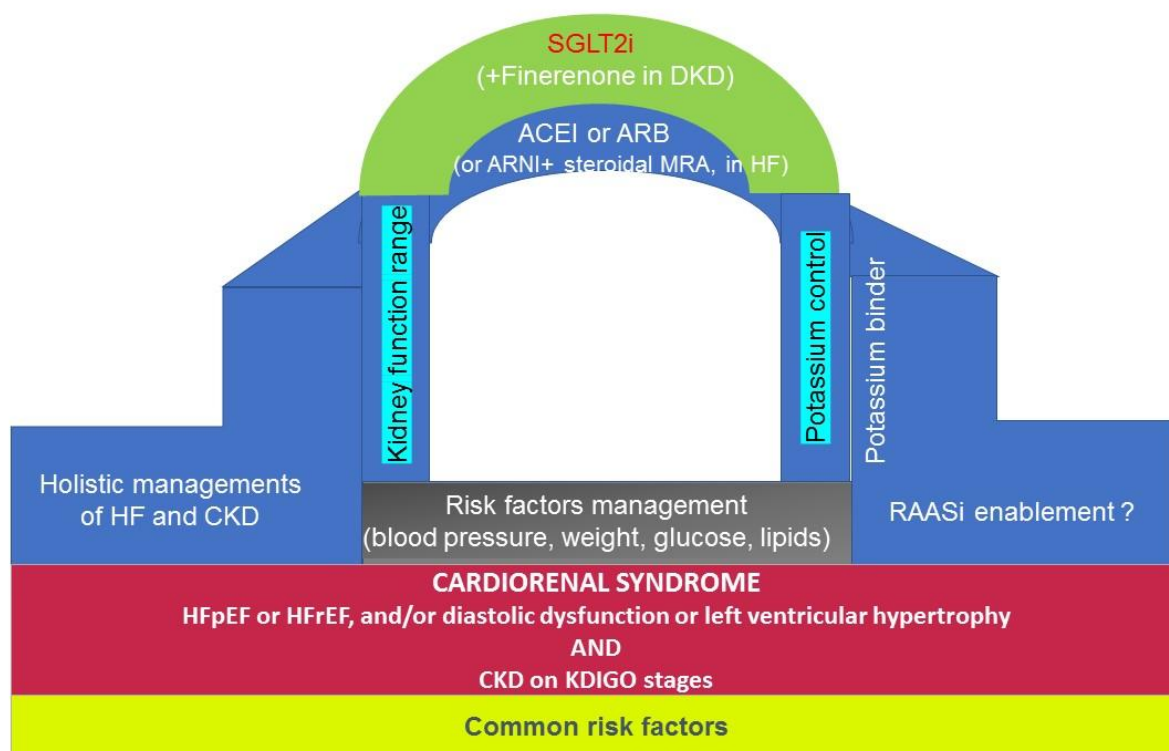
From our perspective, the DAPA-CKD trialists should be commended for having prespecified this well conducted analysis, which represents an important contribution to the whole concept that the new standard of care to achieve cardiorenal protection throughout the cardiorenal continuum may ultimately encompass an ACEI (or an ARB), along with a SGLT2i, both in diabetic and non-diabetic patients. Whether this dual combination should be systematically complemented with an MRA (unless contra-indicated) as a new treatment paradigm throughout the cardiorenal continuum remains to be ascertained (figure), as for instance the value of such approach in non proteinuric/non HF CKD is yet to be determined. So far, steroidal MRAs are already strongly recommended in HFrEF, while the level of evidence is

so far lower in HFpEF(1). The role of the non-steroidal MRA finerenone in HFpEF is currently under investigation (NCT04435626). In the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, in patients with diabetic nephropathy (predominantly stage 3 or 4 CKD with severely elevated albuminuria), finerenone improved kidney outcomes. In the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD), finerenone improved cardiovascular outcomes, as compared with placebo, in patients with type 2 diabetes who had stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria. This difference was driven predominantly by a lower incidence of hospitalization for HF in the finerenone group. Consistent cardiovascular benefits of finerenone therapy were observed independent of, and in combination with the use of an SGLT2i (6). In FIDELIO-DKD and in FIGARO-DKD, the run-in periods allowed adjustment of ACEI or ARB therapy to a maximum labeled dose that did not cause unacceptable side effects.

Altogether, these data suggest that a new treatment paradigm associating renin angiotensin aldosterone system inhibitors (RAASi) and SGLT2i to improve cardiovascular and renal protection throughout the (chronic) cardiorenal continuum is emerging. Acknowledging the challenges of the wide implementation of RAASi during the last two decades, converting such a new paradigm into a new standard of care should be the next frontier to target in cardiorenal medicine.

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Figure. A New Paradigm for the Cardiovascular and Renal Protection of Chronic Cardiorenal



Patients?

Source: (1); Adapted from Rossignol P, Pitt B. Heart Failure and Chronic Kidney Disease Patients: First It Is Necessary to Act. *JACC*. 2021;78(4):344-347.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CKD = chronic kidney disease; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF : heart failure and preserved ejection fraction ; HFrEF: Heart failure and reduced ejection fraction ; KDIGO (Kidney Disease: Improving Global Outcomes) ; MRA = mineralocorticoid receptor antagonist; RAASi = renin angiotensin aldosterone system inhibitors; SGLT2i = sodium–glucose cotransporter 2 inhibitor.

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